THE REPUBLIC OF BOTSWANA

MINISTRY OF HEALTH AND WELLNESS

NATIONAL MALARIA ELIMINATION PROGRAMME

nyeletsa malaria

REVISED GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF MALARIA IN BOTSWANA

OCTOBER, 2020

PREFACE

Malaria remains an important cause of morbidity and mortality for children and adults in Botswana. This is despite the goal to eliminate Malaria in the country. Botswana envisages to achieve zero local malaria transmission by 2020. The 2018-2023 National Malaria Strategic Plan outlines five objectives through which this would be achieved; 1) To achieve universal coverage of appropriate preventive interventions for all populations at risk of malaria in all transmission foci, 2) By 2020 to identify and provide treatment to all persons with malaria infections according to the national guidelines, 3) To strengthen social behavior, communication and community engagement to achieve at least 85% utilization of malaria interventions by 2020. 4) Establish a fully functional malaria elimination surveillance, monitoring and evaluation system to enable effective detection and response to 100% of malaria infection, 5) To strengthen capacity of the NMEP for effective leadership and coordination of malaria elimination

Among the many strategies, to accomplish these; the NMEP guarantees universal access to free malaria prevention and treatment services to all patients.

Case Management remains a core intervention in malaria elimination; this includes quality malaria diagnosis, and the use of effective treatment and transmission blocking medicines to manage the disease.

Due to declining incidence of malaria in the country, Botswana adopted personal protective measures for prevention against the infection for local travelers; and Mefloquine for international travelers. The use of Artemisinin-based Combination therapy (ACT) is espoused as both first line and second line treatment for uncomplicated and complicated malaria. Artemether-Lumefantrine

(AL) plus Primaquine is the first line treatment of choice for uncomplicated Malaria. Further, Artesunate (also Artemisinin derived) is the drug of choice for severe malaria.

The treatment approaches in this guideline are based on best practices, and WHO recommendations aligned with Botswana's local situation. Best efforts have been made by the guideline review team to make it a simple, yet comprehensive guide for clinicians to follow. Therefore, I strongly encourage our health care workers and health partners to use this updated version of Malaria treatment guideline; to test and treat Malaria; as well as manage morbidity and prevent mortality in Botswana.

_____

Dr. M. Ramotsababa

Ag. Deputy Permanent Secretary – Health Services Management

ACKNOWLEDGEMENTS

This updated version of the Malaria Treatment Guideline was made possible and led by efforts from the National Malaria Elimination Program and Malaria focal persons from District Health Management Teams. The work was guided by the World Health Organization.

The NMEP would like to thank private consultants who volunteered their time without compensation to develop this document. We thank the Botswana Defence Force, the Central Medical Stores, the National Health Laboratory, various District Health Management Teams and all Ministry of Health and Wellness officers who participated in the development process.

LE KA MOSO!!

TABLE OF CONTENTS

Deleted: 8
Deleted: 9
Deleted: 10
Deleted: 12
Deleted: 12
Deleted: 12
Deleted: 13
Deleted: 15
Deleted: 17
Deleted: 17
Deleted: 18
Deleted: 19
Deleted: 20
Deleted: 21
Deleted: 22
Deleted: 23
Deleted: 23
Deleted: 23
Deleted: 28
Deleted: 30
Deleted: 31
Deleted: 34
Deleted: 34
Deleted: 35
Deleted: 35
Deleted: 40
Deleted: 41
Deleted: 43
Deleted: 43
Deleted: 44
Deleted: 47
Deleted: 48
Deleted: 7

ACRONYMS

ACT	Artemisinin-based Combination Therapy
AL	Artemether-Lumefantrine
ATQ+PG	Atovaquone-Proguanil
BEDAP	Botswana Essential Drug Action Programme
CQ	Chloroquine
DHA+PPQ	DiHydro-artemesinin + Piperaquine
DOT	Directly Observed Therapy
LLINs	Long Lasting Insecticidal Nets
MOHW	Ministry of Health & Wellness
MRG	Malaria Reference Group
NMEP	National Malaria Elimination Programme
PCR	Polymerase Chain Reaction
PQ	Primaquine
PV	Pharmacovigilance
QA/QC	Quality Assurance/Quality Control
Qn	Quinine
RDT	Rapid Diagnostic Test
SP	Sulphadoxine-Pyrimethamine
TWG	Technical Working Group
WHO	World Health Organization

1. INTRODUCTION

Malaria, is a major public health problem in most parts of the world; and remains the most important parasitic disease that kills young children and adults.

In Botswana, malaria is classified as a notifiable disease; and ought to be reported within 24 hours. Transmission is seasonal and closely related to the amount of rainfall. There is a significant variation in the degree of transmission from year to year, and major epidemics may occur during heavy rainfall. The country experienced epidemics in 1988, 1993, 1996, and 1997. Since then the malaria disease burden has decreased progressively until 2016/17, when there was a rise of cases due to another episode of malaria epidemic in the country.

The seasonality of malaria transmission leads to unstable malaria transmission. Unstable malaria confers negligible acquired immunity leaving all age groups at risk of developing severe malaria. The level of malaria transmission varies throughout the country, giving rise to three epidemiological strata. Malaria is endemic in the northern part of the country with regular and high transmission; there is a central area of intermediate transmission, and a southern area where few or no malaria cases occur. Within these zones there is significant difference in the levels of transmission in different localities. In years of heavy rainfall when both the distribution and intensity of transmission increases, the transmission areas may move southwards such that outbreaks of malaria occur in the central zone of the country, and sporadic malaria cases occur in traditionally non-malarious areas.

1.1 Overview of National Treatment Policies and Drug Resistant Pattern

Chloroquine was the recommended drug for treatment of uncomplicated malaria in the whole country until the mid-1990's. There were anecdotal reports of apparent increase in chloroquine treatment failures, especially after the 1993 malaria epidemic. Between 1994 and 1997, several chloroquine sensitivity and review studies established that parasite resistance to chloroquine and chloroquine treatment failures had reached unacceptable levels. Drug resistance is defined by WHO as the ability of a parasite strain to survive, and/or multiply despite the administration and absorption of drug in doses equal to or higher than that recommended but within the limits of tolerance of the subject.

A decision was taken after wide consultations to replace chloroquine with Sulphadoxine-Pyrimethamine (SP) as first line treatment for uncomplicated malaria. This was achieved successfully in 1996 in the Chobe sub-district as a pilot; and in 1998 rolled out to the entire country.

Over a period of years, reports from the districts indicated that patients were responding very well to SP as first line treatment for uncomplicated malaria. However, the 2006 SP efficacy studies revealed failure rates of 9%. The findings from the 2006 efficacy studies were in conformity to sub-regional and global situation about SP resistance. In view of this level of resistance, and the regional move towards malaria elimination, a decision was taken in 2007 to change the first line drug policy from SP to ***Artemether-Lumefantrine (AL)***, which is an Artemisinin-based Combination

Therapy (ACT).

In response to increasing resistance to SP, other countries in the region also changed their treatment policies to ACT following WHO recommendations. To date almost all the countries in the sub region have adopted ACT policy. Artemisinin-based Combination therapy is defined as the simultaneous use of two or more **blood schizonticidal** drugs with different biochemical targets in the parasites and independent modes of action. Artemisinin-based combination therapy is an antimalarial combination therapy with an artemisinin derivative as one component of the combination.

Artemisinin-based Combination Antimalarial Therapy is preferred over other combinations not containing artemisinin for the following reasons:

- Rapid and sustained reduction of the parasite biomass,
- Reduction of gametocyte carriage thus breaking the malaria parasite's life cycle,
- Rapid resolution of clinical symptoms,
- Safety profile is high,
- Excellent tolerability- well tolerated compared to other antimalarial drugs,
- AL is a fixed dose combination treatment enhancing compliance,
- It demonstrates a high cure rates (more than 95 %), and
- Minimizes emergence of resistance.

Botswana adopted the use of quinine as its first line drug of choice for the management of severe malaria in 2007. World Health Organization recommended artesunate as first line antimalarial

drug on its third edition guideline for the treatment of malaria. This recommendation was based on the largest randomized clinical trials ever conducted on the management of severe falciparum malaria; which showed a substantial reduction in mortality with IV or IM artesunate as compared to quinine. Therefore, Botswana changed its first line treatment of choice to parenteral artesunate for the management of severe cases of malaria. It is also simpler and safer to use.

2. MALARIA DISEASE

Malaria disease is caused by infection with any of the five species of genus plasmodia known to infect humans, namely; *Plasmodium falciparum, P. ovale, P. vivax, P. malariae and P. knowlesi.* Malaria infection in humans is transmitted mainly through the bite of an infected female anopheles mosquito. In Southern Africa, the most common type is the Anopheles gambiae complex. The most prevalent closely related species of anopheles vector found in Botswana is Anopheles arabiensis.

2.1 Parasite Distribution

The major clinical malaria parasite species in Botswana is *P. falciparum*, which causes up to 98% of all malaria cases. *P. malariae* and *P. ovale* share the remaining 2% of clinical cases.

2.2. Disease Presentation

Malaria may present clinically as either uncomplicated malaria, severe malaria or remain as asymptomatic infection especially in people living in malaria endemic areas. In Botswana, due to the highly seasonal and epidemic nature of malaria transmission,

infection with malaria invariably leads to clinical manifestation of the disease.

2.2.1 Uncomplicated Malaria

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence of vital organ dysfunction. The clinical features of uncomplicated malaria are non-specific for a clinical diagnosis. *P. falciparum* malaria is the most prevalent cause of uncomplicated malaria disease in Botswana. In acute *P. falciparum* malaria, there is a continuum of presentation ranging from mild to severe forms of malaria. *Plasmodium vivax* is the second most important causative agent of human malaria globally, accounting 40% of malaria cases worldwide, but it is rare in most of African countries including Botswana.

Uncomplicated malaria characteristically presents with fever, but fever may be absent. Other symptoms may include: -:

- Headache,
- Joint or muscle aches,
- Chills and rigors,
- Fatigue,
- Abdominal discomfort, anorexia, nausea, vomiting.

In children malaria may present subtly as refusal to eat, lethargy and irritability.

Assessment of Uncomplicated Malaria

The primary goal of assessment of a case of uncomplicated malaria is to be able to:

- Promptly and effectively treat malaria to prevent progression to severe disease,
- Limit duration of disease and minimize the risk of the spread of drug resistant parasites, and
- Exclude other common causes of febrile illness.

History:

In addition to the symptoms; age, place of residence, recent history of travel and drugs taken prior to or during current illness are important. History should focus on **asking for;**

- Nature, frequency, duration and pattern of fever and associated chills and rigors, if any
- In children cough, difficulty in breathing, diarrhea, ear pain, history of measles in the last 3 months.

