CHEMOTHERAPY

Antimalarial Drugs Drugs – Chemotherapy Course

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Chemotherapy PHAR 5

Semester one

Week number 13 and 14

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Learning Objectives

- By the end of this lecture, students will be able to:
- 1. Classify antimalarial drugs based on their mechanism of action, chemical structure, and stage of the Plasmodium life cycle they target.
- 2. Describe the mechanism of action of key antimalarial agents such as chloroquine, artemisinin derivatives, primaquine, and antifolate combinations.
- 3. Identify the appropriate therapeutic uses of antimalarial drugs in treating different types of malaria, including P. falciparum and P. vivax.
- 4. Recognize the adverse effects and contraindications associated with common antimalarial drugs, especially in special populations (e.g., G6PD deficiency, pregnancy).
- 5. Discuss the principles of antimalarial drug resistance and the rationale for combination therapies such as ACT (Artemisinin-based Combination Therapy).

Learning Outcomes

- After completing this lecture, students should be able to:

1. **Accurately classify** antimalarial drugs into their respective chemical and therapeutic groups.
2. **Explain how antimalarials act** on different stages of the malaria parasite and how this guides treatment decisions.
3. **Select appropriate antimalarial regimens** for uncomplicated, severe, and relapsing malaria based on current guidelines.
4. **Identify and counsel patients** on key side effects, contraindications (e.g., G6PD screening for primaquine), and adherence issues with antimalarial therapies.
5. **Apply knowledge of drug resistance and pharmacology** to suggest rational combinations and alternatives for antimalarial treatment and prophylaxis.

Introduction to Antimalarial Drugs

- **Malaria** is a life-threatening parasitic disease caused by Plasmodium species, transmitted through the **bite of infected female Anopheles mosquitoes**. Effective chemotherapy is central to malaria control and eradication strategies.

MALARIA

* INFECTION CAUSED by PLASMODIUM SPECIES

SINGLE - CELLED PARASITES

MALARIA

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MALARIA

* INFECTION CAUSED by PLASMODIUM SPECIES

~ P. falciparum
~ P. vivax
~ P. malariae
~ P. ovale
~ P. knowlesi

SINGLE - CELLED PARASITES

MALARIA

* INFECTION CAUSED by PLASMODIUM SPECIES

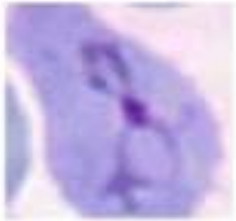
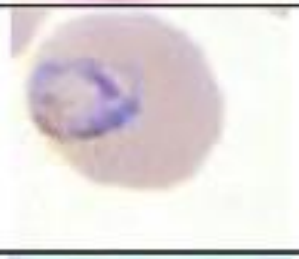
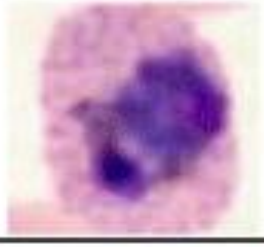
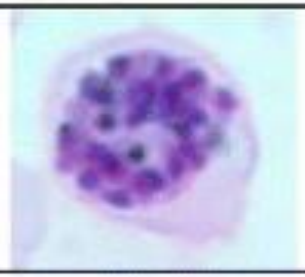
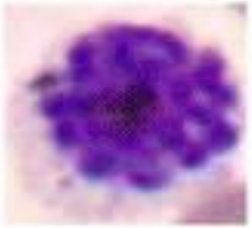
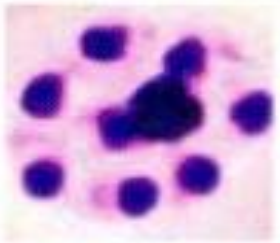
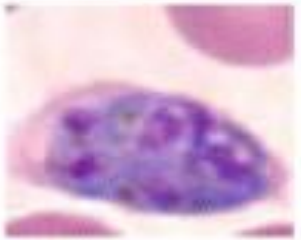
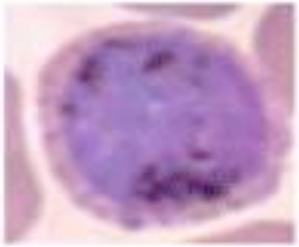
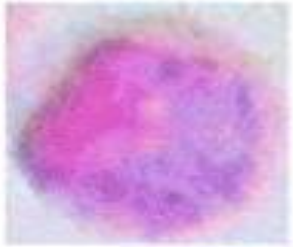
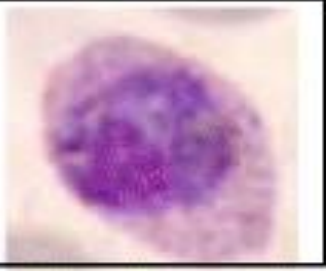
~ P. falciparum
~ P. vivax
~ P. malariae
~ P. ovale
~ P. knowlesi

SINGLE - CELLED PARASITES

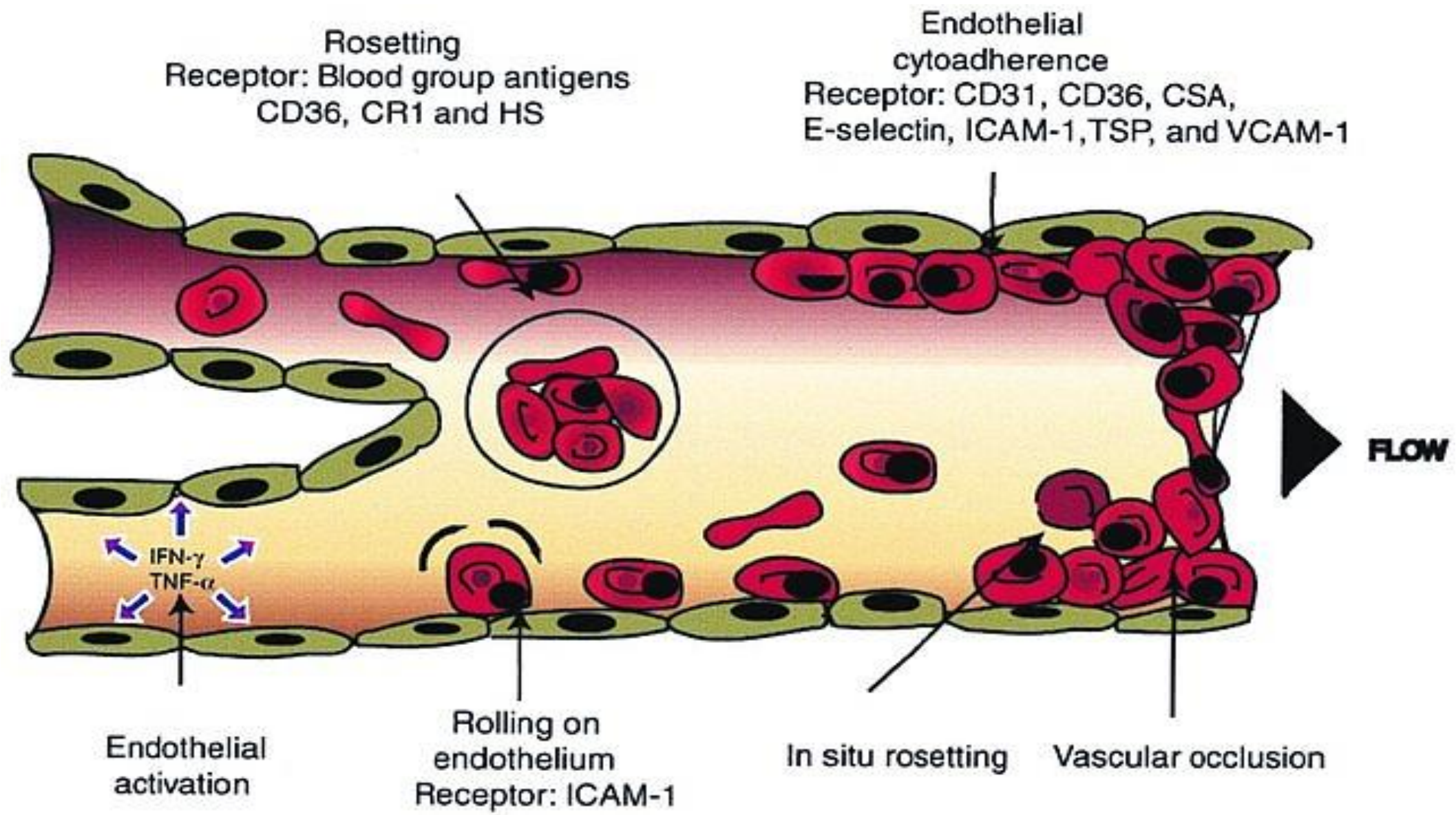
GETS INTO the BLOODSTREAM

Common Plasmodium Species in Humans:

1. *Plasmodium falciparum* (most deadly)
2. *Plasmodium vivax*
3. *Plasmodium malariae*
4. *Plasmodium ovale*
5. *Plasmodium knowlesi* (zoonotic)

Species / Stage	Falciparum	Vivax	Malariae	Oval
Ring Stage				
Trophozoite				
Schizont				
Gametocyte				

Malaria must be recognized promptly in order to treat the patient in time.



The binding of P. falciparum mature infected erythrocytes to endothelial lining and to uninfected erythrocytes, rosetting, contributes to occlusion of blood flow and resultant severe disease.

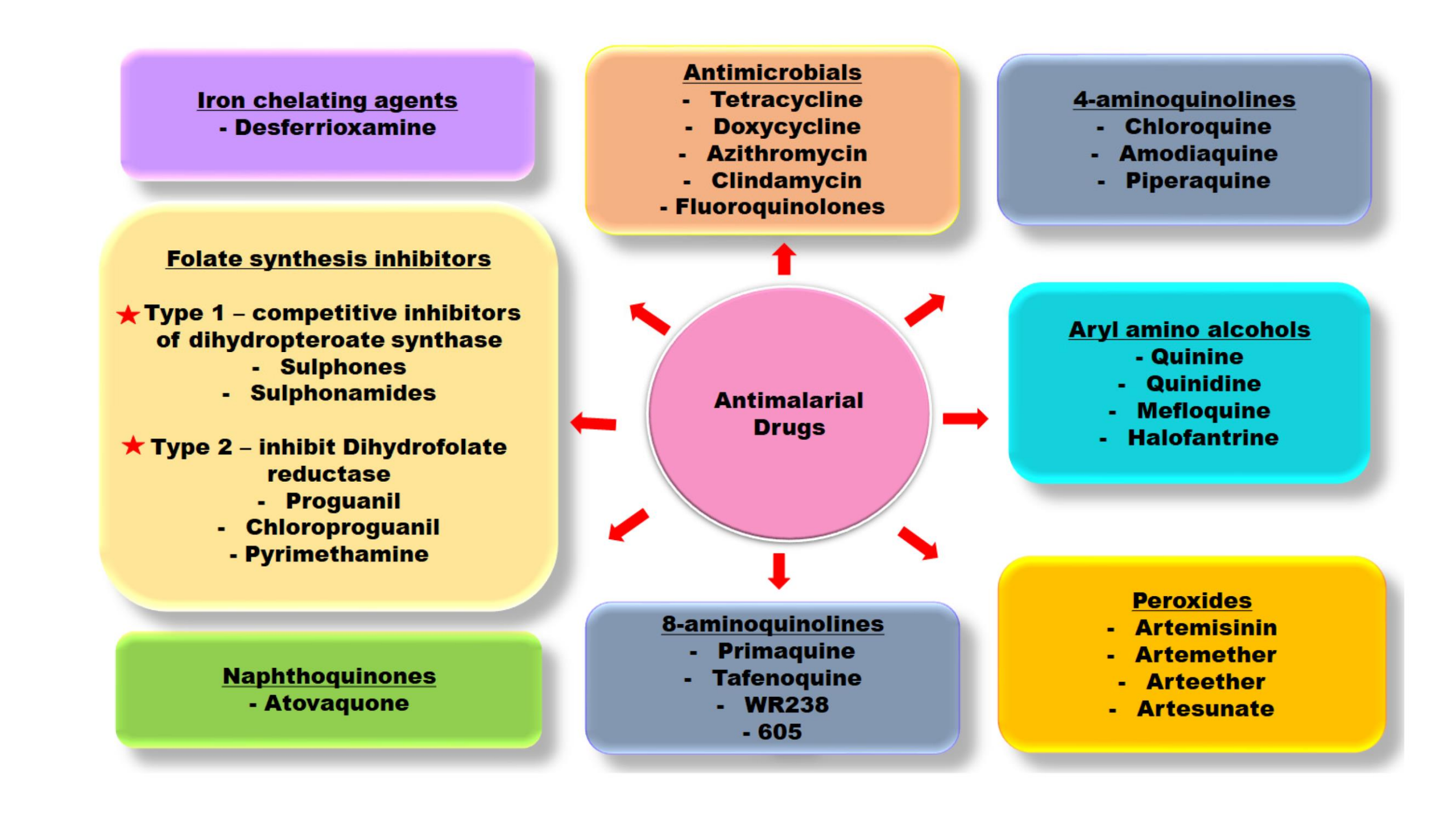
Antimalarials

- Antimalarials are a class of drugs used to treat or prevent malaria. Malaria is caused by parasites belonging to the plasmodium species, and can be deadly if not treated quickly.
- Antimalarial drugs work by killing these parasites that cause the disease. There are different types of antimalarials usually taken as pills or injections.
- Common brands include artemisinin, chloroquine, quinine sulfate, doxycycline , and quinine. Antimalarial drugs are effective at treating malaria, but they can have various side effects depending on the drug.

