ANTIPARASITIC AGENTS // MALARIA

LIFE CYCLE
- **Vector:** anopheles (female mosquito)
- **Parasite:** *Plasmodium (falciparum, vivax, ovale, malariae)*
- **Mosquito** → Men

DRUG TARGETS
- **Hypnozoiticides:** liver, dormant form → relapse, for *P. vivax* & *P. ovale* (*M. tertiana*) → **8-sub quinolones**
- **Schizontocides:** asexual
  - Liver → **8-sub quinolones**
  - Blood → **4-sub quinolones, DHFR inhibitors, artemisinins**
- **Gametocytocides:** blood, female & male → **8-sub quinolones, artemisinins**

DRUGS
- **Quinolines**
  - 4-substituted: quinine, chloroquine, mefloquine, halofantrine
  - 8-substituted: primaquine
- **Quinine:** first known anti-malarial, from bark of tree quinquina
  - SAR: 3° amide, essential R+S 9° methanol (connects quinuclide to quinoline)
- **Chloroquine:** not 4 methyl but 4 amino (need to recognize structure: look for NH connector)

MOA
- **Quinolones**
  - Food vacuole of plasmodium digests Hgb because needs amino acids to make new plasmodium cells → heme is toxic to plasmodium → polymerizes to detox to non-toxic product hemozoin
  - Quinolines bind to hemozoin: aromatic ring system binds to π bonds
    - Bind to hemozoin → blocking polymer extension → ↑accumulation of toxic heme → cell death
  - Ion trapping: since food vacuole is acidic but drug is weak base, need receptors to get drug in
- **Chloroquine**
  - Resistance: spontaneous gene mutations (*pfcrt* transporter protein, drug efflux against ion trapping), ↑CYP450 metabolism to inactive metabolite
  - SAR: N-deakylation for more efficient metabolism which ↑resistance; ↑activity through hydroxylation, chlorination, alkylation; ↓activity through alkylation (at different part of structure)
- **8-substituted quinolone**
  - **Primaquine**
  - Only drug that works on dormant forms to prevent relapses
  - SAR: 8-amino group auto-oxidation → reactive O2 species → oxidative cell damage
- **Antifolates**
  - **Pyrimethamine**
  - DHFR inhibitor
- **Artemisinin**
  - Sesquiterpene (15 carbon) lactone (cyclic ester)
  - Free radical formation → oxidative damage to parasites’s membrane

PREVENTION
- **Chloroquine:** for long trips, SE (vision problems)
- **Mefloquine:** for long trips, SE (mental side effects, tingling feet/fingers)
- **Doxycycline:** for short last minute trips
- **Atovaquone/proquina:** for short last minute trips, well tolerated
- **Primaquine:** for preventing *P. vivax* (good for locations with high *P. vivax* prevalence)