Signs:

Look for:

Prostration, (extreme weakness), irritability,

Examine for:

- Increased body temperature ($\geq$ 38.5º c)
- Pallor, especially in children and pregnant women
- Enlarged liver, spleen or both, especially in children

Presentation of malaria may mimic other acute febrile diseases or illness. Therefore, it is important to consider malaria in any febrile illness and in travelers coming from malaria endemic regions. The diagnosis of uncomplicated malaria is based on history of fever with high index of suspicion for malaria confirmed by RDT or microscopy, in the absence of signs of severe malaria and having excluded other possible cause of acute febrile illness. Key is early detection, correct diagnosis and prompt treatment.

2.2.2 Severe Malaria

The definition of severe malaria disease varies in children and adults. The definition of severe disease is described as in a patient with a *P. falciparum* asexual parasitaemia and no other confirmed cause for symptoms, with the presence of one or more of the clinical or laboratory features associated with severe malaria. *Plasmodium vivax* malaria is generally considered to be benign, but it may cause severe and debilitating febrile illness with a very low case fatality ratio. It can also occasionally result in severe disease. Severe *P.vivax* malaria is defined as for *P.falciparum* malaria but with no parasite density thresholds.

Clinical features associated with severe malaria

- Prostration
- Impaired consciousness (Glasgow coma score <11 in adults or Blantyre coma score <3 in children – see Annex IV)
- Respiratory distress
- Convulsions (more than two episodes within 24 hours)
- Circulatory collapse
- Pulmonary oedema
- Abnormal bleeding
- Jaundice
- Haemoglobinuria

Laboratory Features

- Severe anaemia
- Hypoglycaemia
- Acidosis

- Hyperparasitaemia (*P. falciparum* parasitaemia>10%)
- Renal impairment

Diagnosis of severe malaria disease must always be confirmed by parasitological testing using RDT or blood slide examination. However, rapid initiation of treatment is critical for improved outcome for suspected cases of severe malaria. Hence the non-availability of laboratory results should not delay initiation of treatment of suspected severe malaria, and anti-malarial therapy should be commenced immediately, together with supportive care. However, a blood slide or blood sample for RDTs and blood sugar should be taken when available to guide further management.

3. MALARIA DIAGNOSIS

3.1 Suspected malaria

The signs and symptoms of malaria are non-specific, and clinically malaria is suspected on the basis of fever or a history of fever. There is no combination of symptoms that reliably distinguishes malaria from other causes of fever and as such, other causes should always be carefully considered in a patient. In malaria elimination settings like Botswana, it is important that health workers obtain a detailed travel history to determine the risk of exposure to malaria and the need to test for malaria.

All suspected malaria cases should be confirmed with a parasitological test

3.2. Parasitological Diagnosis

Parasitological diagnosis has the following advantages:

- Improved patient care in parasite-positive patients owing to greater certainty that the patient has malaria,
- Parasite species identification (microscopy, and to a limited extent by some RDTs) and determination of parasitaemia (by microscopy).
- Identification of parasite-negative patients in whom another diagnosis must be sought and appropriately managed,
- Prevention of unnecessary exposure to antimalarials, thereby reducing side-effects, drug interactions and selection pressure for drug resistance,
- Improved surveillance and health information, and
- Identification of treatment failures.

The two methods in use for routine parasitological diagnosis are light microscopy and rapid diagnostic tests (RDTs).

3.3 Guidelines for Malaria Laboratory Diagnosis:

- All cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis before treatment is given.
    - The results of parasitological diagnosis should be available within a short time (< 2 hours) of the patient presenting.
    - If the Initial test is negative and there is still strong suspicion of malaria, repeat parasitological tests can

be done at 6-12h intervals (can be repeat slide examination or repeat RDT)

- All positive malaria RDTs should be followed up by microscopy to identify the malaria species to inform further malaria case management
- Both microscopy and RDTs should be supported by a quality assurance programme

- All febrile patients living in the endemic areas or with history of travel to malarious areas should have a malaria diagnostics test either by microscopy or RDT,
- Clinicians must adhere to the test result for the management of uncomplicated malaria.
- Where parasitological confirmation is not possible, treatment of unconfirmed malaria should be on strong clinical reasons or the patient having one or more characteristics of severe malaria as stipulated above, in which case the classification of the disease becomes severe disease. These should be indicated in the patients file as a standard of good clinical management practice.

In elimination setting a malaria slide should be taken after confirmation of diagnosis with an RDT for parasite speciation.

Note: There should be a continuous flow of information between laboratory and clinical staff.

3.4 Microscopy

Good quality assured microscopy remains the gold standard for routine malaria diagnosis and will be performed in all health facilities with microscopy services. Blood films for malaria diagnosis are prepared from capillary blood obtained by finger prick but in some health facilities venous blood samples usually treated with EDTA are used to prepare blood films. Good quality blood films are essential to establish accurate diagnosis. There are two types of blood films used in malaria diagnosis which are Thick Blood films and Thin Blood films. A minimum of a thick blood film is required for microscopy and this will be prepared at all levels by both laboratory and non-laboratory personnel. Microscopy blood films should be transported as soon as is possible to the facility of examination to avoid autofixation of thick blood films. The use of Giemsa stain is the recommended and most reliable procedure for staining thick and thin blood films. The role of microscopy is:

- Species identification for all malaria RDT positive samples
- Parasite quantification for parasites counts
- Treatment monitoring of Severe malaria treatment
- Patient follow up including as part of routine surveillance for Integrated Drug Efficacy Surveillance

3.5 Malaria Rapid Diagnostic Tests (RDTs)

Malaria Rapid Diagnostic Tests (RDTs) provide useful diagnosis of clinically significant malaria infections. They complement microscopy based diagnosis where such services are not available. In Botswana, RDTs are performed in Health Posts, Clinics, Out-Patient Departments of hospitals by non-laboratory personnel and

in laboratories by laboratory personnel when microscopy is temporarily unavailable.

RDTs are immunochromatographic lateral flow devices for the detection of malaria parasite antigens. RDTs are called “rapid” because they give results within a short time, usually around 10-20 minutes and require less technical expertise as compared to microsocpy. Most RDTs detect malaria species-specific antigens produced by parasites present in the blood of infected individuals and not the parasites nor antibodies to the parasites. These antigens are normally proteins produced during normal parasite biochemistry. Enough blood for the diagnostic test is usually obtained from a finger-prick.

Histidine-rich protein 2 (HRP- 2) of *P.falciparum* is produced by *Plasmodium falciparum* only and is localized in the parasite cytoplasm and on PRBC membrane. It persists for several weeks after parasite death. pLDH (parasite Lactate Dehydrogenase enzyme) is an enzyme of the parasite glycolytic pathway and is expressed by all stages of malaria parasites and is found in all the four human plasmodium species (Pf, Pm, Po and Pv). pfhrp2/3 gene deletions may cause false negative results with HRP2-detecting RDTs and therefore Botswana has put measures in place to detect and monitor the prevalence of pfhrp2/3 gene deletions malaria parasites.

The malaria RDT kit being used in Botswana is a combo kit for detection of Pf (HRP2) and Pan (pLDH) and detects all four malaria species. These are *P. falciparum, P. vivax, P. ovale and P. malariae*. (See Annexure II). HRP2 persists after successful

treatment and therefore the current RDTs remain positive for several weeks after successful treatment of malaria and therefore if fever occurs within 3 weeks of a full course of treatment, microscopy should be used. If microscopy is unavailable, an RDT may be performed and a positive result treated, but the patient should be referred for blood slide to confirm the diagnosis. Persistent fever despite treatment should always be further investigated and/or referred.

3.6 Molecular Testing

Drug resistance can lead to treatment failure. A combination of clinical picture and molecular markers can help us understand drug resistance. A number of genes with a potential to cause resistance of *P.falciparum* to anti-malarial drugs have been isolated. Genotyping can assist to distinguish between reinfection and recrudescence. In elimination setting, the risk of re-infection to occur on a treated patient is very low because of the low malaria transmission.

As a standard practice Dried Blood Samples for molecular testing will be collected at Day 0 when the diagnosis is made. Further, additional samples can be collected on the day of parasite recurrence, if this occurs before day 28. It is also recommended that samples be collected on final day of follow up (Day 28).

Consequently, recurrent parasitemia will be considered by default treatment failure, and managed as such. It will only be confirmed once molecular analysis of samples has been carried out.

Patients with treatment failure (ie. recurrence of parasite with same genetic make-up during follow up period) should be given

supervised second line treatment, and followed up for 28 days until cured. Treatment should be directly observed, for close monitoring.

3.7 Quality Assurance

A comprehensive quality assurance programme is critical for the provision of accurate, timely test results that are interpreted correctly, thereby enhancing patient satisfaction and decreasing costs brought about by misdiagnosis. Good quality results are an essential component of effective case management and malaria surveillance systems. False-negative results can lead to untreated malaria and potentially severe consequences, including death. False-negative results can also significantly undermine both clinical confidence in laboratory results and the credibility of the health services. Surveillance systems need to capture true malaria cases for informed interventions.

Botswana has therefore developed comprehensive malaria diagnosis quality assurance guidelines that outline Botswana's malaria diagnosis quality assurance programme, which applies to malaria microscopy and rapid diagnostic tests. It includes quality policies with regard to each test, the approach for assuring quality testing, and how all the elements are carried out within the system. It also outlines how training of health workers will be conducted as well as evaluation of competency to perform malaria diagnosis. In addition to these guidelines, detailed documents, such as standard operating procedures (SOPs), training curricula, reporting and record keeping forms, provide specific guidance to staff on how to perform various activities related to malaria diagnosis and quality assurance.

4.0 MANAGEMENT OF UNCOMPLICATED MALARIA

4.1 Treatment Objectives

The primary objective of treating uncomplicated malaria is to cure the infection. Cure of the infection means clearance of the parasites from the body causing that particular infection. This is important, as it will prevent progression to severe disease and prevent additional morbidity associated with treatment failure.

The overall public health goal of the treatment is to reduce transmission of the infection to others, i.e. to reduce the infectious reservoir. Primaquine is added in the regimen as gametocidal drug to interrupt the transmission of *p. falciparum*. A secondary, but equally important objective of treatment is to prevent the emergence and spread of resistant strains to antimalarials. Tolerability, the adverse effects and the speed of therapeutic response are important considerations in choosing the type of treatment.

4.2 Treatment of uncomplicated *P. falciparum* malaria

4.2.1 First line treatment

The first line antimalarial drug for the treatment of uncomplicated *P. falciparum* malaria is Artemether-Lumefantrine (AL) with a single dose of primaquine.

AL is a fixed-dose combination tablet containing 20 mg Artemether and 120 mg Lumefantrine. The total recommended treatment dosing using AL is a 6 dose regimen over 3 days. Once a decision

to give antimalarial treatment has been reached, a full course of an effective antimalarial drug must be given.