Classification of Antimalarial Drugs

◦ Antimalarials are classified based on:

- **Stage of parasite targeted**
- **Chemical structure**
- **Clinical use (prophylactic vs curative)**


Iron chelating agents
- Desferrioxamine
Antimicrobials
- Tetracycline
- Doxycycline
- Azithromycin
- Clindamycin
- Fluoroquinolones
4-aminoquinolines
- Chloroquine
- Amodiaquine
- Piperaquine
Folate synthesis inhibitors
★Type 1 – competitive inhibitors of dihydropteroate synthase
- Sulphones
- Sulphonamides
★Type 2 – inhibit Dihydrofolate reductase
- Proguanil
- Chloroproguanil
- Pyrimethamine
Antimalarial Drugs
Aryl amino alcohols
- Quinine
- Quinidine
- Mefloquine
- Halofantrine
Naphthoquinones
- Atovaquone
8-aminoquinolines
- Primaquine
- Tafenoquine
- WR238
- 605
Peroxides
- Artemisinin
- Artemether
- Arteether
- Artesunate

◈ I. Based on Stage of Parasite Targeted

Class	Target Stage	Examples
Blood schizonticides	**Erythrocytic stage**	**Chloroquine, Artemisinin, Mefloquine**
Tissue schizonticides	**Liver stage**	**Primaquine, Atovaquone-proguanil**
Gametocides	**Sexual forms in blood**	**Primaquine, Artemisinins**
Sporontocides (rare)	**Inhibit transmission to mosquito**	**Primaquine**

◈ II. Based on Chemical Structure

1. **4-Aminoquinolines**
   - *Examples:* Chloroquine, Amodiaquine
   - *Target:* Blood schizonts
2. **8-AminoquinolinesStructure Search**

o Examples: Primaquine, Tafenoquine

o Target: Liver schizonts and gametocytes

3. **Chloroquine.png**
   - *Examples:* Primaquine, Tafenoquine
   - *Target:* Liver schizonts and gametocytes

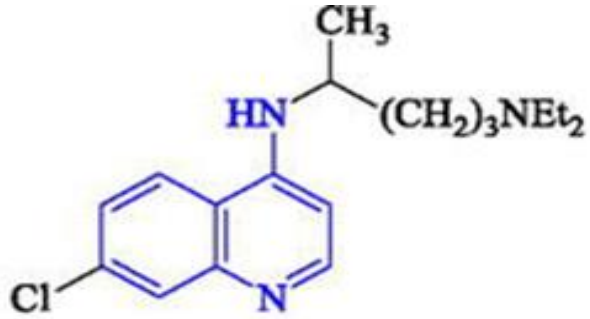
4. Quinoline Methanols

- *Example:* Mefloquine
- *Target:* Blood schizonts

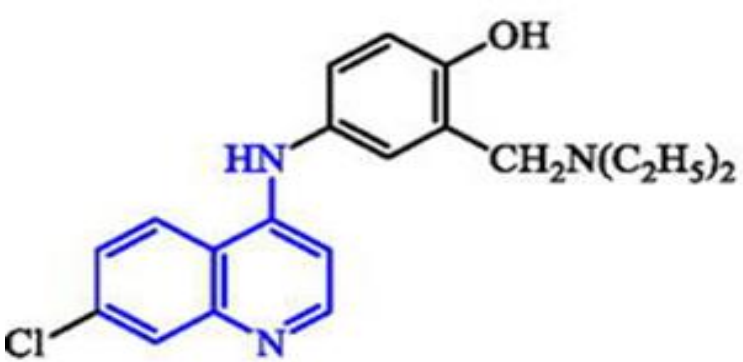
◈ II. Based on Chemical Structure

4. **Artemisinin Derivatives**
    - *Examples:* Artesunate, Artemether, Dihydroartemisinin
    - *Target:* Blood schizonts and gametocytes
    - *Used in combination therapy (ACT)*
5. **Antifolates**
    - *Examples:* Pyrimethamine, Proguanil, Sulfadoxine
    - *Target:* Parasite folate metabolism
6. **Antibiotics with antimalarial action**
    - *Examples:* Doxycycline, Clindamycin
    - *Used in combination therapy or for prophylaxis*
7. **Naphthoquinones**
    - *Example:* Atovaquone
    - *Often combined with proguanil (Malarone)*

4-Aminoquinolines

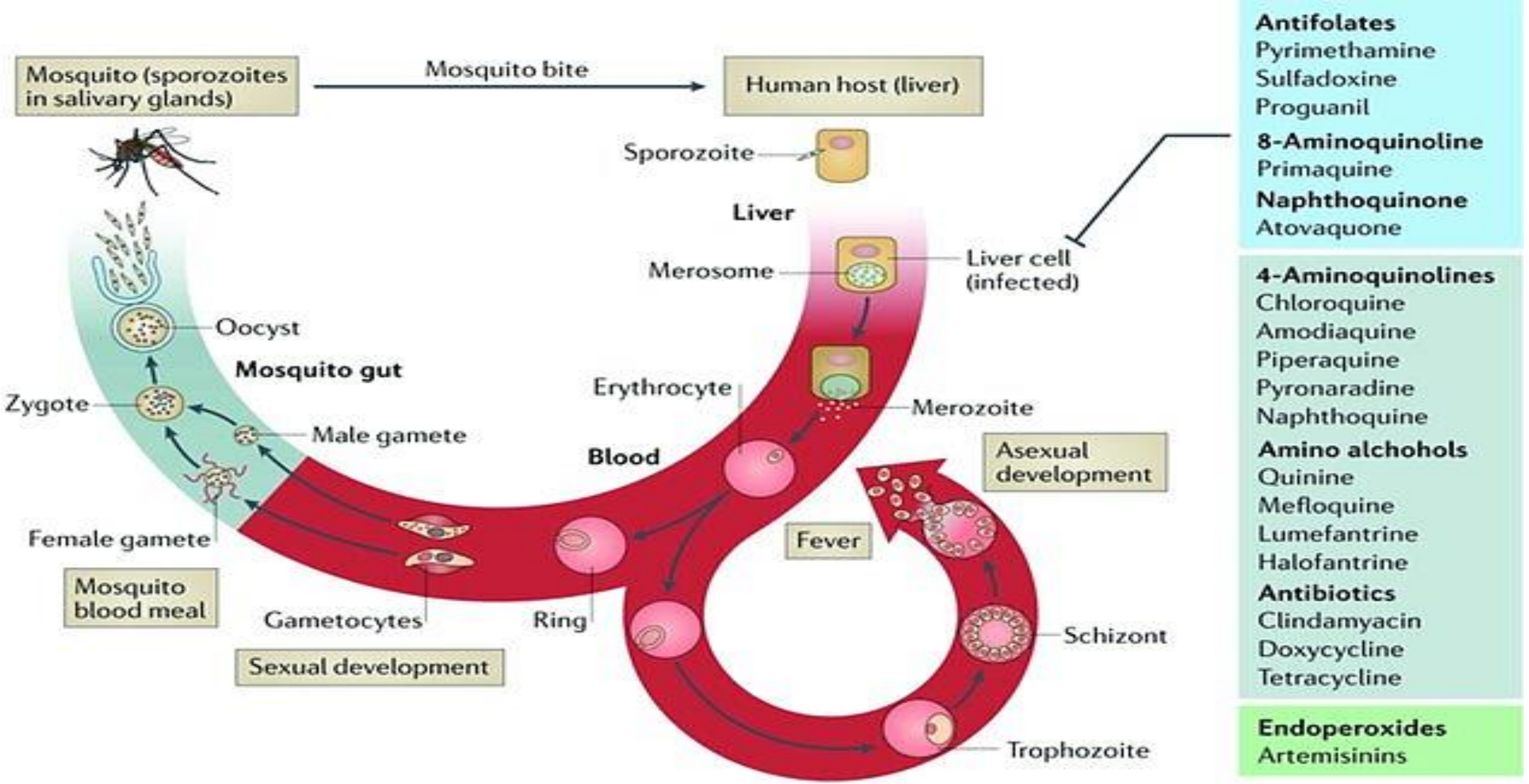


Chloroquine (Nivaquine®)

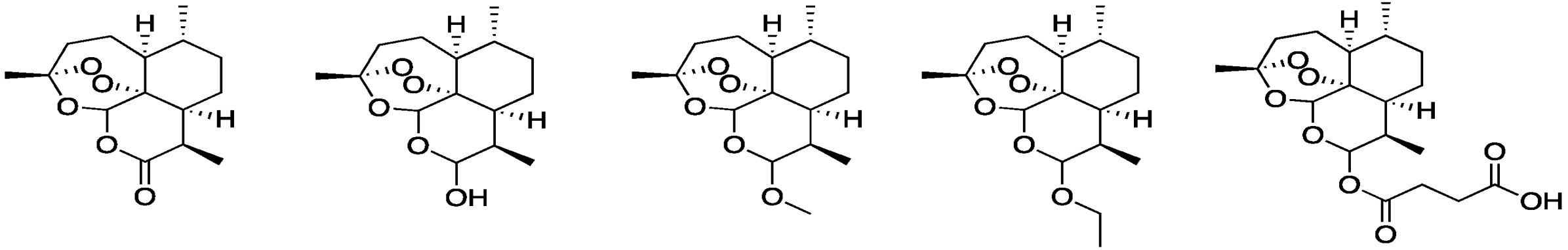


Amodiaquine (Flavocine®)

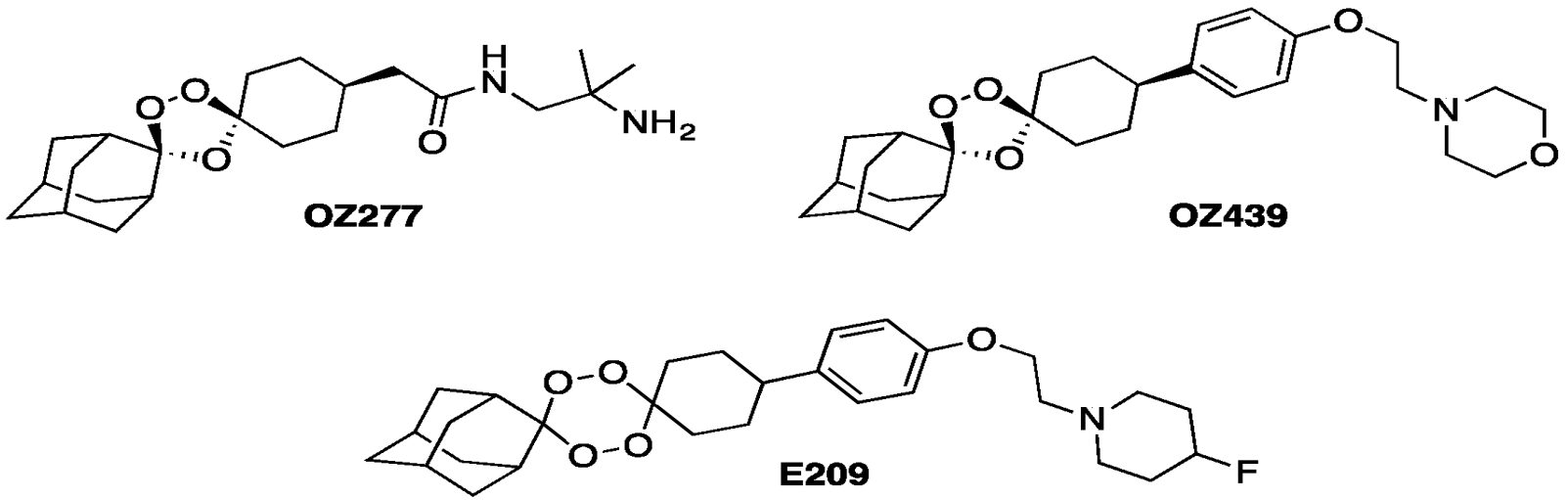
Piperaquine (Eurartesim®)



The P. falciparum life cycle stages that are targets of the antimalarial drugs. All antimalarial drugs target the asexual trophozoite and schizont blood stage. The antifolates, primaquine and atovaquone also target the liver stage parasites. Artemisinins also target the asexual ring stage and the early sexual blood stages.

