Drug and spectrum	MOA	Pharmacokinetics	ADRs
Drugs that PREVENT RELAPSES and Spread (Tissue hypnotocidal and gametocide)			
PRIMAQUINE : 8-AMINOQUINOLINES: **Hypnozoitocides → against liver hypnozoites (*Radical cure of P. ovale & P. vivax)* &** gametocytocides **(*Prevent spread of all forms*)**	Not well understood. It may be acting by; • Generating **ROS** → can damage lipids, proteins & nucleic acids • Interfering with the electron transport in the parasite → no energy • Inhibiting formation of transport vesicles →no food vacuoles	• Well absorbed orally • Rapidly metabolized to etaquine & tafenoquine → more active • t½ → 3-6h	**At regular doses :** patients with G-6-PD deficiency → **hemolytic anemia.** **At larger doses :** • Epigastric distress & abdominal cramps. • Mild **anemia, cyanosis & methemoglobinemia** • **Severe methemoglobinemia** → rarely in patients **with deficiency of NADH methemoglobin reductase.** • Granulocytopenia & agranulocytosis → rare
Drugs that treat the Attack (Blood schizontocidal drugs)			
1-Lactone endoperoxides:e.gartemisinin ,artemether,**artesunate** • **artemisinin →Poor solubility** • **artemether ,artesunate → Soluble** • **Fast acting (The most rapid acting drugs) blood Schizontocide (so, it prevents the attack)** • **Affect all forms including multi-drug resistant *P. falciparum***	They have **endoperoxidase** bridges that are cleaved **by haeme iorn** to yeild **carbon-centred free radicals**, that will→ • **Alkylate** membranes of parasite's food vacuole and mitochondria→ no energy • **Irreversibly bind & inhibit** sarco-endoplasmic reticulum Ca^{2+}-ATPase of the **parasite**, thereby inhibiting its **growth** Inhibiting formation of **transport vesicles** →no food vacuoles	• Derivatives are rapidly absorbed orally • Rapidly biotransform in liver into **artenimol**→ active metabolite • Widely distributed • t½ **artemisinin → 4hrs / artesunate → 45min (shortest) / artemether 4-11hrs**	• Transient (bradycardia) , heart block • Transient ↓neutrophil count • Brief episodes of fever • Neuro, hepato and bone marrow toxicity (rare)
2-Aminoquinolines derivative(have the same MOA)			
A)**Chloroquine : (4-Aminoquinolines)** **Potent blood Schizontocide(Can be active against all forms of the schizonts (exception is chloroquine-resistant P.falciparum. & P.vivax.) &** a Gametocide **(Against →P.vivax., P.ovale., P.falcipaum).** **N.B. Safe in pregnancy : (Late pregnancy)**	**Chloroquine concentrates** → 1000-fold in food vacuole of parasite.by: -Its protonation & ion trapping due to ↓ pH of vacuole (the drug like the acidic media) -Its active uptake by a parasite transporter(s) -Its binding to a specific receptor in the food vacuole. **Mechanism:** • Malaria Parasite digest host cell's Hb to obtain a.a (for feeding and growth). • Heme is released → Toxic • So parasite detoxifies it by heme polymerase → Hemozin	• Rapidly & completely absorbed from the GIT • Has high volume of distribution(100-1000l/kg) • Concentrated into parasitized RBCs. • Released slowly from tissues • Metabolized in the liver • Excreted in the urine 70% unchanged • Initial t½ =2-3days & terminal t ½=1-2months **Resistance against the drug** develops as a result of enhanced efflux of parasite vesicle →↑expression of the human **multi drug resistance transporter P-glycoprotein**	**ADR:-** **Short-term** • Mild headache and visual disturbances • Gastro-intestinal upsets; Nausea, vomiting • Pruritus, urticaria. **Prolonged therapy** • Retinopathy, (the commonest ADRS) • Lichenoid skin eruption, bleaching of hair • Weight loss ★ Bolus injection→ hypotension & dysrhythmias