The dosing schedule of **AL** and **Primaquine** in all age groups is as follows:

- 1st dose at the health facility under **Direct Observed Treatment (DOT)**. If the patient vomits then repeat the dose.
- 2nd AL dose given after 8 hours
- Subsequently the 3rd to the 6th AL dose is given twice daily (morning and evening) for two more days (Refer to table-1.)

Table 1: Dosage schedule of Artemether-Lumefantrine

Body Weight in KG	**Age in Years**	**Day1**		**Day 2 and Day 3**
		1st dose	**After 8hrs**	**Twice a day**
<5 Kg	<6 months	1 tablet	1 tablet	1 tablet
5-14	6 months– 2 yrs	1 tablet	1 tablet	1 tablet
15-24	3-8	2 tablets	2 tablets	2 tablets
25-34	9-14	3 tablets	3 tablets	3 tablets
>34	>14	4 tablets	4 tablets	4 tablets

Give: Primaquine 0.25mg/kg stat dose (except for pregnant and lactating mothers and children less than 6 months of age) along with the first dose of AL for all *P.falciparum* cases.

Note: Treat infants weighing less than 5kg with uncomplicated *p. falciparum* malaria with AL dosed at the same mg/kg as for children weighing 5kg. They should be treated under medical supervision.

Lumefantrine absorption is enhanced by co-administration with fatty foods. It is essential that patients or caregivers be informed of the need to take these tablets with food, preferably milk or **fat-containing food.**

Decreased exposure to Lumefantrine has been documented in young children (<3 years) as well as pregnant women, large adults, patients taking rifampicin or efavirenz and in smokers. As these target population has increased risk for treatment failure, their response to treatment should be monitored more closely and full adherence ensured.

Health workers are required to perform RDT and collect blood samples for microscopy before initiating treatment with AL. However, in instances where RDTs are unavailable, expired or the test is negative, but the clinician has high index of suspicion, treatment should be initiated on the basis of clinical assessment. In such cases, blood slide should be collected for microscopy.

Note: Patients who cannot tolerate oral treatment (AL) may require parenteral artesunate until they can swallow and retain oral medication; then administer a full course of oral AL. In case parenteral artesunate is unavailable give parenteral Artemether and refer the patient to the nearest hospital. (**AL should be dissolved in water and NOT to be crushed**)

Primaquine is given as a single dose of 0.25mg/kg body weight **concurrently with the first dose of AL**. Glucose- 6-Phosphate Dehydrogenase (G6PD) deficiency testing is not required prior to administration of primaquine at this dose.

Table 2. Administering a single dose of Primaquine for *P. falciparum* malaria cases

Body weight (kg)	Single dose of Primaquine (mg base)
10* to < 25	3.75 (half tablet)
25 to < 50	7.5 (1 tablet)
50-100	15 (2 tablets)

* Dosing of young children weighing <10 kg is limited by the tablet sizes currently available.

4.2.2 Second line treatment

The second line antimalarial drug for the treatment of uncomplicated *P. falciparum* malaria is Dihydro-artemisinin plus Piperaquine (DHA/PPQ). This is used in the following instances; i) AL treatment failure, ii) AL contraindicated.

DHA/PPQ is manufactured as a fixed dose of two drug; dihydro-artemesinin (an artemisinin) and piperaquine (a tetra-phosphate). Piperaquine kills parasites by disrupting the detoxification of host heme.

This drug is formulated in two strengths of 20mg DHA + 160mg PPQ and 40mg DHA + 320mg PPQ. These are administered once daily for three days as shown in table 3. Administration should be over three consecutive days for a total of three doses taken at the same time each day. Dosing is based on body weight.

Table 3. Dosing schedule for dihydroartemisinin+piperaquine

Body weight (kg)	Dose in mg		Tablet strength	Number of tablets
	DHA	PPQ		
5 - <7	10	80	20/160	1/2
7- 13	20	160	20/160	1
13-24	40	320	40/320	1
24-36	80	640	40/320	2
36-75	120	960	40/320	3
75-100	160	1280	40/320	4

- The first dose of DHA+PPQ is taken DOT (Directly Observed Therapy).
- DHA+PPQ is taken with water without food. Each dose should be taken no less than 3 hours after the last food intake. No food should be taken within 3 hours after each dose.
- For patients unable to swallow the tablets, such as infants and young children, the drug may be dissolved in water and administered as slurry.
- If a patient vomits within 30 minutes of taking, re-administer the whole dose. If a patient vomits within 30-60 minutes, half the dose should be re-administered. Re-dosing of DHA+PPQ should not be attempted more than once. If second dose is vomited, parenteral medicine should be administered.
- DHA+PPQ is safe to use in second and third trimesters of pregnancy.

4.3 Supportive treatment

- Ensure temperature stabilization. Expose child by uncovering and do tepid sponging as a supportive measure.
- Aspirin is contraindicated in children less than 12 years of age.
- Maintain adequate nutrition by offering small, frequent, high energy density foods

4.3.1 Use of antipyretics in uncomplicated *P.falciparum* malaria

Fever is a cardinal sign of malaria and is associated with constitutional symptoms of lassitude, weakness, headache, anorexia and nausea. If fever (core temperature >38.5°C) is recorded give Paracetamol 10 mg/kg in children or 500 – 1000 mg in adults (1-2 tablets) every 4 hours

4.4 Management of uncomplicated *P.falciparum* malaria in specific populations and situations

4.4.1 Children less than 5kg

Malaria in children under 6 months or less than 5kg is uncommon but potentially fatal. Fevers in such groups are most likely to be associated with septicemia. As they constitute an acute emergency, where possible they should be managed under expert pediatric care. AL is the drug of choice for managing uncomplicated malaria in this age group at the same dose as children above 5kg.

4.4.2 Pregnant Women

Malaria during pregnancy causes fever, anaemia and risk of miscarriage, stillbirths, low birth weight, neonatal and maternal death.

As with all cases, a parasitological diagnosis of malaria is required before treatment.

AL is first line treatment for uncomplicated malaria in all trimesters.

Table 4: Dosing schedule for treatment of uncomplicated malaria in pregnant women

Trimester	Regimen
1st	AL
2nd	AL
3rd	AL

Primaquine is contraindicated in pregnancy.

4.4.3 Lactating Women

Lactating women who present with uncomplicated malaria should be treated with AL. **Primaquine is contraindicated in the first 6 months of breastfeeding.**

4.4.4 Patients Co-Infected: HIV/AIDS

HIV infection increases susceptibility to malaria that may lead to severe disease and death, particularly in areas of unstable malaria.

Patients with HIV infection who present with uncomplicated malaria should be treated with AL and primaquine.

Caution:

Avoid treatment of *p. falciparum* malaria with Artesunate + Sulphadoxine- Pyrimethamine(AS + SP), if on treatment with co-trimoxazole; and

Avoid treatment with Artesunate + Amodioquine (AS + AQ), if on treatment with efavirenz and zidovudine.

4.4.5 Malnourished Patients

Although there are many reasons why drug kinetics may be different in malnourished patients, there is insufficient evidence to suggest changing current dosage recommendation of anti-malarial drugs. AL remains the drug of choice for treatment of uncomplicated malaria in malnourished patients.

4.5 Treatment Failures

Patients with uncomplicated *P.falciparum* malaria who deteriorate by developing features of severe disease or do not improve whilst on Artemether-Lumefantrine treatment taken correctly for at least 48 hours, showing persistent parasitemia should be considered as having treatment failure. Treatment failures may result from drug resistance, or inadequate drug exposure (sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetic properties or substandard medicines). Treatment failure must be confirmed parasitologically, preferably with a blood slide examination. Use of RDTs to confirm treatment failure is not recommended.

The following conditions should be considered in treatment failure:

- Persistence or a rising parasitaemia

- Progression from uncomplicated to severe malaria
- Recurrence of malaria within 28 days

4.5.1 Treatment failure within 28 days

The second line recommended antimalarial treatment for use in treatment failure occurring within 28 days of initial treatment is dihydro-artemisinin+piperaquine (DHA+PPQ).

Caution:

- Quinine-containing regimens are not well tolerated. Adherence to 7-day treatment regimens (quinine which should be co-administered with clindamycin or tetracycline or doxycycline) is likely to be poor, if treatment is not directly observed.

The use of oral artesunate monotherapy is strongly discouraged.

4.5.2 Treatment failure after 28 days

If failure occurs after 28 days, distinction between **recrudescence** or a **new infection** can only be made by PCR parasite genotyping of the initial and recurrent infections. As PCR are not routinely used in patient management, all presumed treatment failures after 4 weeks of initial treatment should, from an operational standpoint, be considered new infections and be treated with AL + PQ.

4.6 Treatment of Uncomplicated Non-*P. falciparum* Malaria

4.6.1 *P. malariae*

AL and single dose of primaquine are the recommended 1st line treatment of choice for *P. malariae*.

4.6.2 P. vivax and P. ovale treatment

When confirmed, treat *P. vivax* or *P. ovale* malaria with AL and in children more than 6 months of age and adults, add a 14-day course of primaquine to prevent relapse.
Therapeutic dose: 0.25mg/kg/day primaquine once a day for 14 days.

In people with G6PD deficiency, consider preventing relapse by giving primaquine base **at 0.75 mg/kg body weight once a week for 8 weeks,** with close medical supervision for potential primaquine-induced adverse hematological effects – this includes daily checking of urine color for changes associated with hemolysis.

In all cases, clinicians should be aware and have the capacity to identify and safely monitor and then manage primaquine-induced hemolytic reactions

Note: Primaquine should always be taken with food as it causes dose-limiting abdominal discomfort when taken on an empty stomach.

Primaquine is contraindicated in:

- pregnant women
- infants aged < 6 months
- women breastfeeding infants aged < 6 months
- women breastfeeding older infants with G6PD deficiency
- people with G6PD deficiency

4.7 Preventing relapse in Pregnant and breastfeeding women

For women who are pregnant or breastfeeding, **give weekly chemoprophylaxis with chloroquine** until delivery and breastfeeding are completed, then, based on G6PD status, treat with 14 days of primaquine to prevent future relapse.

4.8 Recommendations on G6PD testing and primaquine anti-relapse therapy

Any person with red cell G6PD activity <30% of the normal mean has G6PD deficiency and will experience hemolysis after Primaquine. Therefore, G6PD status should be ascertained if possible, before administering daily primaquine therapy for 14 days to prevent relapses in patients with confirmed *P. vivax* or *P ovale* infection.

Males who have tested or who have a history of testing normal using a reliable G6PD test should receive standard daily primaquine therapy, as they are not expected to experience harmful adverse drug effects.

G6PD qualitative tests will not identify the majority of heterozygous females some of whom may be at risk of developing Acute Hemolytic Anemia (AHA) secondary to primaquine therapy. Therefore, females who test G6PD normal with a qualitative test should only receive daily primaquine therapy if they can be monitored for signs and symptoms of AHA during the first week of treatment.