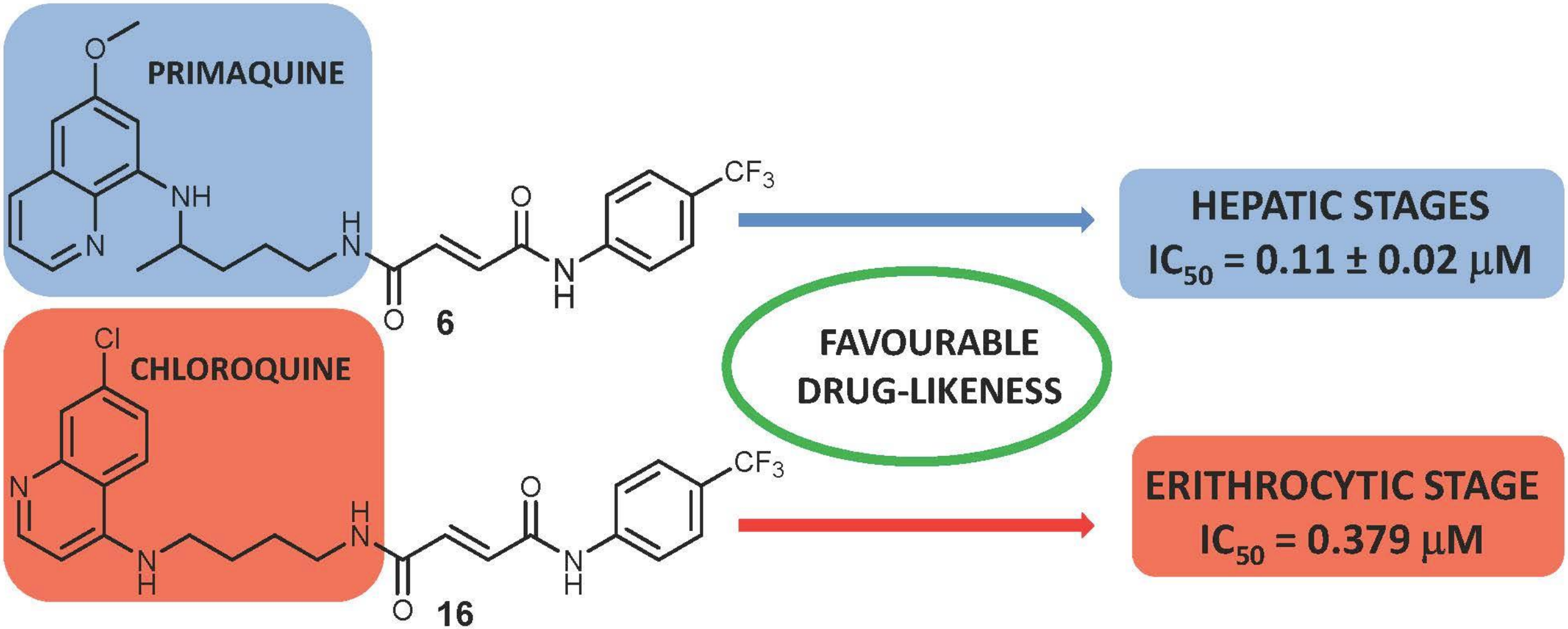


(A)

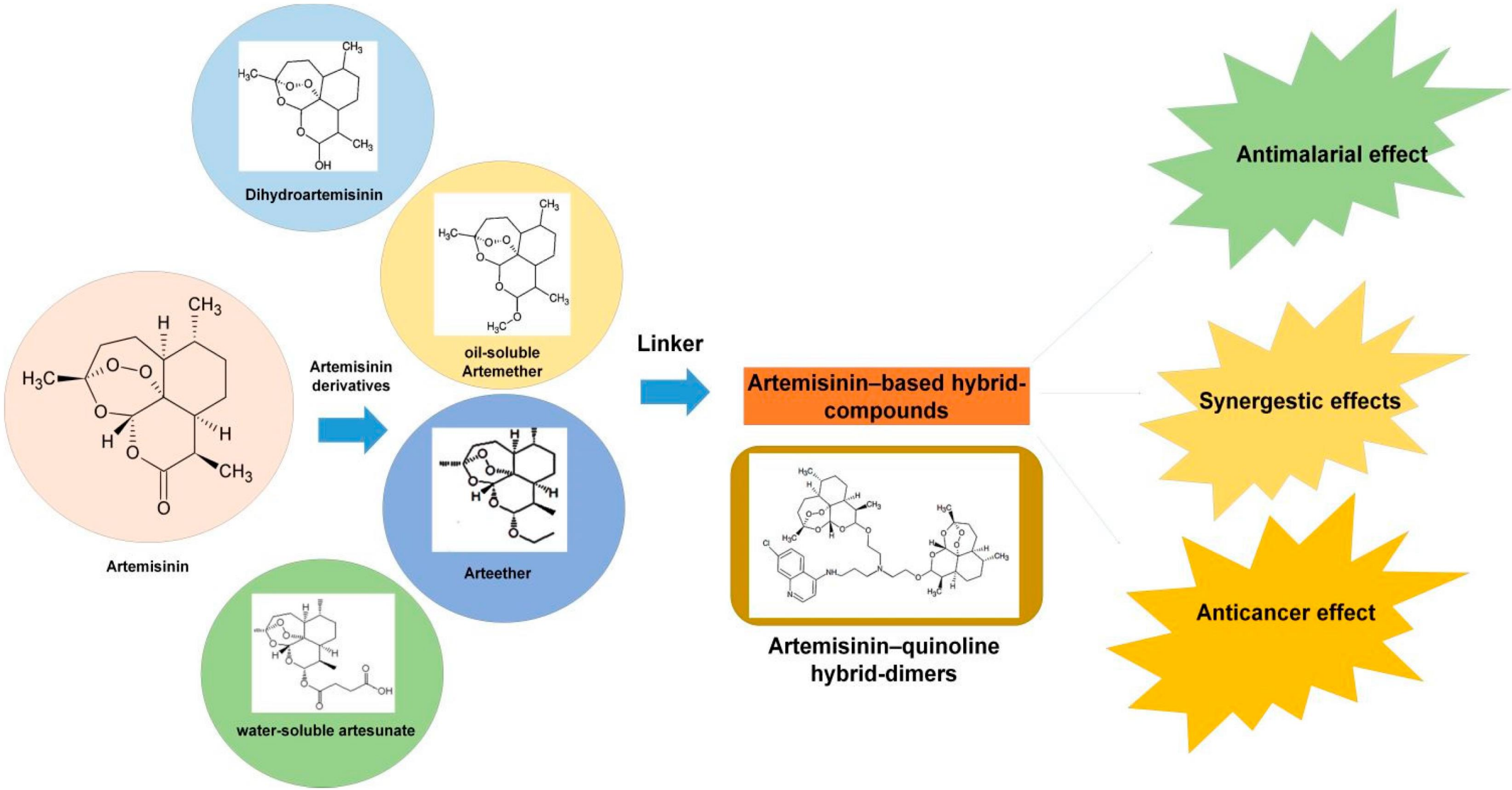


(B)

(A) Structures of artemisinin (ART) and other clinically viable derivatives. (B) Synthetic trioxane and tetraoxane ART analogs (see OZ277, OZ 439; E209).

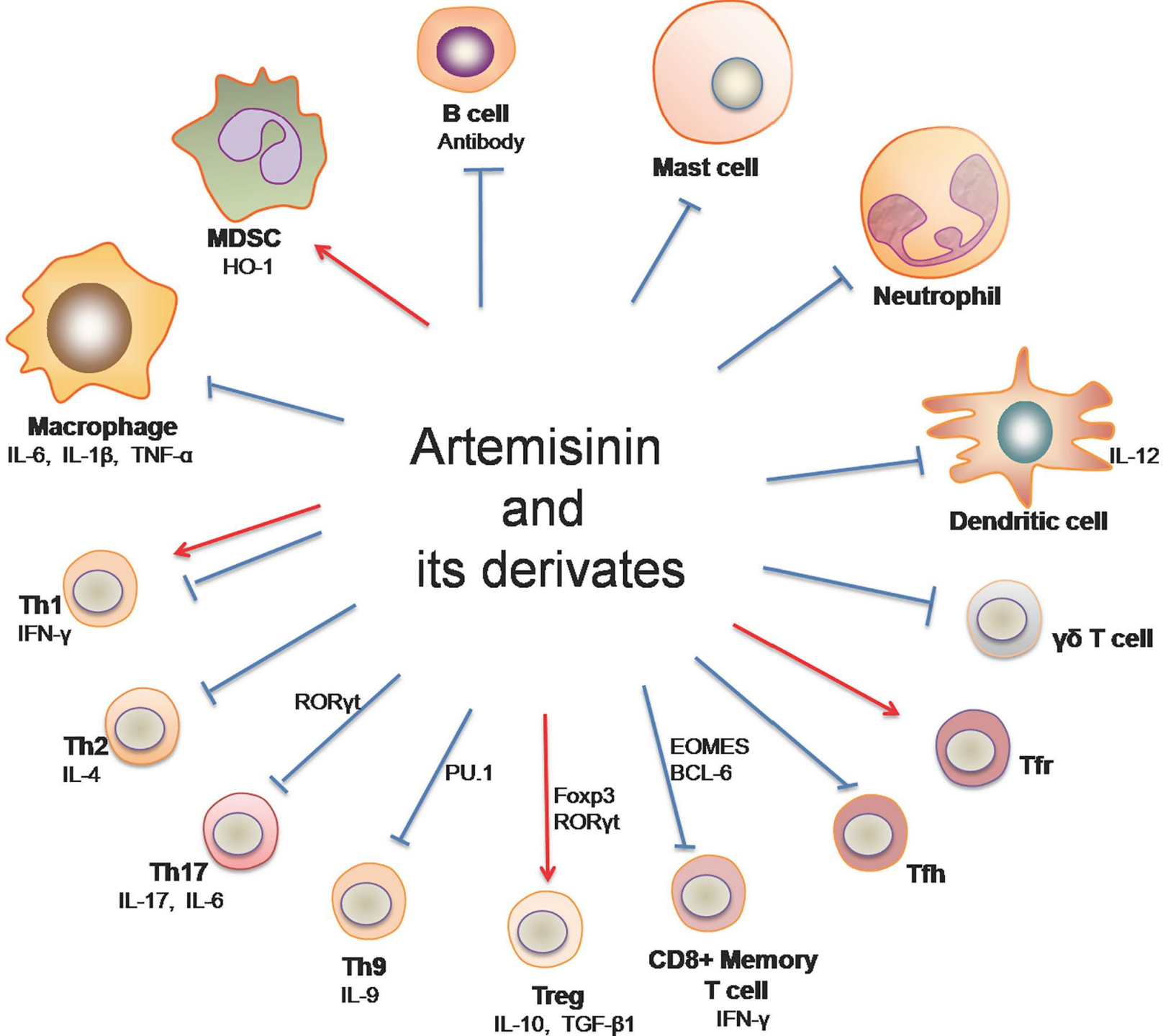


Chloroquine.png



Structure of artemisinin and its derivatives forming artemisinin-based hybrid dimers for various biological activities.