Drug and spectrum	Pharmacokinetics	ADRs	Contraindications
2-QUININE **Aminoquinolines derivative :** **Arylaminoalccohols** • **Quinoline methanols: quinine, quinidine & mefloquine** • **Phenanthrene methanols: halofantrine.** **Potent blood Schizontocide & weak Gametocide** **N.B. Safe in pregnancy :** (early pregnancy)	• Rapidly & completely absorbed from the GIT • Peaks after 1-3 hrs • Metabolized in the liver • 5% excreted in the urine unchanged • t½ = 10 hrs but longer in sever falciparum infection • **N.B:**Administered: orally in **a 7 day course** or by **slow IV** for **severe P. falciparum infection**	**With therapeutic dose :** poor compliance → **bitter taste**. (No ADRS) **Higher doses :** • **Cinchonism** → *(tinnitus, deafness, headaches, nausea & visual disturbances)* (most common) • Abdominal pain & diarrhea • Rashes, fever, hypersensitivity reactions • Hypotension & arrhythmias • **Blood dyscarasis** :anaemia, thrombocytopenic purpura &hypoprothrombinaemia • Blackwater fever: a fatal condition in which acute haemolytic anaemia is associated with renal failure (dark urine) • IV → neurotoxicity → tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration & coma	• Prolonged QT Interval (because it can cause arrhythmia) • Glucose-6-Phosphate Dehydrogenase Deficiency (because it cause hemolytic anemia) • Myasthenia Gravis (because it has neuromuscular blocking effect) • Hypersensitivity (because it initiate hypersensitivity reaction) • Optic Neuritis, auditory problems (because it cause cinchonisim) • Dose should be reduced in renal insufficiency
Other Actions • **Quinidine – like action** (antiarrhythmic drug) • **Mild oxytoxic effect on pregnant uterus** • **Slight neuromuscular blocking action** • **Weak antipyretic action**	**Interactions :** • **Antacids :** Antacids containing aluminum &/or magnesium may **delay or decrease absorption** of quinine. (increase its level → toxicity) • (CYP3A4 inhibitor): Cimetidine – Mefloquine - Erythromycin • **Quinine can raise plasma levels of warfarin and digoxin.**		

DRUGS USED IN COMBINATIONS with Artemether:

Drug	MOA	ADR
Lumefantrine	↓heme polymerase [like chloroquine]	Palpitation, dizziness,allergic reaction, hepatotoxicity
Amodiaquine	↓heme polymerase [like chloroquine]	Nausea, vomiting, itching, stomach upset & headache.
Mefloquine	↓heme polymerase [like chloroquine]	neuropsychiatric disorders
Sulfadoxine-pyrimethamine	Sequential block of dihydropteroate synthase & dihydrofolate reductase ↓ DNA synthesis(then the parasite die)	Allergic skin reactions, Agranulocytosis; aplastic anemia
Doxycycline	Inhibit protein synthesis by binding to 30S subunit of ribosome	Yellowish discoloration of teeth, Dental carries, bone deformity, vertigo, hypersensitivity

Artemisin-based combination therapies (ACTs):

- Artemether + lumefantrine
- Artemether + amodiaquine
- Artemether + mefloquine
- Artemether + sulfadoxine-pyrimethamine

Summary

- Artesunate IV or IM preparations for severe complicated cases as in cerebral malaria (emergency) (24h) followed by complete course of ACT.

- **Artemisinin ,Chloroquine ,Quinine** are drugs of choice to abort the attack (Blood schizontocidal drugs)
- **Primaquine** is Tissue (schizontocidal) and Gametocidal drug used as preventive therapy
- **Artesunate IV or IM** is used in cerebral malaria
- **Artemisin** never used alone ->Artemisin-based combination therapies (ACTs) is the base standered in treatment of malaria
- Artesunate and Artemisin Have endoperoxidase bridges that yield free radicals which destroy the parasites
- The common Artemisin ADRs are Transient heart block,↓neutrophil count and fever

- **Chloroquine** concentrates ➔ 1000-fold in food vacuole of parasite

- The common ADRs of chloroquine are Retinopathy , Lichenoid skin eruption

- **QUININE** have no ADRs in the therapeutic dose except it's bitter taste however in larger doses it causes Cinchonism ,Blood dyscarasis and Blackwater fever
- **QUININE** is Safe in pregnancy and it has many intraction with Antacids and CYP3A4 inhibitors

- **Primaquine** ADRs At regular doses ➔ hemolytic anemia however At larger doses it cause Epigastric distress ,Mild anemia, cyanosis & methemoglobinemia

- **Sulfadoxine-pyrimethamine** is one of the drug which used in compination with **Artemisin** and it dose Sequential block of dihydropteroate synthase & dihydrofolate reductase so↓ DNA synthesis

- **In vivax** if it sensitive we use **Chloroquine** for 3 days followed by **Primaquine** for 14 days however If it was resistance **ACT (full course)** followed by Primaquine for 14 days
- **In falciparum** if it is uncomplicated ➔**ACT** and if it's complicated we can use IV Artisunate for 24 hrs followed **by ACT**