Male or female patients diagnosed with acute *P. vivax* or *P. ovale* malaria should not receive daily primaquine to prevent relapses when they have tested G6PD deficient. However, G6PD deficient patients may receive a weekly dose of 0.75 mg/kg/wk for 8 weeks, while those patients whose G6PD status is un-known may receive a standard daily dose of 0.25 mg/kg/day for 14 days, provided that they are under close medical supervision for signs and symptoms

of AHA; and provided they have access to health facilities with capacity for safe blood transfusion.

If G6PD status is unknown and testing is not available then a decision to prescribe daily primaquine to prevent relapses must be based on a balanced assessment of the following:

i) The available data regarding the local prevalence of G6PD deficiency in the population;

ii) The capacity to identify and safely monitor and then manage primaquine-induced hemolytic reactions in the treatment setting;

iii) The benefits of treatment in terms of expected reduction in number of relapses.

5 MANAGEMENT OF SEVERE MALARIA

5.1 Management Objectives

The main objective is to prevent the patient from dying; secondary objectives are prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities**.**

Death from severe malaria often occurs within hours of admission to hospital or clinic, so it is essential that therapeutic concentrations of anti-malarials are achieved as soon as possible. Mortality from untreated severe malaria approaches 100%; however, with prompt, effective antimalarial treatment and supportive care, the rate falls to 10-20%. The risk of death increases with the presence of multiple complications.

5.2 Treatment of Severe Malaria

Treat children and adult with severe malaria, including: infants, pregnant women in all trimesters, and lactating women with Artesunate IV for at least 24 hours and until able to tolerate oral medication.

Once the patient has received at least 24 hours of parental treatment and able to tolerate oral medication, the patient should complete full course of AL. A single dose of primaquine should then be given with the first dose of AL.

Parenteral Artemether is the recommended **second line drug** for the treatment of **all** severe malaria cases.

5.3 Treatment Schedule for Severe Malaria

5.3.1 Artesunate

Artesunate 2.4 mg/kg body weight given IV/IM at admission (time =0), then after 12 hours, and after 24 hours; then once a day until patient is able to tolerate oral medication when AL is given.

Children weighing less than 20kg should receive a higher dose of Artesunate (3mg/kg/dose) than larger children and adults (2.4mg/kg/dose) to ensure an equivalent drug exposure.

Note: Artesunate powder is dissolved in sodium bicarbonate (5%). The solution is then diluted in approximately 5ml of 5% dextrose and given by intra venous or Intra muscular route to the anterior thigh.

- IV fluids given with medication should be based on hydration status, urine output, etc.

- Monitor blood sugar every 4 hours and whenever symptom of hypoglycemia occurs provide treatment, e.g. convulsions or changing level of consciousness.
- The solution should be prepared freshly for each administration and remainder should not be stored.

Table 5: Parenteral Artesunate dosing schedule for the treatment of severe malaria **(see Annex III for reconstitution illustration)**

Timing	Children <20kg	Children ≥20kg and Adults
Artesunate dose on admission	3mg/kg/dose	2.4mg/kg/dose
Artesunate dose after 12 hours	3mg/kg/dose	2.4mg/kg/dose
Artesunate dose After 24 hours	3mg/kg/dose	2.4mg/kg/dose
Daily Artesunate dose, until oral antimalarial is tolerated	3mg/kg/dose	2.4mg/kg/dose
When oral antimalarial is tolerated	Full course of AL for three days + stat dose of Primaquine (i.e. for *P.falciparum case*) with the 1st dose of AL	

Note: If parental Artesunate is not available use intramuscular Artemether for treating children and adults with severe malaria.

5.3.2 Artemether

Intramuscular injection with Artemether is recommended as the alternative treatment when injectable Artesunate is not available.

Injectable Artemether should be given for at least 24 hours, up to a maximum of 7 days. When a patient can tolerate oral medication, they should be prescribed a full course of oral ACT therapy. The use of injectable Artemether is recommended and preferred over injectable quinine. Artemether is given as an oil-based intramuscular injection into the anterior thigh. Since artemether is administered intramuscularly, its absorption is erratic and slower than Artesunate, which is water-soluble.

Table 6: DOSING TABLE FOR INJECTABLE ARTEMETHER (IM)

For Adults and children over 6 months.

Table 6:

TIMING	**DOSE**
Initial Dose	**3.2mg/kg bodyweight**
Maintenance	**1.6mg/kg bodyweight daily**

DOSAGE TABLE ACCORDING TO THE WEIGHT

WEIGHT IN KILOGRAMS	**LOADING DOSE IN ML**	**MAINTENANCE DOSE IN ML**
3-4	**0.2**	**0.1**
5-6	**0.3**	**0.15**
7-9	**0.4**	**0.2**
10-14	**0.6**	**0.3**
15-19	**0.8**	**0.4**
20-29	**1.2**	**0.6**
30-39	**1.6**	**0.8**
40-49	**2**	**1**
50-59	**2.5**	**1.2**

When oral antimalarial is tolerated, full course of AL for three days + stat dose of Primaquine (i.e. for P*. falciparum case*) with the 1st dose of AL should be given.

5.3.3 Quinine

A loading dose of intravenous (IV) quinine 20mg/kg (to a maximum of 1.2g quinine) diluted in IV solution containing 5% dextrose (1-2ml/kg) is infused over four hours; then four hours after completing the loading dose (i.e. 8hrs from starting the first dose) give 10mg per kg infused over 4 hours and continue the same dose 8hrly. If the patient requires IV quinine for more than **48hrs reduce the dose to 5-7 mgs per kg per dose 8hrly**

Note:

- The loading dose is not given if **quinine, chloroquine, or mefloquine** have been given in any form during the previous one week. In this case commence with a dose of 10 mg/kg of body weight.
- IV fluids given with quinine should be based on hydration status, urine output, etc. Once the IV fluid rate has been decided then quinine is added to the amount of IV fluid to be infused over 4 hour period or as a separate IV infusion or piggy bag in 5% Dextrose.
- Monitor blood sugar with dextro-stix every 4 hours to promptly manage hypoglycemia, and whenever symptom of hypoglycemia occurs, e.g. convulsions or changing level of consciousness, manage it accordingly.
- Patient with severe malaria will be treated with quinine for at least 24 hours and as long as they cannot take oral medication. If the patient is well enough to take oral

medication, before completing 7 (seven) day treatment, a full course of AL + PQ should be given.

How to Give IM Quinine

- Weigh the patient or (in children) estimate the weight using the formula:
  2 x age (years) + 8 = weight in kg (gives a good estimate up to age 10 Years)
- Draw up 5 ml sterile normal saline.
- Draw up 300 mg (1 ml) quinine from an ampoule into the same syringe.
- The syringe now has 50 mg quinine per ml of solution
- Give 10 mg (0.2 ml) per kg body weight by IM injection into the upper thigh. If the volume to be injected is more than 3 ml, give half into each thigh.

Note:

- Quinine must never be given by IV bolus injection as **lethal hypotension** may result.
- The adult dose for IM quinine is the same as for children, i.e. 10 mg/kg.
- In the case of heavy adults who might require up to 16 ml of the diluted quinine preparation, the total need to be divided into 3 or 4 parts of 3 or 4 ml, each which can be injected into different sites.
- The quinine that is used for IM injection is the same preparation, which is given IV. In other words there is no difference in the ampoules, which can therefore be used for

either IM or IV administration. However when given IM it must be diluted as described above.

Note: The importance of supportive or ancillary measures is emphasized.

5.4 Initial treatment considerations for severe malaria

- Clear and maintain the airway
- Position semi-prone or on side
- Make rapid clinical assessment
- Weigh the patient (if possible) and calculate dosage
- Take blood for diagnostic smear, hematocrit and other laboratory tests
- Exclude hypoglycemia and meningitis
- Start the recommended anti-malarial treatment immediately
- Monitor blood glucose
- Start recommended treatment for hypoglycemia and meningitis where indicated
- Measure and monitor fluid intake and urine output. If necessary insert urethral catheter
- Plan the first 8 hours intravenous fluids, including diluents for antimalarial drug, glucose therapy and blood transfusion
- If body temperature exceeds 37.5^{o}C, remove patient's clothes, tepid sponge, and fan, use cooling blanket and give antipyretic
- Manage convulsions as recommended, if they occur
- Consider need for additional drugs (vitamin-k, antibiotics etc.) (Ref Table-7 for the management of complications).

5.5 Pre-Referral Treatment

In settings where complete treatment of severe malaria is not possible, but injections are available, give children and adults a single dose of intramuscular Artesunate and refer to an appropriate facility for further care. Use Artemether if Artesunate is not available. Quinine is the third-line drug of choice.

In the event that referral is not possible, IM Artesunate should be continued (3mg/kg/dose pediatric, 2.4mg/kg/dose adult) eight-hourly until the patient is able to take oral medication. When oral treatment is tolerated, then administer a complete course of AL. Give a single dose of Primaquine with the first dose of AL.

Treat children below the age of six years with a single dose of rectal artesunate 10mg/kg and refer immediately to an appropriate facility for further care. Rectal artesunate is not recommended for older children and adults.

5.6 Treatment of Other Severe Malaria Complications

Table 7: Treatment of Other Severe Malaria Complications.

Manifestation/ complication	Immediate management
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycemia, bacterial meningitis); avoid harmful ancillary treatment such as corticosteroids, heparin and adrenaline; intubate if necessary.

Hyperpyrexia	Administer tepid sponging, fanning, cooling blanket and antipyretic drugs.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde.
Hypoglycemia (blood glucose concentration of <2.2 mmol/l; <40 mg/100ml)	Check blood glucose, correct hypoglycemia and maintain with glucose-containing infusion.
Severe anemia (hemoglobin <5 g/100ml or packed cell volume <15%)	Transfuse with fresh whole blood screened for HIV and hepatitis
Acute pulmonary edema	Prop patient up at an angle of 45^{o}, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxemia.
Acute renal failure	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add hemofiltration or

	hemodialysis, or if unavailable, peritoneal dialysis. The benefits of diuretics/dopamine in acute renal failure are not proven.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycemia, hypovolemia and septicemia. If severe add hemofiltration or hemodialysis.
Shock	Suspect septicemia, take blood for cultures; give potential antimicrobials, correct hemodynamic disturbances. Monitor frequently.

Source: As adapted from the Guideline for the treatment and Diagnosis of malaria in the Africa region.

6 MALARIA PREVENTION

6.1 Malaria Prevention in Pregnancy

In Botswana where malaria transmission is low, no prophylactic antimalarial is recommended for pregnant women in malaria endemic areas. The combined regimen of chloroquine and proguanil is no longer recommended as its effectiveness is not known. The emphasis is on vector control measures (i.e. bed nets

and other personal protective measures) and effective case management. However intermittent testing for malaria infection (RDT/MS) is recommended for pregnant women in malaria endemic areas.