Artemisinin and its derivatives on both adaptive and innate immune cells. Artemisinin and its derivatives have the capacity to regulate expressions of proinflammatory and anti-inflammatory cytokines, the frequency and activation of T helper and B cells, and the responsiveness of macrophages, DCs, neutrophils, mast cells and MDSCs. "↓" denotes "enhancing" while "⊥" indicates "suppressing". (Th1, T helper 1 cell; Th2, T helper 2 cell; Th9, T helper 9 cell; Th17, T helper 17 cell; Treg, regulatory T cells; Tfh, follicular helper T cells; Tfr, follicular regulatory T cells; MDSC, myeloid-derived suppressor cells).



Mechanism of Action (By Class)

Drug Class	Mechanism of Action
Chloroquine	Inhibits heme polymerase → toxic heme accumulates
Artemisinins	Generates free radicals that damage parasite proteins
Primaquine	Interferes with mitochondrial function in liver/gametocytes
Antifolates	Inhibit dihydrofolate reductase or synthetase (folate cycle)
Atovaquone	Inhibits mitochondrial electron transport
Doxycycline	Inhibits protein synthesis in apicoplast of the parasite

Therapeutic Uses of Antimalarials

- **Uncomplicated Malaria**

1. **First-line:** Artemisinin-based Combination Therapy (ACT)
   e.g., Artemether + Lumefantrine, Artesunate + Mefloquine

Therapeutic Uses of Antimalarials

- **2. Severe Malaria (usually due to *P. falciparum*)**

- **Parenteral Artesunate** (preferred)
- Quinine (alternative if artesunate not available)

Therapeutic Uses of Antimalarials

- **3. Relapsing Malaria (due to P. vivax or P. ovale)**

- Chloroquine + Primaquine (to eliminate hypnozoites in the liver)

Therapeutic Uses of Antimalarials

- **4. Malaria Prophylaxis**

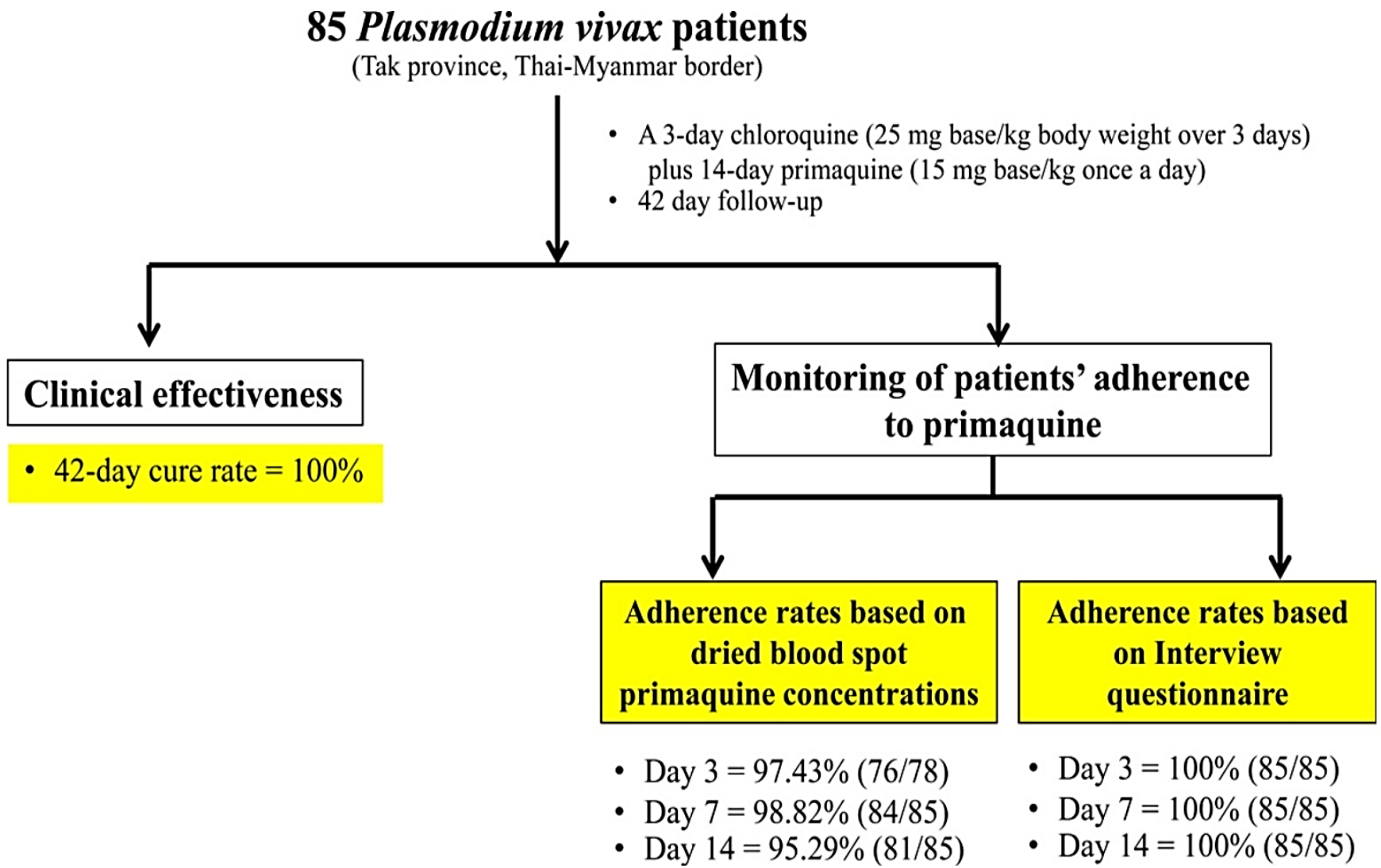
- Mefloquine, Doxycycline, or Atovaquone-Proguanil

⚠ Adverse Effects of Key Antimalarials

Drug	Common Adverse Effects
Chloroquine	GI upset, pruritus, retinopathy with prolonged use
Artemisinins	Generally safe; rare neurotoxicity or QT prolongation
Primaquine	Hemolysis in **G6PD-deficient** patients
Mefloquine	Neuropsychiatric effects (anxiety, hallucinations, seizures)
Quinine	Cinchonism (tinnitus, headache), hypoglycemia, arrhythmias
Doxycycline	GI upset, photosensitivity, contraindicated in pregnancy
Atovaquone-proguanil	Well tolerated, occasional GI upset or mouth ulcers

Pharmacokinetics Overview (Selected Drugs)

Drug	Route	Half-life	Notes
Chloroquine	Oral, IV	Long (~1–2 months)	Accumulates in tissues
Artemisinin	Oral, IV	Short (~1 hr)	Given in combination therapy (ACT)
Primaquine	Oral	Short	Must screen for G6PD deficiency
Mefloquine	Oral	Long (~2–4 weeks)	Used for prophylaxis
Atovaquone-proguanil	Oral	Medium	Daily use for treatment or prevention


85 Plasmodium vivax patients
(Tak province, Thai-Myanmar border)
• A 3-day chloroquine (25 mg base/kg body weight over 3 days) plus 14-day primaquine (15 mg base/kg once a day)
• 42 day follow-up
Clinical effectiveness
• 42-day cure rate = 100%
Monitoring of patients' adherence to primaquine
Adherence rates based on dried blood spot primaquine concentrations
• Day 3 = 97.43% (76/78)
• Day 7 = 98.82% (84/85)
• Day 14 = 95.29% (81/85)
Adherence rates based on Interview questionnaire
• Day 3 = 100% (85/85)
• Day 7 = 100% (85/85)
• Day 14 = 100% (85/85)

Key Considerations for Pharmacy Practice

1. **G6PD Screening**: Essential before prescribing **primaquine** or **tafenoquine**.

2. **Drug Resistance**: *P. falciparum* has developed resistance to **chloroquine**, **mefloquine**, and **sulfadoxine-pyrimethamine** in many regions.

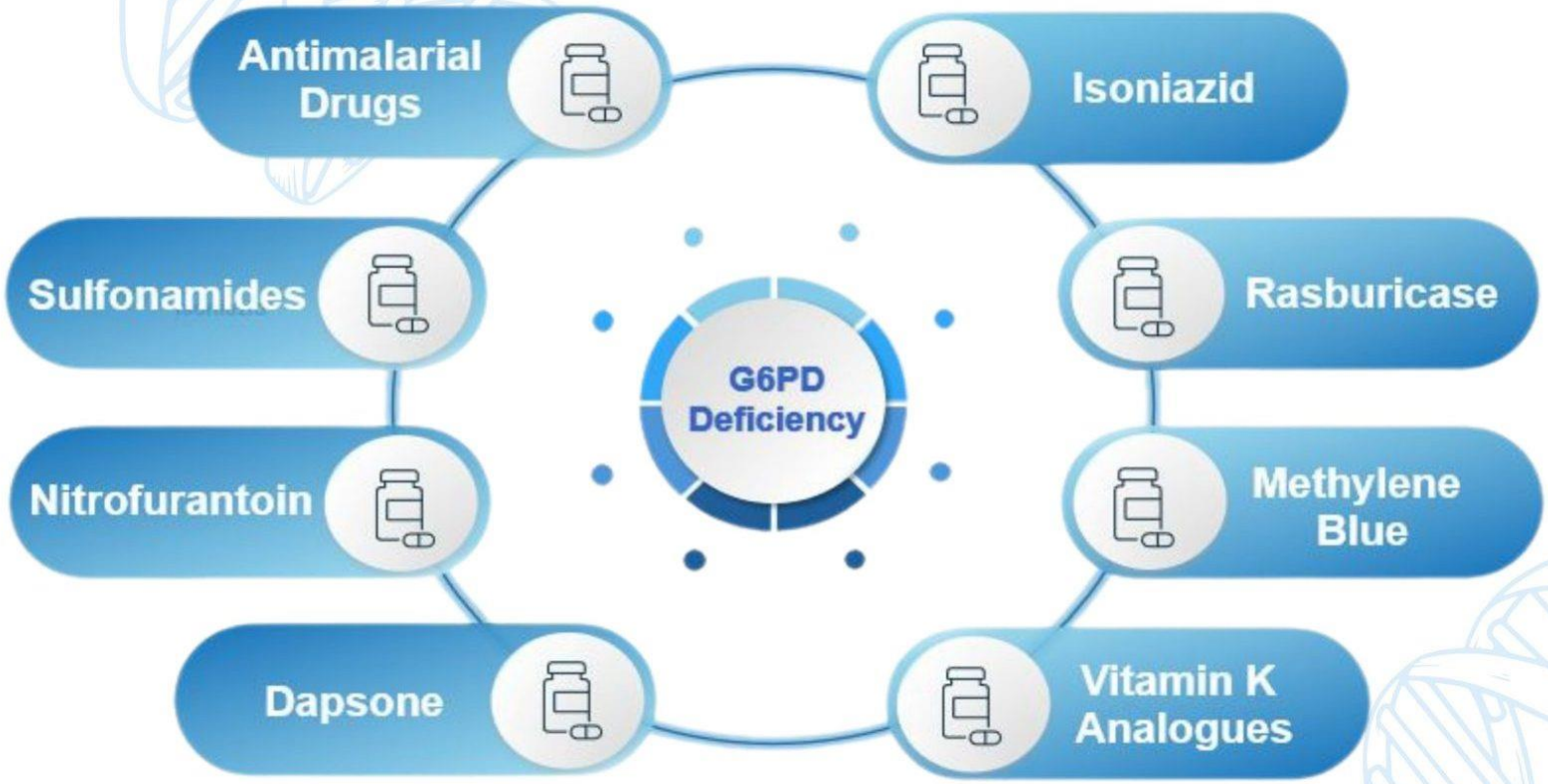
3. **Combination Therapy**: Use of **ACTs** prevents resistance and improves efficacy.

