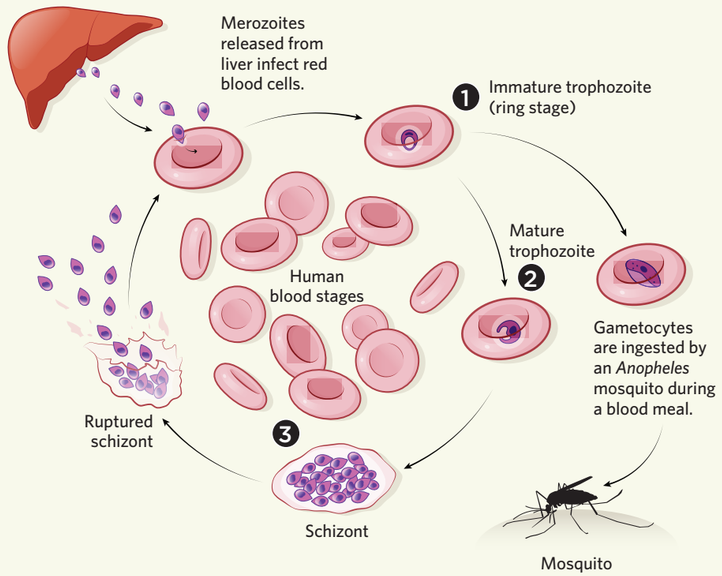
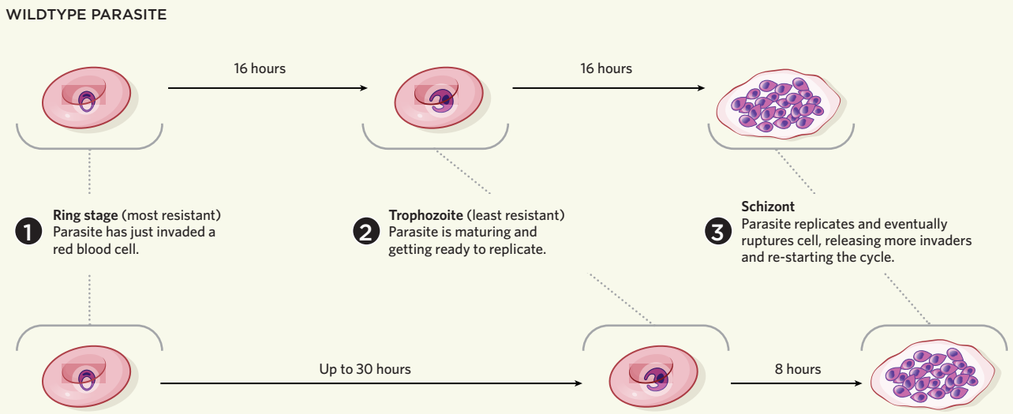
ACT OF RESISTANCE

Plasmodium falciparum resistance to artemisinin-based combination therapies (ACTs) started to crop up around 2007. This largely arose from pairing artemisinin derivatives with older drugs that had existing resistance problems. But the emergence of partial resistance to artemisinin itself—which allows parasites to persist for longer in the body following treatment—may also play a role.

PARTIAL ARTEMISININ RESISTANCE

Researchers have linked partial resistance to artemisinin-derived drugs with several mutations in the *kelch13* gene, which encodes a binding protein whose role in the parasite's ability to persist is still unclear. Delayed parasite clearance has also been linked to a prolonged ring stage, which appears to be the only part of the parasite's lifecycle during which it is able to partially survive artemisinin derivatives such as artemether, artesunate, or dihydroartemisinin. A single dose of these ACT ingredients stays in the body for only a few hours, and patients are typically treated with an artemisinin derivative for only the first couple of day of malaria therapy, so it's thought that the prolonged ring stage may help the parasites survive the therapy. Preliminary evidence suggests that resistant parasites also rush through the subsequent trophozoite stage, which appears to be the most susceptible to artemisinin.

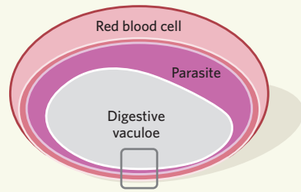




Data taken from *Antimicrob Agents Chemother*, 59:3156–67, 2015. Times are approximate.

PARTNER DRUG RESISTANCE

In red blood cells, *P. falciparum* digests human hemoglobin to feed itself. In addition to amino acids, this releases toxic heme. Normally, the parasite polymerizes the heme into harmless clumps of hemozoin or degrades it through a handful of poorly understood pathways. But most ACT partner drugs inhibit detoxification. Some partner drugs also attack the parasite through other mechanisms. Here are examples of how *P. falciparum* strains resist these drugs.



During the blood stages of malaria infection, the parasite resides within red blood cells, digesting hemoglobin to support its growth and maturation.