6.2 Chemoprophylaxis in the General Travelers

In Botswana malaria is unstable and people are mobile; these put the whole population at risk. No prophylactic antimalarial is recommended for local travelers. Therefore, this revised guideline strongly encourages promotion of personal protective measures such as the use of LLINs, insect repellents and protective clothing.

The drug of choice for travellers going out of the country to endemic countries is Mefloquine. Chemoprophylaxis with Mefloquine can be taken by adults, children, pregnant and lactating women. Mefloquine chemoprophylaxis is taken 2 weeks before travel. Continue weekly doses while at destination. Mefloquine intake should continue weekly for 4 weeks after return.

Table 8: Mefloquine dosage

Weight (Kg)	Age(Years)	Number of Tablets per week (1 tab=250mg)
<5	<3 months	Not recommended
5-12	3-23 months	1/4
13-24	2-7	1/2
25-35	8-10	3/4
36-50+	11-14+	1

If Mefloquine is not available Atovaquone + Proguanil combination is recommended.

Atovaquone plus proguanil is the drug of choice for those travelling to areas where there is mefloquine resistance (Asia) or mefloquine is contraindicated. Taken a day or two before traveling; daily while at destination and taken for seven days upon returning. Atovaquone + Proguanil combination is not recommended in these instances;

- During pregnancy and lactation
- Children less than 11kg body weight

Personal protective measures are emphasized.

Atovaquone+Proguanil is available as adult strength 250mg Atovaquone / 100mg Proguanil Hydrochloride tablet.

The dosage for pediatric patients is based upon body weight.
ATQ-PG is not recommended for pediatric patients under 11kg body weight.

Table 9: Pediatric patients dosage

WEIGHT IN KILOGRAMS	ATQ-PG TOTAL DAILY DOSE	DOSAGE
11-20	62.5mg/25mg	1 pediatric tablet daily
21-30	125mg/50mg	2 pediatric tablets as single daily dose
31-40	187.5mg/75mg	3 pediatric tablets as single daily dose
>40	250mg/100mg	1 adult strength single daily dose

IN BOTSWANA DOXYCYCLINE IS NOT RECOMMENDED FOR CHEMOPROPHYLAXIS, AND SHOULD NOT BE USED AS SUCH.

7. PHARMACOVIGILANCE

The use of a new drug or combination of drugs in the population requires careful monitoring of adverse drug reactions that maybe associated with the use of such drugs in the broader population. WHO defines pharmacovigilance (PV) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. Pharmacovigilance therefore is a critical component for the implementation of the new drug policy. Hence, the monitoring, documentation and reporting of adverse drug reaction by health workers cannot be over emphasized.

All health care providers and patients are therefore advised to identify report and document all new and already noted adverse effects and report to Ministry of Health National Malaria Elimination Programme and Botswana Medicines Regulatory Authority (BOMRA).

Pharmacovigilance of all drugs used for treatment of Malaria is important as it will go a long way in providing information thereby providing a tool for decision making to preventing harm to our patients.

7.1 Drug resistance surveillance through routine iDES

Integrated Drug Efficacy Surveillance (iDES) as recommended by WHO, is the gold standard for monitoring drug efficacy to inform treatment policy in elimination settings. It is designed for efficacy monitoring for both Pf and Pv, and for any recommended first- and second-line drugs as well as any drug that needs to be monitored prior to possible introduction into the treatment policy.

In very low transmission areas pursuing malaria elimination, the number of malaria cases are most often too low for the needed number of cases to be reached at sentinel sites for routine therapeutic efficacy monitoring studies. In such instances, the strengthened surveillance system can be used to also collect and analyze data on drug efficacy. Thus, in areas pursuing malaria elimination with strong surveillance systems, efficacy monitoring is shifted from using a sentinel surveillance system to relying on data collected via routine surveillance systems.

iDES therefore, ensures that the data collected on all malaria cases in the routine surveillance system can and are being used to also generate information about drug efficacy.

7.2 Inclusion criteria for routine iDES

The following will be criteria used to select malaria patients for inclusion;

- All confirmed malaria cases including asymptomatic cases, of all age groups and with any parasitaemia.

- A detailed case investigation and recording of likely origin of the malaria infection
- Identification of symptoms (uncomplicated, severe)
- Species identification by RDT and/or microscopy
- Supervised treatment (DOT) all doses
- Follow-up on Days 3 and 28 /or - any day where the patient presents with recurrent parasitaemia +/-symptoms after a treatment (additional full follow-up period is needed with second line treatment – day 42 for DHA/PPQ).
- Clinical symptoms, temperature, presence of parasitaemia documented by microscopy on day 0, 28, (day 42 for DHA/PPQ) or any day of recurrent parasitaemia.

8. DISEASE MANAGEMENT AT DIFFERENT LEVELS OF THE HEALTH CARE DELIVERY SYSTEM

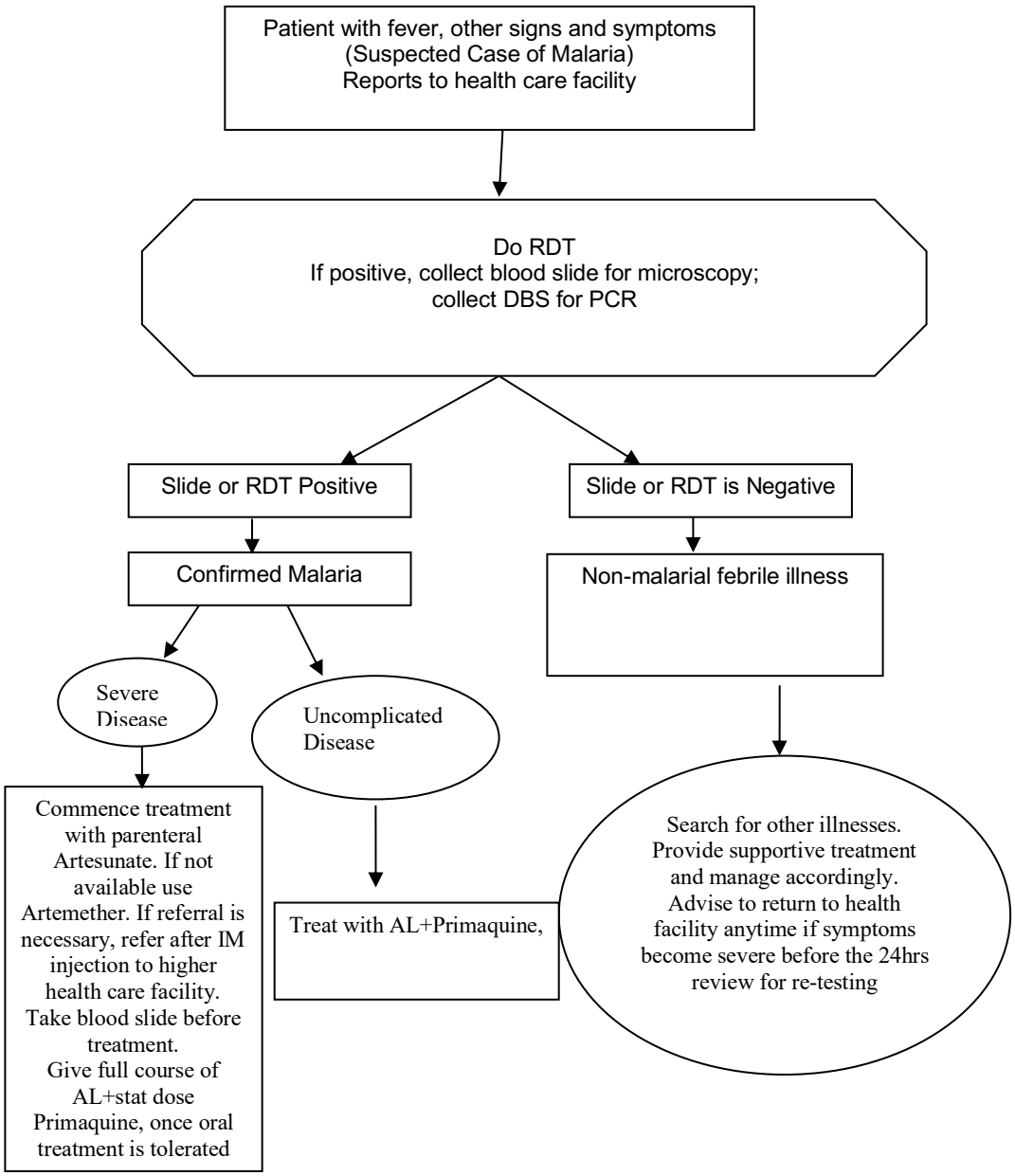
The goals of malaria case management are stated against each level. It is hoped that this will serve as a useful guide in focusing the use of this treatment manual.

HEALTH CARE FACILITY	CADRE OF STAFF	EXPECTED HEALTH CARE LEVEL
Tertiary Referral Hospitals	Consultant, Specialists, Medical officers, Nurses, Pharmacy and Medical	Intensive care for severe disease as well as all the services listed under primary and secondary care levels

	Laboratory Personnel	
Secondary District, Primary, Mission, Mines and Private Hospitals	Medical officers, Nurses Pharmacy and Medical Laboratory Personnel.	In-patient care Basic laboratory support for confirming diagnosis and monitoring. Assessing complications
Primary Clinics with/without maternity, Health Posts and Mobile Stops	Medical officers and Nurses	Focusing on disease identification through parasitological diagnosis, initiation of appropriate treatment and urgent referral of severe malaria, Rapid test

9 ANNEXES

Annexure 1 Decision Chart for Treatment of Malaria



Note*: P.falciparum* case: radical treatment with a single dose of Primaquine (except pregnant and lactating mother and children<6months).

Note: P.vivax/P.ovale case: prevent relapse with a daily or weekly primaquine.

Annexure – II Performing and Interpreting Malaria Rapid Diagnostic Test including Plates for performing and interpreting RDTs.

Performing and Interpreting the Test-

If the preparation is delayed after opening the envelope, the humidity can damage the RDT. Test lines may become positive several hours after preparation; and should be read only within the time limit specified by the manufacturers. The result of malaria RDT should always be interpreted in the light of the patient's clinical state, taking into account the fallibility of the test. A control line must be present for the result to be valid. Repetition of the test after 1 or 2 days may therefore be indicated if illness persists or if the patient's condition deteriorates and the initial RDT result was negative.

Acting on the Test Result-

- Treatment algorithms and health workers training allow for the commencement of anti-malarial treatment of cases in which RDT result is negative, whenever there is a strong suspicion of malaria.
- Appropriate further investigation of all case of fever with negative RDT results is essential.
- The possibility of concomitant non-malarial illness in which parasites have been demonstrated should also be considered.