Key Considerations for Pharmacy Practice

4. Counseling: Educate patients on completing full treatment and prophylaxis schedules.

5. Pregnancy: Avoid **primaquine**, **doxycycline**; prefer **chloroquine** or **quinine + clindamycin**.

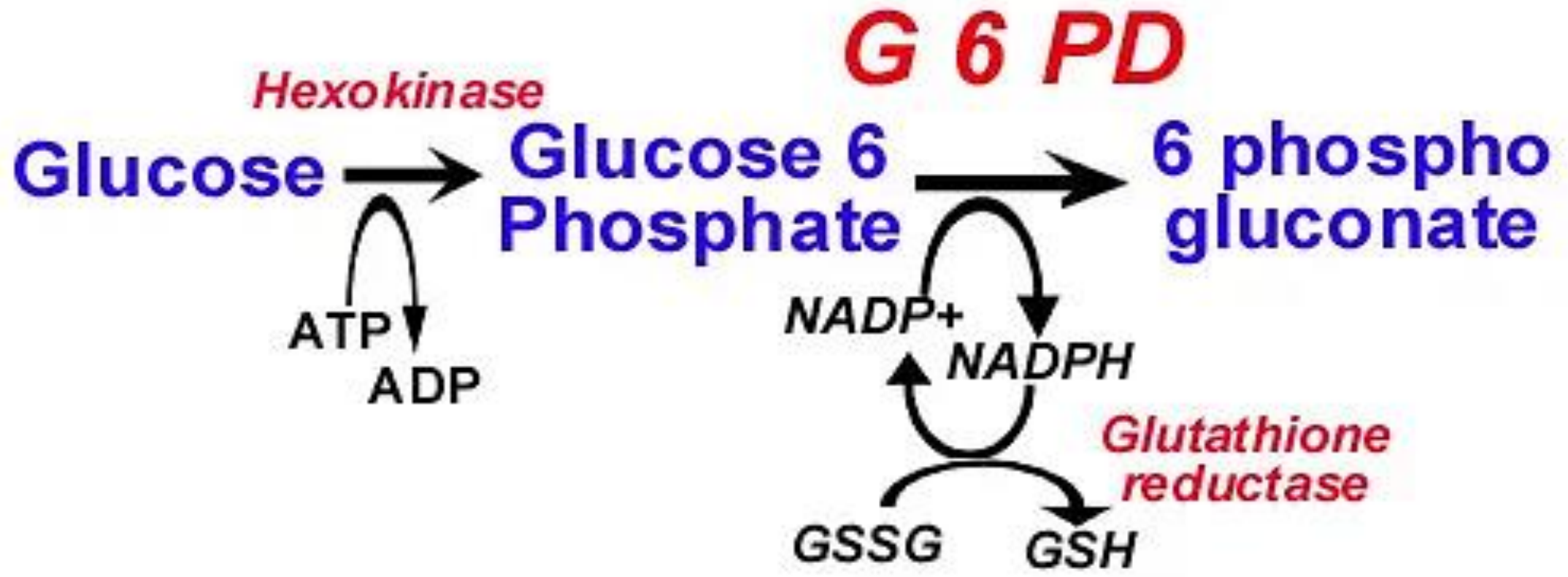
Understanding the Risks: G6PD Deficiency and Medications



baebies

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is among the most common human enzyme defects.

As tabulated by the G6PD deficiency association, 143 drug compounds are stratified as high, medium, and low risk to those with G6PD deficiency



Glucose 6 Phosphate Dehydrogenase Deficiency Glucose 6 phosphate dehydrogenase is an enzyme in the Hexose Monophosphate shunt. This shunt generates reduced glutathione that protects sulfhydryl groups of hemoglobin and the red cell membrane from oxidation by the oxygen radicals. Defects in the shunt leads to inadequate protection against oxidation, resulting in oxidation of sulfhydryl groups and precipitation of hemoglobin as Heinz bodies and in lysis of the red cell membrane.

Primaquine and Tafenoquine with G6PD deficiency

- Antimalarial Drugs: Some antimalarial medications, like primaquine and tafenoquine, are known to cause severe hemolysis in individuals with G6PD deficiency.

- They are often avoided in these patients, although they may be prescribed under strict medical supervision.

INFECTION

Pregnant woman or breastfeeding woman is infected with *P. vivax* malaria

TREATMENT

Treated with 3-day chloroquine or artemisinin-based combination therapy for acute malaria

NO RADICAL CURE WITH PRIMAQUINE

8-aminoquinolines are contraindicated

OUTCOME

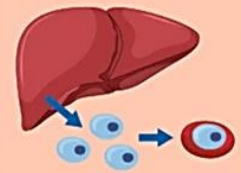
Parasites are cleared from the blood

Hypnozoites persist in the liver

RELAPSE

Breastfeeding woman is at high risk of *P. vivax* relapse

Relapse is caused by hypnozoite reactivation



Merozoites are released and infect red blood cells

CLINICAL CONSEQUENCES

Increased maternal risk of severe anaemia, morbidity, and mortality

Breastfeeding women remain at risk of multiple *P. vivax*

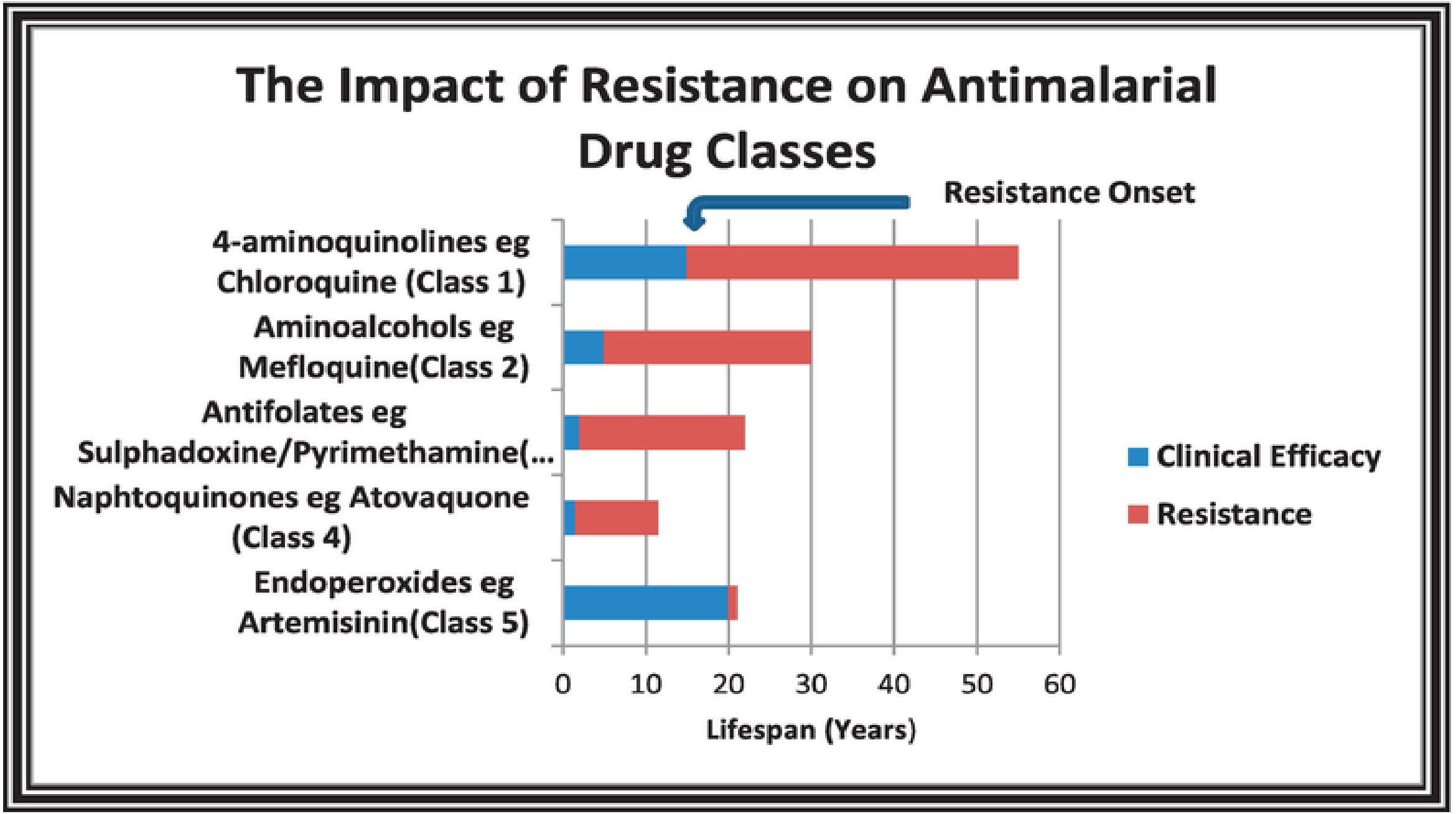
- Breastfeeding women remain at risk of multiple *P. vivax* relapses without access to primaquine.

- Following a single infectious bite from a mosquito during pregnancy or when breastfeeding, without access to effective radical cure with primaquine breastfeeding women are at high risk of repeated *P. vivax* malaria relapses.

Breastfeeding women remain at risk of multiple *P. vivax*

- Relapses are damaging to a patient's health, causing chronic anaemia with associated morbidity and an increased mortality risk.

- Although chloroquine prophylaxis during pregnancy and while breastfeeding is recommended, it is not deployed in endemic regions so most women will be trapped in this cycle of repeated relapses until they complete breastfeeding or until their child is ≥ 6 months old and proven not to be G6PD deficient

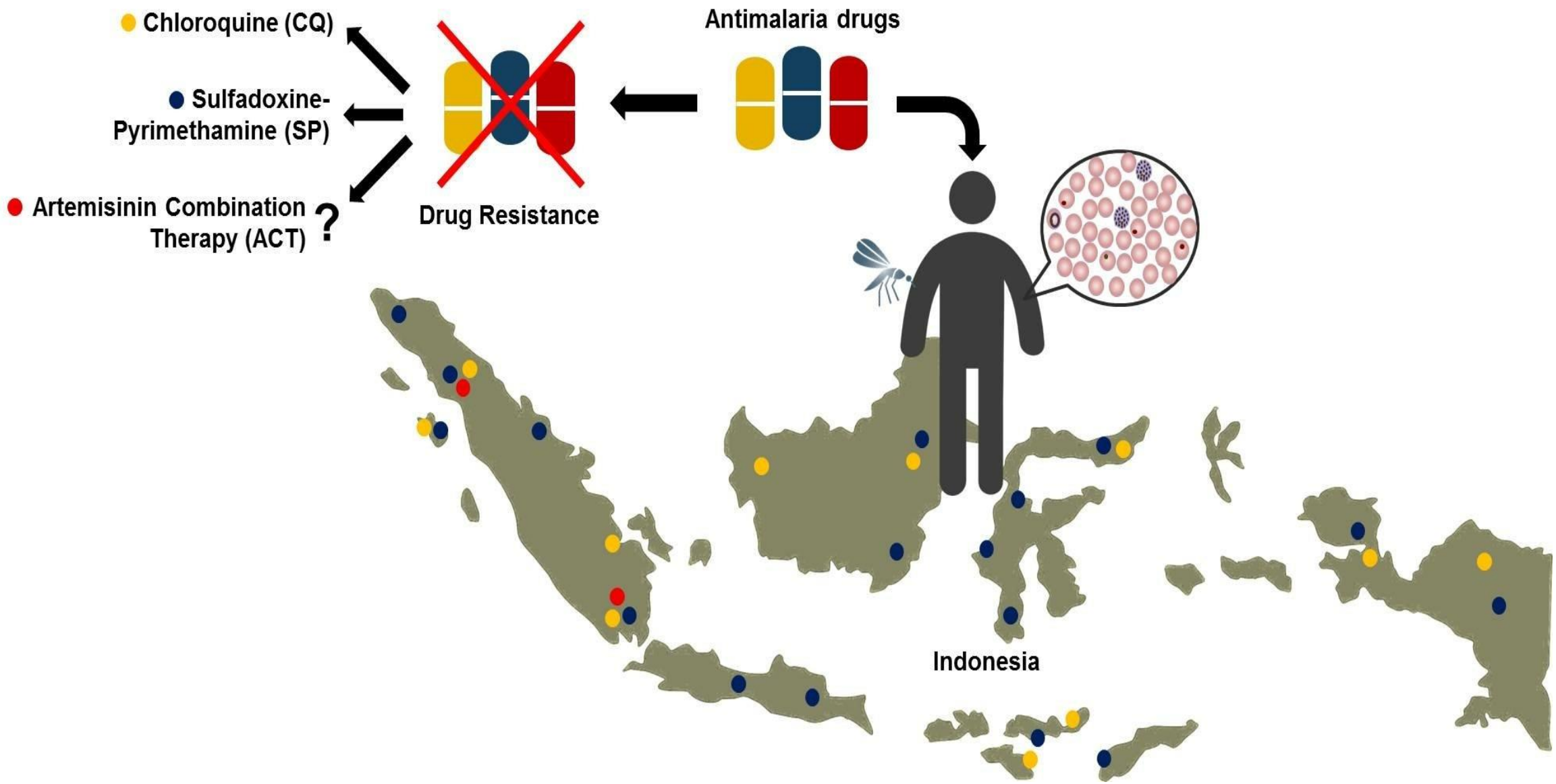


The impact of resistance on antimalarial drug classes.