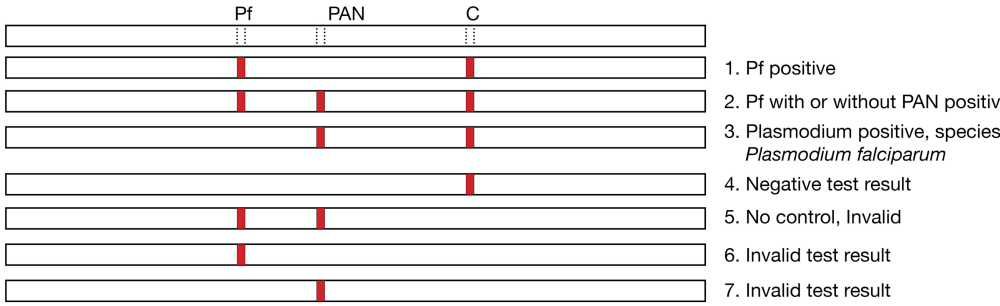
Sometimes RDT results may mislead-

- A negative test result does not always exclude malaria with certainty as:
    - There may be insufficient parasites to register a positive result,
    - The RDT may have been damaged thereby reducing its sensitivity,
    - Illness may be caused by another species of malaria parasite which the RDT is not designed to detect.
- A positive result does not always signify malaria illness because :
    - Antigen may sometimes be detected after the infecting parasites have died (i.e. after treatment) or due to the persistence of malaria gametocytes which do not cause illness,
    - The presence of other substances in the blood may occasionally produce a false positive result, and

- The presence of parasites does not always signify malaria illness in individuals with high immunity as there may be other causes of fever.

- However, any infection with malaria found either incidentally or by presentation of clinical illness should be treated with the recommended first line treatment of choice.

Test results



C= Control line, Pf: *Plasmodium falciparum,* Pf ± PAN: *Plasmodium falciparum with or without other malaria parasite species.*

Annexure –III Artesunate Reconstitution

mmv.org

Annexure IV
Coma Monitoring Scales

Table 1: The Glasgow Coma Score (for Adults and Children over 12yrs)

Eyes open	- Spontaneously	4
	- To speech	3
	- To pain	2
	- None	1
Best verbal	- Oriented	5
	- Response- confused	4
	- In appropriate words	3
	- Incomprehensible sounds	2
	- None	1
Best motor response	- Obeys commands	6
	- Localizes pain *flexion to pain*	5
	-Withdrawal from pain	4
	-Abnormal flexion to pain	3
	- Abnormal Extension to pain	2
	- None	1
	Total	3-15

Note: To obtain the Glasgow coma score obtain the score for each section and add the three figures to obtain the total.

Table 2: The Malaria Coma Scale (The Blantyre Coma Scale) (for children < 12 years)

Eyes movement	-Directed (eg follows mothers face)	1
	- Not directed	0
Verbal response	- Appropriate cry	2
	- Moan or inappropriate cry	1
	- None	0
Best motor response	- Localizes painful stimulus (a or c)	2
	- Withdraws limb from pain (b)	1
	- Non-specific or absent response	0
	Total	0 - 5

Note:
Press knuckles firmly on the patients sternum
Press firmly on the thumbnail bed with side of a horizontal pencil
Press firmly on the supra-orbital groove with the thumb

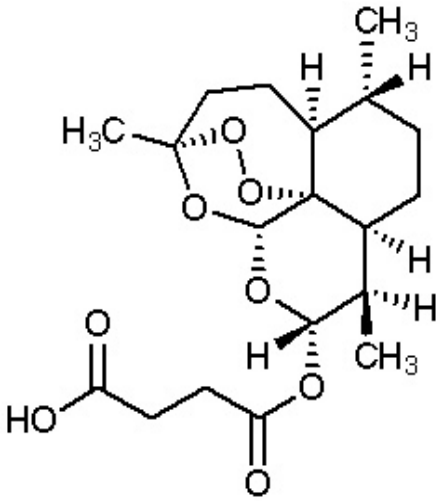
The scales can be used repeatedly to assess improvement or deterioration.

Annex V Pharmacology of the Drugs used for the treatment of malaria in Botswana

PHARMACOLOGY OF ARTESUNATE

Structure and Mechanism of Action

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is obtained by the reduction of artemisinin, a sesquitepene lactone endoperoxide.



The mechanism of action of the artemisinin derivatives is not well defined but involves cation-mediated generation of reactive intermediates and reduction of the peroxide bridge. Artesunate, like other derivatives, kills all erythrocyctic stages of malaria parasites, including the ring stages and early schizonts, as well as the gametocytes responsible for continuing transmission, although it has only partial activity against the mature stage V gametocytes. It is essentially inactive against extra-erythrocytic forms, sporozoites, liver schizonts and merozoites.

Pharmacokinetics

Artesunate is rapidly absorbed and biotransformed into its active metabolite dihydroartemisinin by plasma esterases with a possible contribution from CYP2A6 enzymes. While dihydroartemisinin accounts for nearly all the antimalarial activity of oral artesunate, artesunate contributes more significantly to the antimalarial effect after intravenous administration. Peak concentration of artesunate

is reached within a few minutes of parenteral administration; therefore, artesunate is rapidly eliminated. Plasma protein binding of dihydroartemisinin is approximately 93%. Dihydroartemisinin is metabolized in the gut and liver by glucuronidation and is excreted in the urine.

Artesunate has been successfully and safely administered in the second and third trimesters of pregnancy; in first trimester, treatment of severe malaria with artsunate is recommended as it is potentially life-saving for the mother.

Adverse Effects

Artesunate side-effects include; gastrointestinal disturbances, cough, rash, arthralgia, dizziness and delayed hemolysis, rarely hypersensitivity reactions. Other adverse effects are neutropenia (dose-dependent), hepatotoxicity and neurotoxicity.

Contraindications

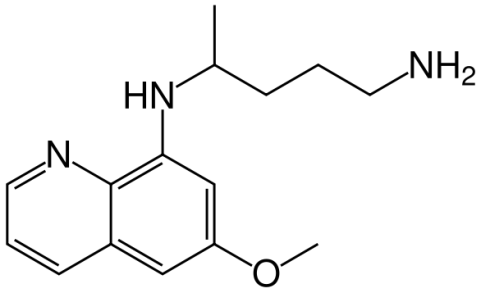
Artesunate is contraindicated in patients with known hypersensitivity to artesunate or artemisinin derivatives.

Cautions

Monitor treatment closely on patients with renal and hepatic impairment and young children with severe anaemia.

PHARMACOLOGY OF PRIMAQUINE

Structure and Mechanism of Action



Primaquine is an 8-aminoquinolone, which is highly active against the exoerythrocytic form

(hypnozoites) and the sexual blood stages of malaria parasites (gametocytes). Hepatic metabolism of primaquine produces reactive intermediate metabolites that generate toxic intracellular oxidative species. The parent compound itself is relatively inactive. The precise mechanism of action of primaquine is not fully understood, but it is thought that the reactive intermediates disrupt the metabolic processes of plasmodial mitochondria and interfere with electron transport in the parasite.

Pharmacokinetics

Primaquine is rapidly absorbed from the gastrointestinal tract, reaching peak concentrations within 1 – 4 hours, with a bioavailability of about 96%. Primaquine is biotransformed by two main routes: by monoamine oxidase to the predominant, but inactive, metabolite carboxyprimaquine, which is relatively slowly eliminated; and via CYP2C19, CYP2D6 and CYP3A4 in the liver, which generate the reactive intermediates responsible for antimalarial effects and hemolytic toxicity. Primaquine is extensively distributed in the body, in plasma, it is about 75% protein bound. Both primaquine and carboxyprimaquine are excreted mainly through the biliary tract and can be found in feces within 24 hours of administration, also it is excreted in the urine as unchanged drugs. Primaquine crosses the placenta but it is uncertain whether significant amounts occur in breast milk.

Adverse Effects

While primaquine is generally well tolerated, it may cause dose-related gastrointestinal discomfort, including abdominal pain, nausea and vomiting. Administration with food improves tolerability. Hypertension and cardiac arrhythmia have been reported rarely.

The most important adverse effect is hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and the degree of hemolysis is proportional to the dose, duration of exposure, and the degree of G6PD deficiency. Leukopenia, methaemoglobinemia with cyanosis and granulocytopenia may also occur. Fortunately, primaquine is eliminated rapidly, so that hemolysis stops once the drug is stopped. Patients should discontinue primaquine if they pass red or black urine, or have symptomatic anemia.

Contraindications

Primaquine is contraindicated in patients with known hypersensitivity to primaquine or related compounds and in patients with severe G6PD deficiency or severe nicotinamide adenine dinucleotide (NADH) methaemoglobin reductase deficiency. Primaquine crosses the placenta and may cause hemolysis in a G6PD-deficient fetus, it is therefore not recommended for use during pregnancy or breastfeeding. Use of primaquine in infants <6 months is not advised.

PHARMACOLOGY OF ARTEMETHER - LUMEFANTRINE

Mode of Actions of AL: The precise anti-malarial action of Artemether and Lumefantrine is unknown, although both appear to act on the parasite's cell structures. Artemether contains an endoperoxide bridge, which interacts with iron in the hemoglobin to generate reactive oxygen radicals which damage the parasite leading to its death. Lumefantrine is thought to interfere with heme-polymerizations, a critical detoxifying pathway for the malaria parasite. Artemether rapidly reduces parasite biomass and quickly

resolves clinical symptoms while long acting Lumefantrine prevents recrudescence. This dual effect also appears to reduce the selective pressure on the parasite to develop resistance.

Adverse/Side Effects and Their Management*:* Artemether-Lumefantrine is relatively safer compared to other antimalarial drugs. The side effects are minimal and these may include:

- **Common side effects:** Gastrointestinal disturbances such as abdominal pain, anorexia, nausea, vomiting, diarrhea, central nervous system such as headache, dizziness which cannot be distinguished from symptoms of acute malaria.
- **Less common side effects**: Pruritus and rash (<2% of patients) others include neutropenia, liver enzymes elevation. Cardiovascular effects- bradycardia, palpitation and prolongation of QT interval. Sleep disturbances, cough, asthenia, arthralgia, and myalgia.
- Most of these side effects will resolve without discontinuing treatment. However, in severe cases, treatment with AL must be discontinued and the recommended second line anti-malarial prescribed.

Some of the side effects may be managed as follows;

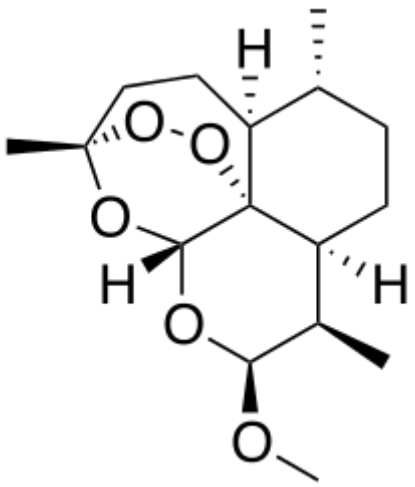
- Anorexia:-Encourage the patients to eat any food that he/she enjoys or is palatable to him/her.
- Nausea and vomiting: - Patients should be advised to take the medication with food.
- Diarrhoea: - Patients should be advised to drink water often or use ORS.
- Rash and Pruritus (mild):– Reassure the patient that it will stop after a short time, if severe, discontinue.

Precautions: Caution should be applied in patients known to have, electrolyte disturbances, hepatic and renal impairment. Concomitant use AL with drugs known to cause QT-interval prolongation (e.g. quinine and mefloquine) should be discouraged. Monitor patients who are unable to take food while on AL therapy, as they are at greater risk of recrudescence.

Contra indications*:* AL is contraindicated in patients with history of arrhythmias, clinically relevant bradycardia, heart failure, family history of sudden death or of congenital, QT interval prolongation and persons with known hypersensitivity to either of the components in AL. It is contraindicated in children weighing less than 5 Kg.

It is also contraindicated in severe malaria. **Drug Interaction***:* Patients should avoid **grapefruit juice,** antiarrhythmic such as amiodarone, disopyramide, flecainide, procainamide and quinidine; antibacterials such as macrolides and quinolones, all antidepressants, antifungals such as imidazoles and triazoles, terfenadine; other antimalarials, all antipsychotic drugs; and beta blockers, such as metoprolol and sotalol. However, there is no evidence that co-administration with these drugs would be harmful especially in short term treatment. But where possible, avoid concomitant administration of AL with any of the drugs above or administer giving a sufficient time in-between the drugs.

PHARMACOLOGY OF ARTEMETHER



Artemether is a lipid-soluble methyl ether of dihydroartemisinin. Artemisinin derivatives kill parasites more rapidly than conventional antimalarial drugs, and are active against both the sexual and asexual stages of the parasite cycle. The antimalarial activity of artemether and other artemisinin derivatives is a result of the peroxide bridge found in the active metabolite dihydroartemisinin. Dihydroartemisinin is formed from the rapid demethylation of artmether via CYP3A4 and CYP3A5. It then undergoes glucuronidation catalyzed by the UDP-glucuronosyltransferases UGT1A9 and UGT2B7 into inactive metabolites that are eliminated in the bile.

Artemether has very rapid schizontocidal activity against *P. falciparum* and *P. vivax* blood forms.
Peak plasma concentrations are attained within 6 hours post intramuscular administration of the drug.

ADVERSE EFFECTS

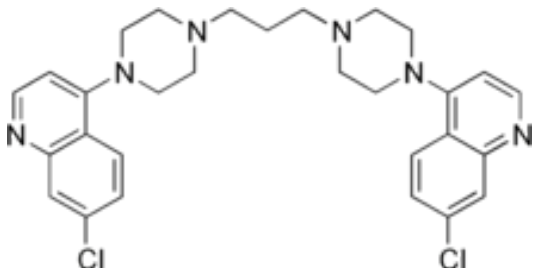
Artemether causes relatively few side effects. Possible side effects include cardiac effects such as(bradycardia , QT interval prolongation, hypotension) convulsions, dizziness GI disturbances such as abdominal pains, nausea and vomiting .Also a possible central nervous system toxicity has been shown in animal studies.

DRUG INTERACTION

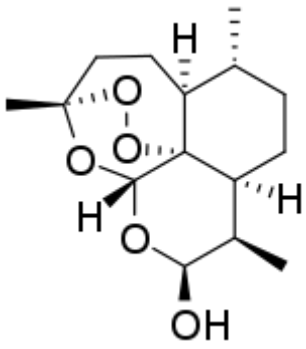
Combination products if used with lopinavir/ritonavir found to lower plasma levels of artemether and should not be used with drugs that inhibit CYP3A4. Reduced efficacy of oral contraceptives if used with combination products.

PHARMACOLOGY OF DIHYDROARTEMESININ-PIPERAQUINE

Piperaquine



Dihydroartemesinin



Dihydroartemesinin is the active metabolite of all artemisinin drugs. Piperaquine is a bisquinoline with blood schizonticidal properties. It is absorbed slowly, and has a long biological half-life.
Dihydroartemesinin is a fast acting drug with a short biological half-life.

Dihydroartemesinin - Piperaquine is contraindicated in patients with cardiac disorders (CHF, heart rhythm conditions). Patients taking drugs that prolong QT interval amiodarone, fluconazole, macrolides, flouroquinolones) should not be prescribed DHA-PPQ. Care should be taken when administering to patients over the age of 60. Patients on anti-retroviral drugs should be closely monitored.
There are no contra-indications in pregnancy or breast-feeding.

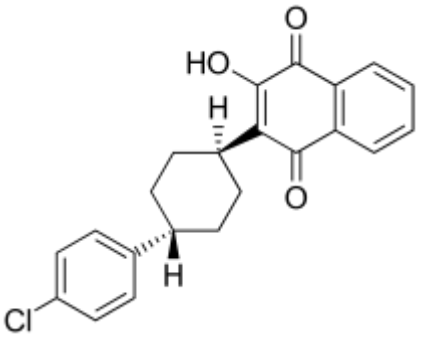
PHARMACOLOGY OF ATOVAQUONE-PROGUANIL

ATQ+PG is a fixed-dose combination of antimalarial drugs atovaquone and proguanil hydrochloride. ATQ-PG interfere with 2 different pathways required for the parasite replication. Atovaquone selectively inhibits the parasite mitochondrial electron transport.

Proguanil Hydrochloride exerts effect through the metabolite cycloguanil. Cycloguanil inhibits dihydrofolate reductase in the parasite resulting in the disruption of deoxythymidylate synthesis. Atovaquone and cycloguanil are active against both the erythrocytic and exoerythrocytic stages of Plasmodium sp.

STRUCTURES

Atovaquone **Proguanil**



PHARMACOKINETICS

The pharmacokinetics of proguanil and cycloguanil are similar in both adult and pediatric patients.

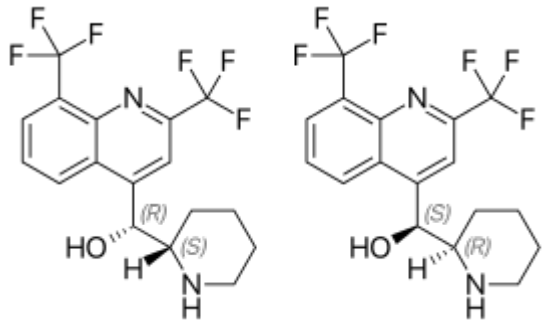
Bioavailability: Atovaquone is highly lipophilic with poor water solubility. Oral absorption of atovaquone is poor but increases to 23% with high-fat meal (AUC increased 2-3 times and Cmax 5 times over fasting). Absorption is aided by administering with food or milk. Proguanil is extensively absorbed regardless of food intake. Between 40% to 60% of proguanil is excreted by the kidneys. Proguanil is metabolized to cycloguanil (primarily via CYP2C19)

and 4-chlorophenylbiguanide; and eliminated through the hepatic biotransformation and renal excretion.
The elimination half-life of atovaquone is about 2 to 3 days in adult patients and 1-2 days in pediatric. The elimination half-life of proguanil is 12 to 21 hours in both adult patients and pediatric patients, but may be longer in individuals who are slow metabolizers.

Adverse effects;
ATQ-PG contains 2 substances, as a result, side effects associated with each of the compounds may present. At prophylactic doses ATQ-PG is more likely to be tolerated than at higher treatment doses. Adverse effects include abdominal pains, nausea, vomiting, diarrhea, headaches, dizziness anorexia and abnormal liver function tests.

ATQ-PG is contraindicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or any component of the formulation. Rare cases of anaphylaxis following treatment with atovaquone/proguanil have been reported.
ATQ-PG is contraindicated for prophylaxis of P. falciparum malaria in patients with severe renal impairment (creatinine clearance <30 mL/min). No dosage adjustments are needed in patients with mild to moderate hepatic impairment.

PHARMACOLOGY OF MEFLOQUINE



Mefloquine is a 4-methanolquinoline and is related to quinine. It is soluble in alcohol but only very slightly soluble in water. It should be protected from light. The drug is effective against all forms of malaria.

Formulations*:* Mefloquine is administered by mouth as the hydrochloride salt (250 mg base equivalent to 274 mg hydrochloride salt). Tablets containing either 250 mg salt (United States of America) or 250 mg base (elsewhere)

Pharmacokinetics*:* Mefloquine is reasonably well absorbed from the gastrointestinal tract but there is marked inter individual variation in the time required to achieve peak plasma concentrations. Splitting the 25 mg/kg dose into two parts given at an interval of 6–24 h augments absorption and improves tolerability*)*. Mefloquine undergoes enter hepatic recycling. It is approximately 98% bound to plasma proteins and is widely distributed throughout the body.

Pharmacokinetics: Mefloquine may be altered by malaria infection with reduced absorption and accelerated clearance. When administered with artesunate, blood concentrations are increased,

probably as an indirect effect of increased absorption resulting from more rapid resolution of symptoms. Mefloquine is excreted in small amounts in breast milk. It has a long elimination half-life of around 21 days, which is shortened in malaria to about 14 days, possibly because of interrupted enterohepatic cycling. Mefloquine is metabolized in the liver and excreted mainly in the bile and faeces. Its pharmacokinetics show enantioselectivity after administration of the racemic mixture, with higher peak plasma concentrations and area under the curve values, and lower volume of distribution and total clearance of the SR enantiomer than its RS antipode.

Toxicity*:* Minor adverse effects are common following mefloquine treatment, most frequently nausea, vomiting, abdominal pain, anorexia, diarrhoea, headache, dizziness, loss of balance, dysphoria, somnolence and sleep disorders, notably insomnia and abnormal dreams. Neuropsychiatric disturbances (seizures, encephalopathy, and psychosis occur in approximately 1 in 10 000 travellers receiving mefloquine prophylaxis, 1 in 1000 patients treated in Asia, 1 in 200 patients treated in Africa, and 1 in 20 patients following severe malaria *(24–27)*. Other side effects reported rarely include skin rashes, pruritus and urticaria, hair loss, muscle weakness, liver function disturbances and very rarely thrombocytopenia and leukopenia. Cardiovascular effects have included postural hypotension, bradycardia and, rarely, hypertension, tachycardia or palpitations and minor changes in the electrocardiogram. Fatalities have not been reported following over dosage, although cardiac, hepatic and neurological symptoms may be seen. Mefloquine should not be given with halofantrine because it exacerbates QT prolongation. There is no evidence of an adverse interaction with quinine.