Antimalarial Drug Resistance (ADR)

- Antimalarial Drug Resistance (ADR) can be best described as resistance to antimalarial drugs by the malaria parasite; Plasmodium species particularly *P. falciparum* which is responsible for the most deadly form of malaria - Falciparum malaria.

- *P. falciparum* is responsible for over 90% of the global malaria burden domiciled in Sub-Saharan Africa. It is the most virulent plasmodium species responsible for high morbidity and mortality rates of malaria observed in Africa particularly Sub-Saharan Africa.


Chloroquine (CQ)
Sulfadoxine-Pyrimethamine (SP)
Artemisinin Combination Therapy (ACT)
?
Drug Resistance
Antimalaria drugs
Indonesia

P. falciparum drug resistance

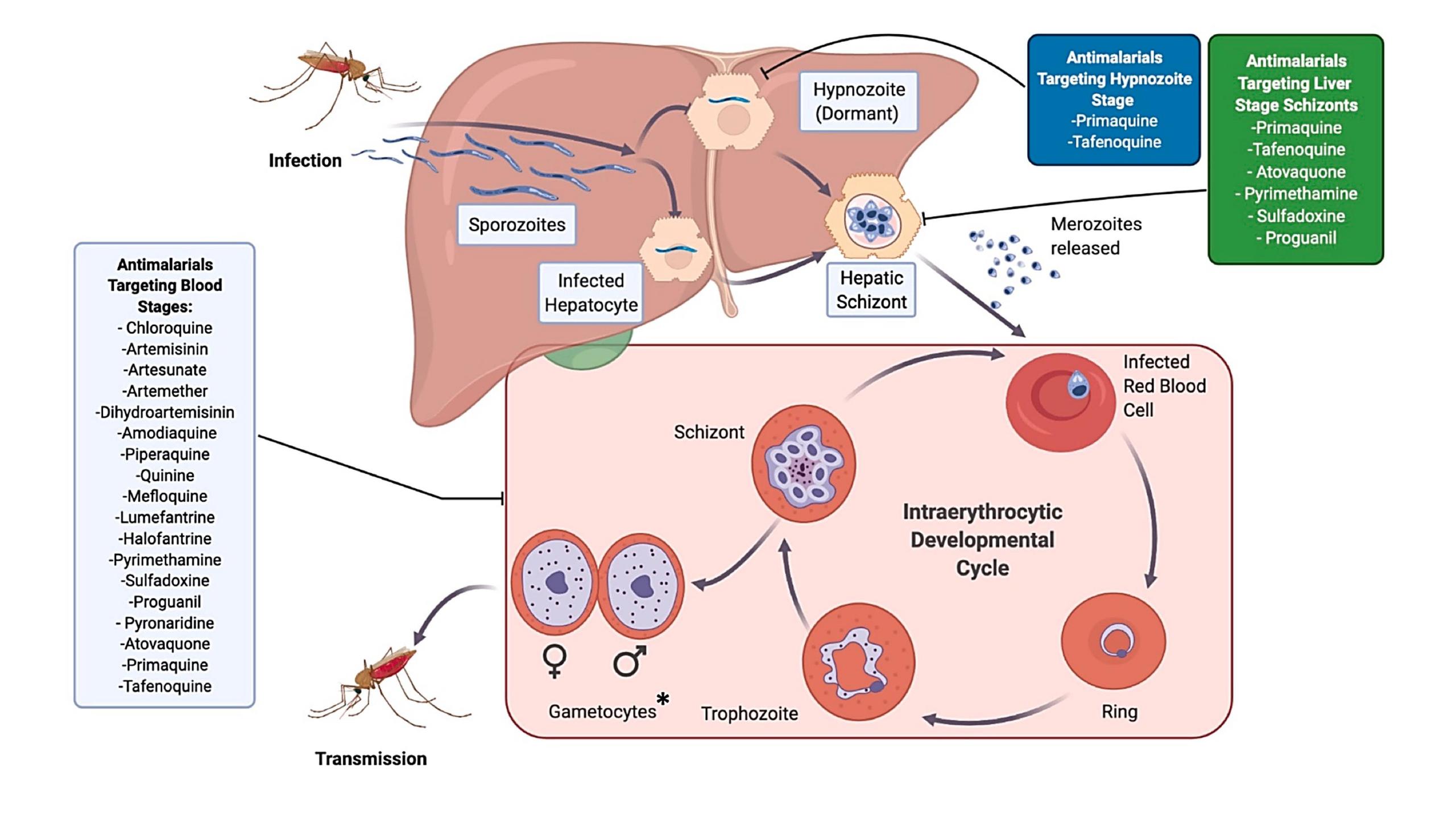
- Several recent evaluations have summed up the state of knowledge around P. falciparum drug resistance. P. vivax resistance to antimalarial drugs, including **chloroquine (CQ), mefloquine (MQ), sulfadoxine, and pyrimethamine (SP),** has also been reported in many regions of the world

Infected mosquitoes life cycle targeted by various antimalarial compounds

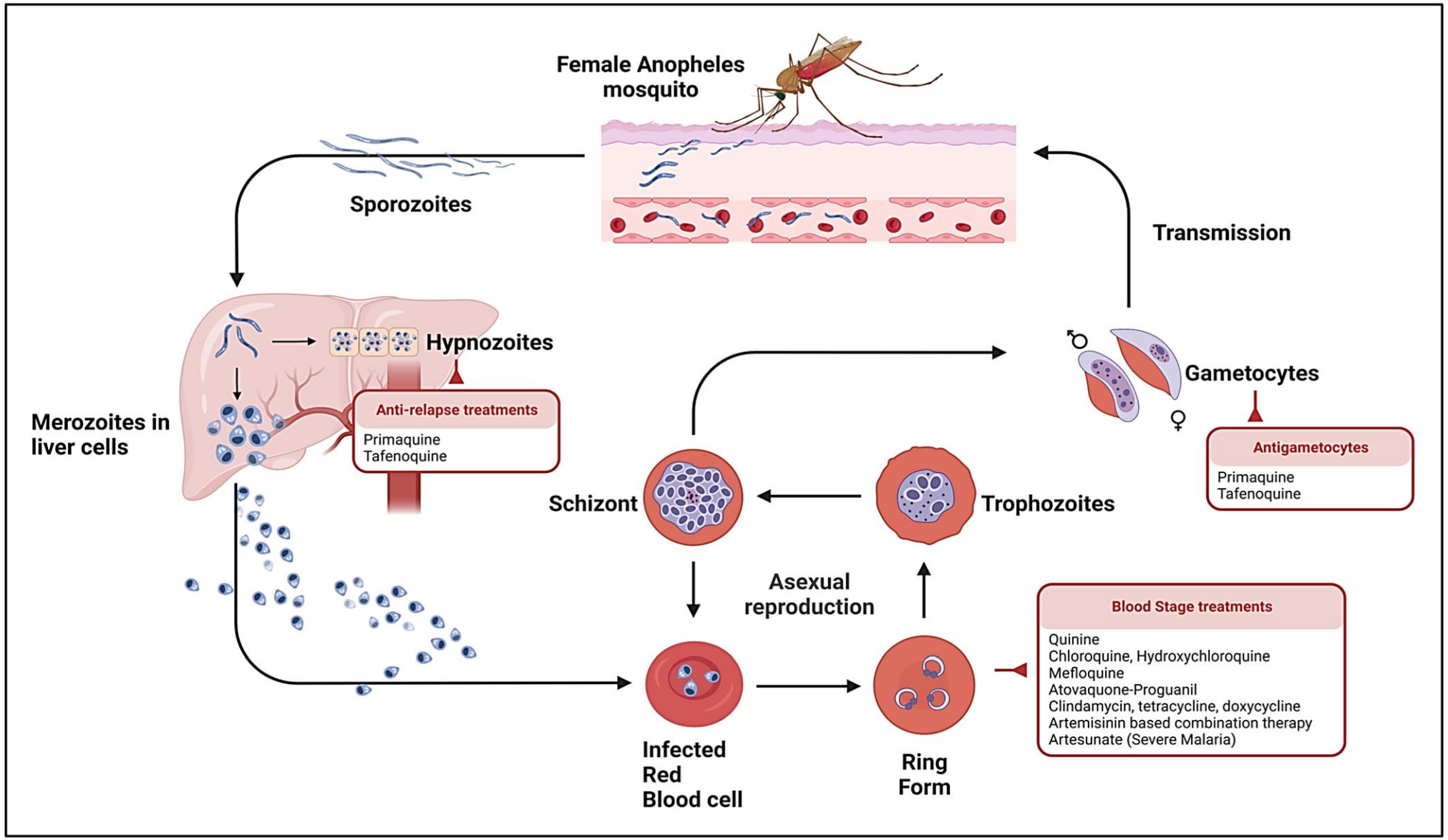
- Phases of the P. vivax life cycle targeted by various antimalarial compounds. Infected mosquitoes take up a human blood meal and inject sporozoites into the bloodstream.
- Sporozoites then migrate to the liver, where they either become hepatic schizonts which release merozoites into the bloodstream, or become dormant hypnozoites.
- Merozoites in the blood infect RBCs, where they develop from rings, to trophozoites and finally to mature schizonts. The majority of antimalarials target this intraerythrocytic stage. *Antimalarial compounds are generally thought to be more active against P. vivax gametocytes compared to P. falciparum.

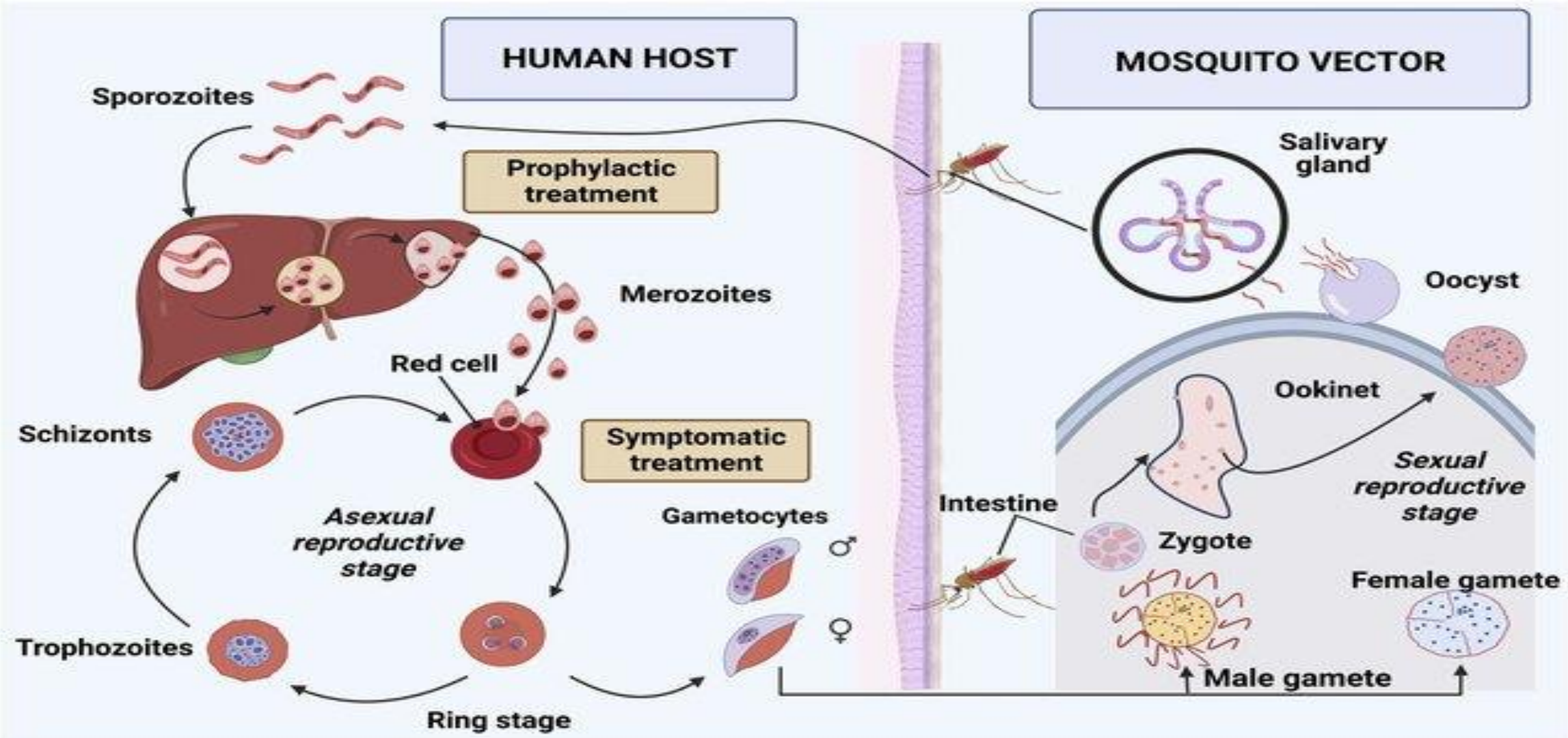
Infected mosquitoes life cycle targeted by various antimalarial compounds

- In P. vivax and P. ovale infections, some sporozoites differentiate in the liver to a latent form called hypnozoites.
- After rupture of the hepatocytes, merozoites are released into the bloodstream and penetrate the erythrocytes (erythrocyte phase), assuming a ring-shaped.
- Proliferative schizogony occurs in infected erythrocytes, where merozoites multiply asexually, differentiating into schizonts and trophozoites.
- Erythrocytes rupture and release schizonts into the bloodstream, where one part differentiates into male and female gametocytes, and another part infects new erythrocytes.


Infection
Sporozoites
Infected Hepatocyte
Hypnozoite (Dormant)
Hepatic Schizont
Merozoites released
Antimalarials Targeting Hypnozoite Stage
-Primaquine
-Tafenoquine
Antimalarials Targeting Liver Stage Schizonts
-Primaquine
-Tafenoquine
- Atovaquone
- Pyrimethamine
- Sulfadoxine
- Proguanil
Antimalarials Targeting Blood Stages:
- Chloroquine
-Artemisinin
-Artesunate
-Artemether
-Dihydroartemisinin
-Amodiaquine
-Piperaquine
-Quinine
-Mefloquine
-Lumefantrine
-Halofantrine
-Pyrimethamine
-Sulfadoxine
-Proguanil
- Pyronaridine
-Atovaquone
-Primaquine
-Tafenoquine
Infected Red Blood Cell
Schizont
Intraerythrocytic Developmental Cycle
Ring
Trophozoite
♀
♂
Gametocytes*
Transmission

Combination Therapy: Use of ACTs prevents resistance and improves efficacy.

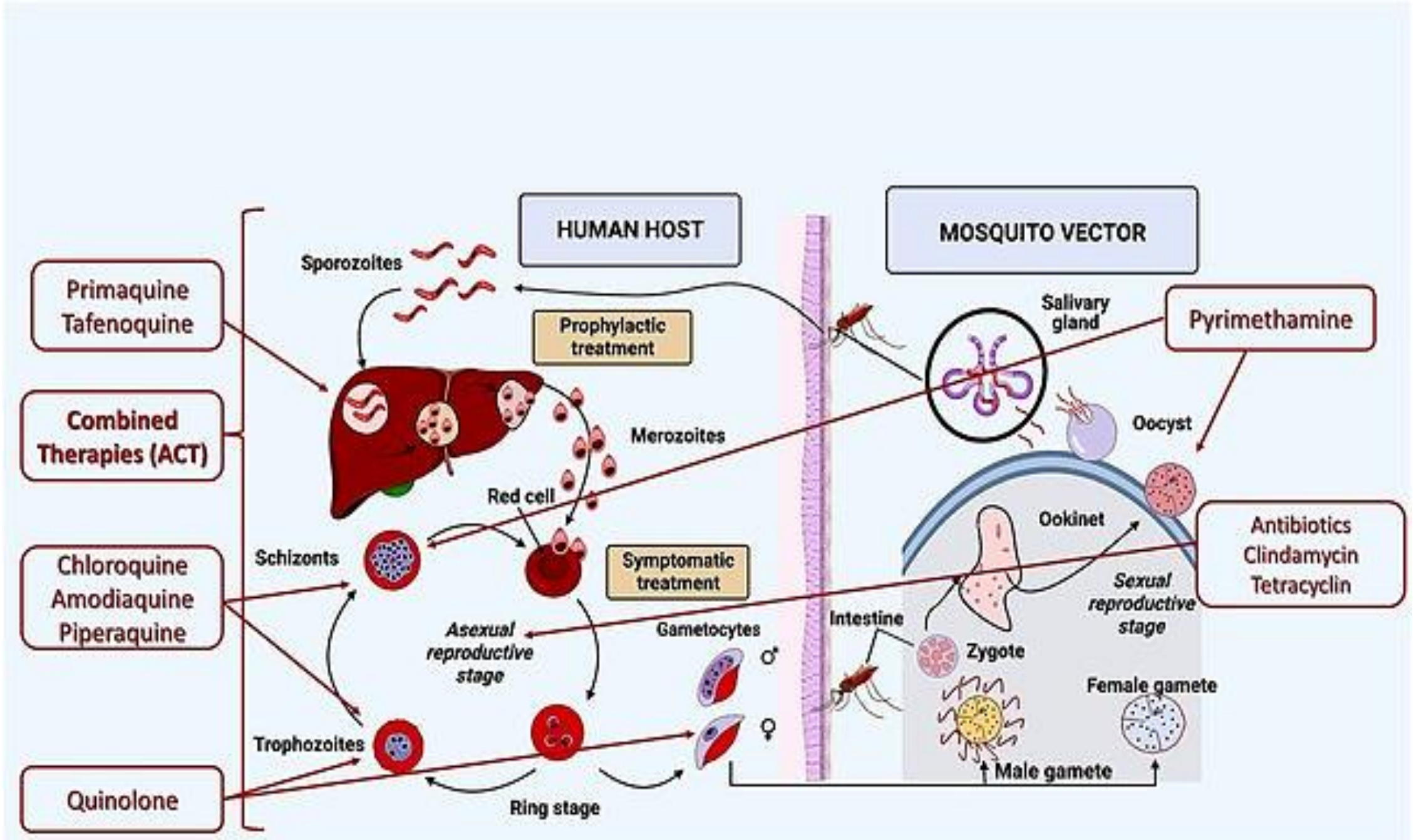




Life cycle of Plasmodium sp. The cycle can be divided into two stages: mosquito vector or sexual cycle and human host or asexual cycle. The mosquito ingests gametocytes while performing hematophagy. The zygote is formed from the union of gametocytes and generates oocyte. It crosses the intestinal wall and forms oocyst that releases sporozoites, which migrate to the mosquito's salivary glands, completing the sexual cycle. The infected female Anopheles sp mosquito inoculates sporozoites, performs hematophagy, and begins the asexual cycle of Plasmodium sp in human.

Current drug targets for malaria treatment

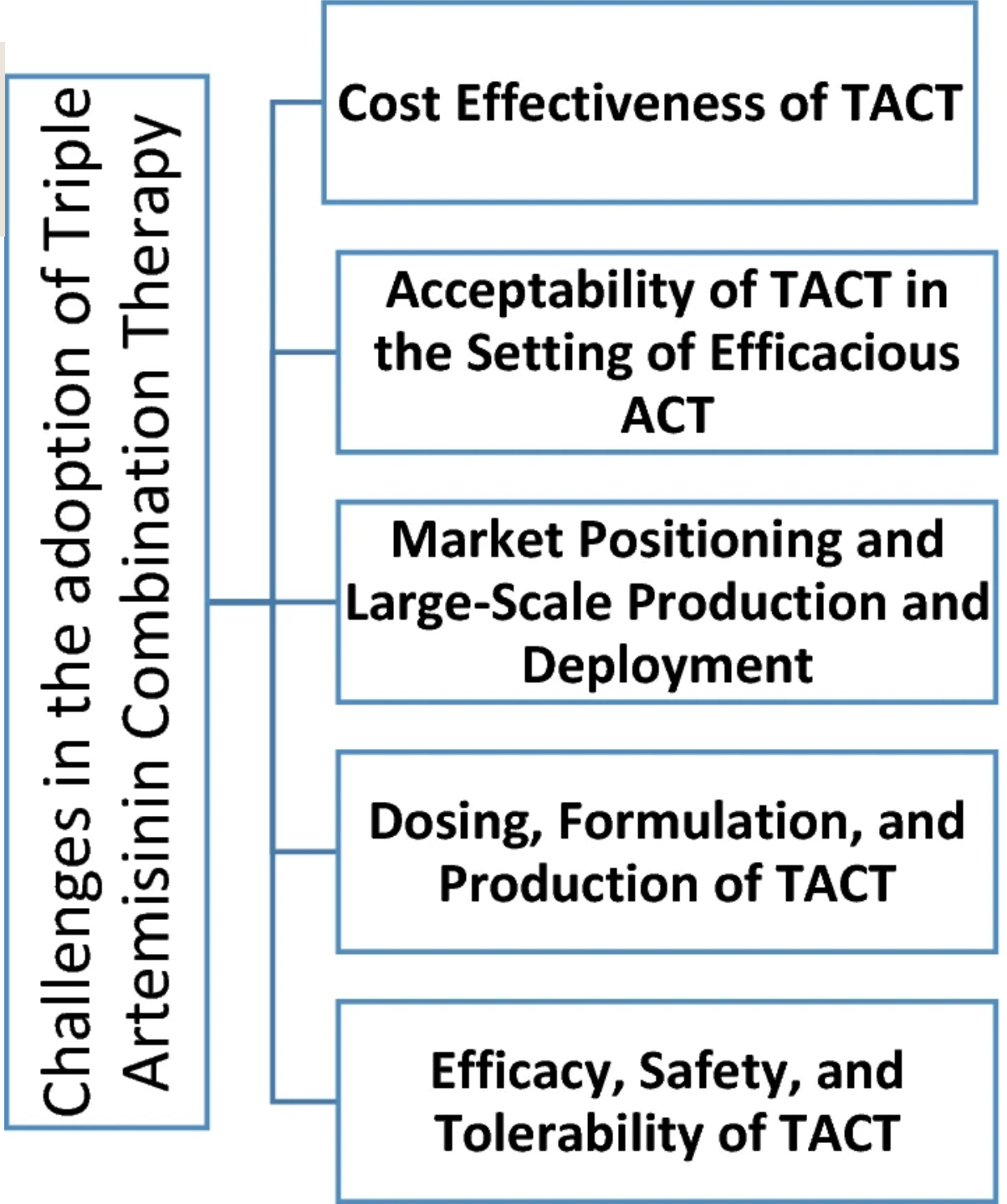
- Current drug targets for malaria treatment: I—Asexual cycle; II—Liver cycle, III, IV, VI—Erythrocytic cycle, V—Asexual and sexual cycles. Source: Artemisinin-based combination therapies (ACTs) are recommended by the World Health Organization


HUMAN HOST
MOSQUITO VECTOR
Sporozoites
Prophylactic treatment
Primaquine
Tafenoquine
Combined Therapies (ACT)
Chloroquine
Amodiaquine
Piperaquine
Quinolone
Merozoites
Red cell
Schizonts
Symptomatic treatment
Asexual reproductive stage
Gametocytes
♂
♀
Trophozoites
Ring stage
Salivary gland
Pyrimethamine
Oocyst
Ookinet
Antibiotics
Clindamycin
Tetracyclin
Sexual reproductive stage
Intestine
Zygote
Female gamete
Male gamete

Counseling: Educate patients on completing full treatment and prophylaxis schedules.