Drug interactions*:* There is a possible increase in the risk of arrhythmias if mefloquine is given together with beta-blockers, calcium channel blockers, amiodarone, and pimozide. Digoxin or antidepressants; there is also a possible increase in the risk of convulsions with chloroquine and quinine. Mefloquine concentrations are increased when given with ampicillin, tetracycline and metoclopramide. Caution should be observed with alcohol.

PHARMACOLOGY OF QUININE

Quinine is an alkaloid derived from the bark of the Cinchona tree. Quinine is the L-stereoisomer of quinidine. It acts principally on the mature trophozoite stage of parasite development and does not prevent sequestration or further development stage of circulating ring stages of *P. falciparum*. It also kills the sexual stages of P*. vivax, P.malariae and P.ovale* but not mature gametocytes of P*. falciparum.* It does not kill the pre-erythrocytic stages of malaria parasites. The mode of action is thought to involve inhibition of parasite heme-detoxification in the food vacuole, but are not well understood. It is also believed to depress oxygen uptake and carbohydrate metabolism; intercalates into DNA, disrupting the parasites replication and transcription.

Pharmacokinetics*:* The pharmacokinetic properties of quinine are altered significantly by malaria infection, with reduction in apparent volume of distribution and clearance in proportion to disease severity. The concentration is slightly higher in older children and adult with severe malaria than in children under 2 years of age. Quinine is rapidly and completely absorbed from Gastro Intestinal Tract (GIT) and peak plasma concentration is reached in 1-3 hours after oral administration of the sulphate. Also it is well absorbed in after I.M. administration in severe malaria. Quinine is widely distributed throughout the body including the cerebrospinal fluid, breast milk and placenta. Extensively metabolized in liver and the elimination of more polar metabolites is mainly renal. Excretion is increased in acid urine. The mean elimination half-life is around 11 hours in healthy subjects, 16 hours in uncomplicated malaria and

18hours in severe malaria. Small amount appear in the bile and saliva.

Adverse effects/ Toxicity*:* Quinine causes complex of symptoms known as cinchonism which could be mild or severe. Mild symptoms include tinnitus, impaired hearing, headache, dizziness and dysphoria and disturbed vision.

Severe manifestations include vomiting, abdominal pain, diarrhea and severe vertigo. Others include hypersensitivity reactions such as urticaria, bronchospasm, flushing, and fever, thrombocytopenia and hemolytic anemia. **The most important adverse effect is hyperinsulinemic hypoglycemia and this is particularly common in pregnancy**. I.M injection of quinine HCL causes pain, focal necrosis and in some cases abscess formation. Hypotension and cardiac arrest may result from rapid intravenous injection. I.V quinine should be given by infusion never injection. It causes prolongation of the electrocardiograph QT interval. Quinine has been used as an abortificient, but there is no evidence that it causes abortion, premature labour or fetal abnormalities in therapeutic use.

Stability*:* Protect from light.

Precautions*:* Use with caution in patients with cardiac arrhythmias and patients with myasthenia gravis.

Contraindication*:* Quinine should not be used in patients with tinnitus, optic neuritis, G-6-Phosphate Dehydrogenase deficiency, hypersensitivity to quinine or any component, history of black water fever (massive hemolysis with renal failure)

Drug interactions*:* Quinine may not be given concurrently with drugs that cause prolongation of QT interval Flecainide and amiodarone, should probably be avoided. There might be an increased risk of ventricular arrhythmias with antihistamines such as terfenadine and with antipsychotic drugs such as pimozide and thioridiazine. Halofantrine, which causes marked QT prolongation, should be avoided but combination with other antimalarials, such as lumefantrine and mefloquine is safe. Quinine increases the plasma concentration of digoxin. Cimetidine inhibits quinine metabolism, causing increased quinine levels and rifampicin metabolic clearance leading to low plasma concentrations and an increased therapeutic failure rate.

PHARMACOLOGY OF CHLOROQUINE

Chloroquine is a 4-aminoquinoline that has been used extensively for the treatment and prevention of malaria. Widespread resistance has now rendered it virtually useless against *P. falciparum* infections in most parts of the world, although it still maintains considerable efficacy for the treatment of *P. vivax, P. ovale* and *P. malariae* infections. As with other 4-aminoquinolines, it does not produce radical cure. Chloroquine interferes with parasite haem detoxification *(1, 2)*. Resistance is related to genetic changes in transporters (PfCRT, PfMDR), which reduce the concentrations of chloroquine at its site of action, the parasite food vacuole.

Formulations: Tablets containing 100 mg or 150 mg of chloroquine base as hydrochloride, phosphate or sulfate.

Pharmacokinetics: Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract when taken orally, although peak plasma concentrations can vary considerably. Absorption is also very rapid following intramuscular and subcutaneous administration *(3–5)*. Chloroquine is extensively distributed into body tissues, including the placenta and breast milk, and has an enormous total apparent volume of distribution. The relatively small volume of distribution of the central compartment means that transiently cardiotoxic levels may occur following intravenous administration unless the rate of parenteral delivery is strictly controlled. Some 60% of chloroquine is bound to plasma proteins, and the drug is eliminated slowly from the body via the kidneys, with an estimated terminal elimination half-life of 1–2 months. Chloroquine is metabolized in the liver, mainly to onodesethylchloroquine, which has similar activity against *P. falciparum*.

Toxicity*:* Chloroquine has a low safety margin and is very dangerous in over dosage. Larger doses of chloroquine are used for the treatment of rheumatoid arthritis than for malaria, so adverse effects are seen more frequently in patients with arthritis. The drug is generally well tolerated. The principle limiting adverse effects in practice are the unpleasant taste, which may upset children, and pruritus, which may be severe in dark-skinned patients. Other less common side effects include headache, various skin eruptions and gastrointestinal disturbances, such as nausea, vomiting and diarrhoea. More rarely central nervous system toxicity including, convulsions and mental changes may occur. Chronic use (5 years continuous use as prophylaxis) may lead to eye disorders, including keratopathy and retinopathy. Other uncommon effects include

myopathy, reduced hearing, photosensitivity and loss of hair. Blood disorders, such as aplastic anaemia, are extremely uncommon.

Acute over dosage is extremely dangerous and death can occur within a few hours. The patient may progress from feeling dizzy and drowsy with headache and gastrointestinal upset, to developing sudden visual disturbance, convulsions, hypocalcaemia, hypotension and cardiac arrhythmias. There is no specific treatment, although diazepam and epinephrine (adrenaline) administered together are beneficial.

Drug interactions: Major interactions are very unusual. There is a theoretical increased risk of arrhythmias when chloroquine is given with halofantrine or other drugs that prolong the ectro-cardiograph QT interval; a possible increased risk of convulsions with mefloquine; reduced absorption with antacids; reduced metabolism and clearance with cimetidine; an increased risk of acute dystonic reactions with metronidazole; reduced bioavailability of ampicillin and praziquantel; reduced therapeutic effect of thyroxine; a possible antagonistic effect on the antiepileptic effects of carbamazepine and sodium valproate; and increased plasma concentrations of cyclosporine.

Annex VI: List of Technical Working Group that Reviewed the Guidelines:

Technical Review Team Members

No	Name	Designation	Organisation
1.	Dr Gobusaone Morupisi	Public Health Specialist	Palapye DHMT/MoHW
2.	Dr Gobeze Solomon	Public Health Specialist	National Malaria Program/MoHW
3.	Captain Dr Pearl Setilo	Military Medical officer	Botswana Defence Force
4.	Dr Wabuya Khonou	Senior Medical Officer/ Malaria focal person	Okavango DHMT/MoHW
5.	Dr James O D Othwolo	Public Health Specialist	Private Consultant
6.	Merapelo Mpuang	PRN/CHN-Malaria Focal person	Goodhope DHMT/MoHW
7.	Musharaf Miazi	Pharmacist	BEDAP/ MoHW
8.	Itumeleng Sampson	Medical Lab Scientist	Chobe DHMT Laboratory-MoHW
9.	Kealeboga Kuswani	Medical Lab Scientist	National Health Laboratory-MoH
10.	Dr Kris Masikara	Pediatrician	Serowe DHMT/ MoHW
11.	Dr Loeto Mazhani	Paediatrician Consultant	Private Consultant
12.	Vitus Izuagba	Principal Pharmacist	Kanye SDA Hospital
13.	Chendzimu Malinga	PRN/FNP- Malaria focal person	Tutume DHMT/MoHW
14.	Lorato C Nfila	PRN/FNP- Malaria focal person	Selibe-Phikwe DHMT/MoHW
15.	Maungo Gasenna	Pharmacist	Central Medical Stores
16.	Dr Gaboratanelwe Gasennelwe	Public Health Specialist	Primary Health Care Support Division- MoHW
17.	Kentse Moakofhi	Malaria National Professional Officer	WHO/Botswana
18.	Tjantilili Mosweunyane	National Malaria Programme- Manager	National Malaria Programme-MoHW
19.	Dr Refilwe Senyatso	Malaria Case Management	National Malaria Programme-MoHW

External Reviewers

No	Name	Title	Organization
1	Dr Elizabeth Juma	Case Management IST/ESA	World Health Organization/Harare
2	Anderson Chinorumba	Technical officer	World Health Organization/Harare
3	Dr Peter Olumese	Global Malaria Programme	World Health Ogranization/Geneva

10. REFERENCES

1. Guidelines for the Treatment of Malaria-Third edition; World Health Organization, 2015.
2. Point of care G6PD testing to support safe use of primaquine for the treatment of vivax malaria. WHO evidence Review Group report, October, 214; Geneva, Swizerland.
3. SADC malaria 2014 status report (draft); SADC Secretariat, Oct, 2015, Gaborone, Botswana.
4. Malaria diagnosis in low transmission settings. WHO evidence review group-2014; Geneva, December, 2013 report.
5. Single dose Primaquine as gametocide in Plasmodium falciparum malaria. Updated WHO policy recommendation, October, 2012.
6. Malaria Manual for Health workers In Botswana, Second Edition, 1999.
7. The Diagnosis and Management of Uncomplicated and Severe Malaria, facilitators Guide, Republic of Botswana, June 2004.
8. The Diagnosis and Management of Uncomplicated and Severe Malaria, Learners guide, Republic of Botswana, June 2004.
9. Malaria case management operational manual draft. World Health Organization. 2006
10. Use of Antimalarial Drugs. Report of an Informal Consultation. World Health Organization. 2000.

11. The Use of Rapid Diagnostic Test, World Health Organization, 2004.
12. Novartis; Coartem Monograph 2001.
13. WHO: Report of World Health Organization Technical Consultation, 25 – 26 October 2004. (Pre- Publication Copy).
14. Malaria Diagnosis and Treatment Guidelines for Health Workers in Ethiopia, July 2004.
15. Guidelines for Administration of injectable artesunate for severe malaria. Malariajournal.biomedcentral
16. Malaria Surveillance, Monitoring & Evaluation: A reference Manual. World Health Organization, 2018.