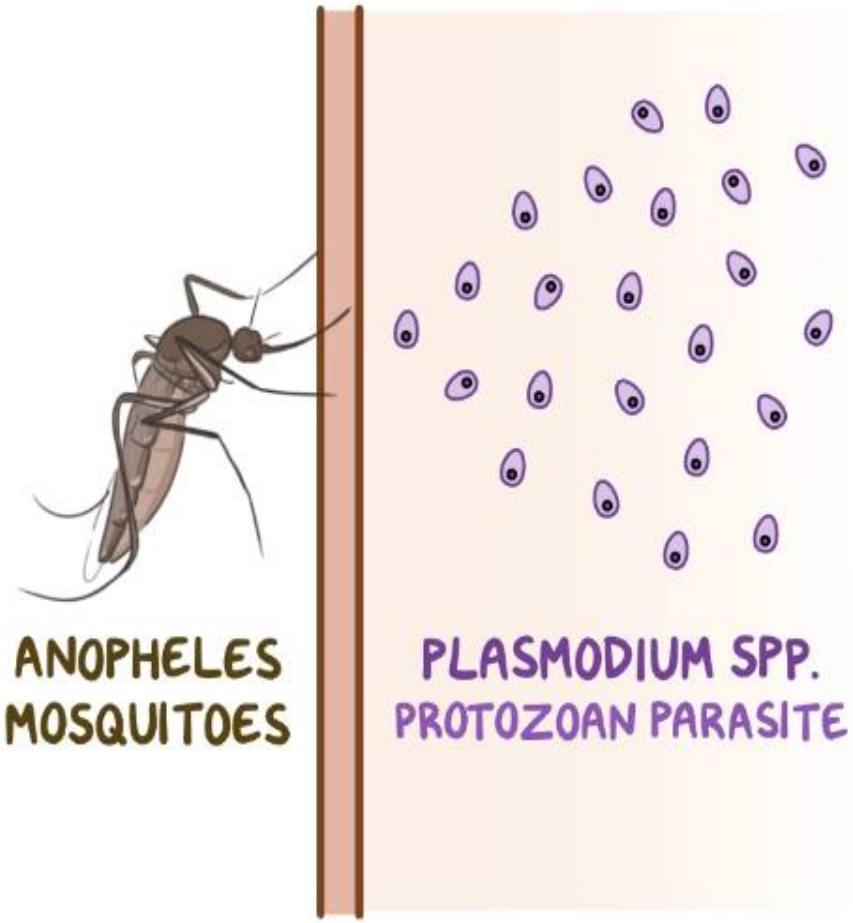
Challenges in the adoption of Triple Artemisinin-Based Combination Therapy

Dosing, formulation, and production of TACT
Optimizing TACT composition and dosing regimens necessitate considering age-stratified pharmacokinetic drug profiles, dose–effect relationships, and dose-related toxicity and tolerability. Inadequate dosing of any TACT component can lead to incomplete parasite clearance, subsequent recurredscences, and the selection of drug-resistant parasites.



ANTIMALARIALS

* PREVENTION & TREATMENT of MALARIA



ANOPHELES MOSQUITOES

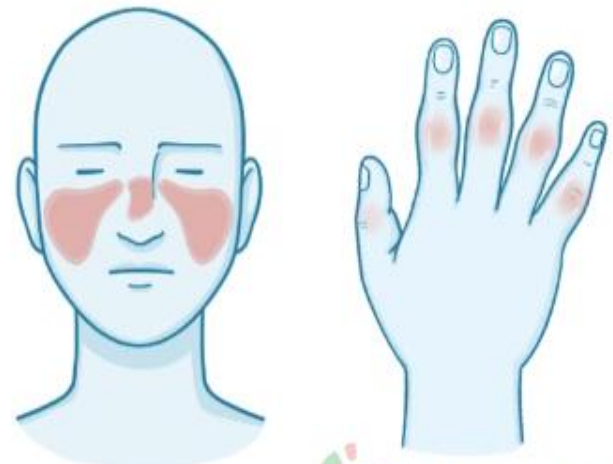
PLASMODIUM SPP.
PROTOZOAN PARASITE

ALSO TREAT AMEBIASIS

(AUTOIMMUNE DISORDERS)

~ SYSTEMIC LUPUS ERYTHEMATOSUS

~ RHEUMATOID ARTHRITIS



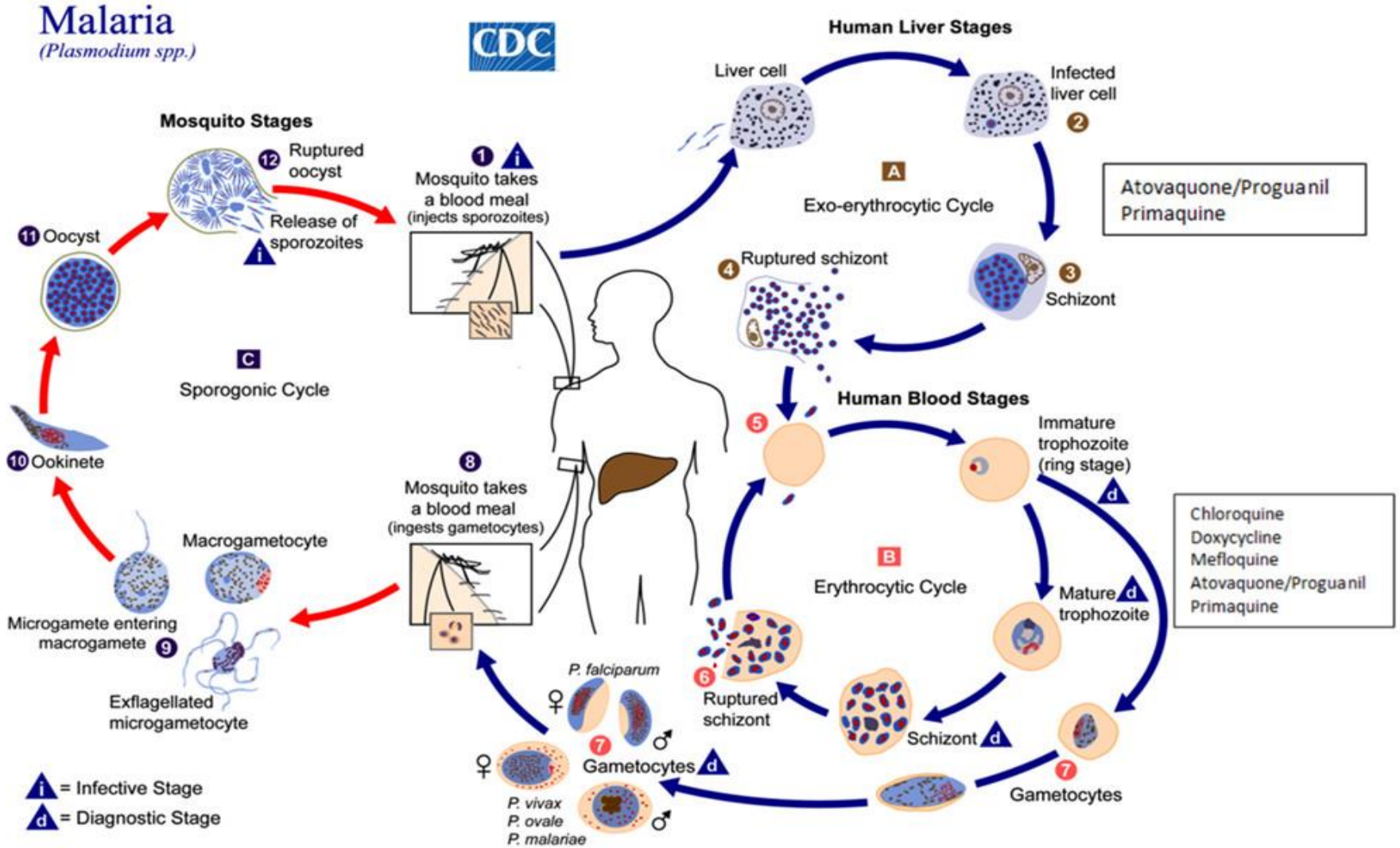
Malaria Life Cycle and Chemoprophylactic Targets

- **Overview**
- Malaria involves **three main cycles**:

1. **Exo-erythrocytic (Liver) Cycle – Human Host**
2. **Erythrocytic (Blood) Cycle – Human Host**
3. **Sporogonic Cycle – Mosquito Host**

- There are **12 sequential stages**, with arrows indicating progression. Two key points are labeled:

- **“i” = Infective stage** (sporozoites from mosquito to human)
- **“d” = Diagnostic stage** (blood stages visible on microscopy)


Malaria
(Plasmodium spp.)
CDC
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
Atovaquone/Proguanil
Primaquine
Ruptured schizont
4
3
Schizont
Mosquito Stages
12 Ruptured oocyst
Release of sporozoites
i
1 i
Mosquito takes a blood meal (injects sporozoites)
11 Oocyst
C
Sporogonic Cycle
10 Ookinete
Human Blood Stages
5
Immature trophozoite (ring stage)
d
8
Mosquito takes a blood meal (ingests gametocytes)
Macrogametocyte
B
Erythrocytic Cycle
Mature trophozoite
d
Chloroquine
Doxycycline
Mefloquine
Atovaquone/Proguanil
Primaquine
Microgamete entering macrogamete 9
Exflagellated microgametocyte
P. falciparum
6
Ruptured schizont
Schizont d
7
Gametocytes d
7
Gametocytes
P. vivax
P. ovale
P. malariae
i = Infective Stage
d = Diagnostic Stage

Malaria life cycle and the sites of action of recommended chemoprophylactic drugs

- The first cycle is the Exo-erythocytic cycle or human liver stages. First, a malaria-infected female anopheline mosquito takes a blood meal from a human and inoculates sporozoites into the human host. The diagram displays the letter “i” in this first step to indicate that this is the infective stage of malaria. Second, the sporozoites infect liver cells. Third, the infected liver cells mature into schizonts. Fourth, the schizonts rupture and release merozoites.
- This leads into the second cycle, the erythrocytic cycle or human blood stages. In the fifth step of the life cycle, the merozoites infect red blood cells. Six, the ring stage trophozoites mature into schizonts, which rupture releasing merozoites. Seventh, some parasites differentiate into sexual erythrocytic stages (gametocytes). The diagram displays the letter “d” during the human blood stage, or erythocytic cycle, to indicate that this is the diagnostic stage of malaria.

Malaria life cycle and the sites of action of recommended chemoprophylactic drugs

- This leads into the third cycle, the sporogonic cycle or mosquito stages. In the eighth step of the life cycle, an anopheles mosquito takes a blood meal from a human host and ingests the gametocyctes. Ninth, the microgametes enter the macrogametes. Tenth, this generates zygotes, which become ookinetes. Eleventh, the ookinetes develop into oocysts. Twelfth, the oocysts rupture and release sporozoites, which brings the cycle back to the first step of the life cycle where the mosquito infects a human host by taking a blood meal.
- The diagram also depicts which drugs are appropriate for each stage of the malaria life cycle. In the human liver stages, atovaquone/proguanil and primaquine can be used. In the human blood stages, chloroquine, doxycycline, mefloquine, atovaquone/proguanil and primaquine can be used. Refer to the text for a further description of the drugs used.

Summary

- Antimalarial drugs are classified by chemical structure and life cycle stage targeted.
- **ACTs** are first-line therapy for uncomplicated malaria.
- **Primaquine** is essential for eradicating liver-stage *P. vivax*/*P. ovale*.
- Pharmacists must assess **G6PD status**, monitor for **toxicity**, and advise on **adherence**.

Thank you

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