The diminished effectiveness of eflornithine against *T. b. rhodesiense* appears to be due to the parasite's ability to replace the inhibited enzyme more rapidly than *T. b. gambiense*.

Eflornithine is less toxic but more costly than conventional therapy. It can be administered IV or PO. The dose should be reduced in renal failure. Eflornithine readily crosses the blood-brain barrier; CSF levels are highest in persons with the most severe central nervous system (CNS) involvement.

Fumagillin† Fumagillin is a water-insoluble antibiotic that is derived from the fungus *Aspergillus fumigatus* and is active against microsporidia. This drug is effective when used topically to treat ocular infections due to *Encephalitozoon* species. When given systemically, fumagillin was effective but caused thrombocytopenia in all recipients in the second week of treatment; this side effect was readily reversed when administration of the drug was stopped. The mechanisms by which fumagillin inhibits microsporidial replication are poorly understood, although the drug may inhibit methionine aminopeptidase 2 by irreversibly blocking the active site.

Furazolidone This nitrofuran derivative is an effective alternative agent for the treatment of giardiasis and also exhibits activity against *Isospora belli*. Because it is the only agent active against *Giardia* that is available in liquid form, it is most often used to treat young children. Furazolidone undergoes reductive activation in *Giardia lamblia* trophozoites—an event that, unlike the reductive activation of metronidazole, involves an NADH oxidase. The killing effect correlates with the toxicity of reduced products, which damage important cellular components, including DNA. Although furazolidone had been thought to be largely unabsorbed when administered orally, the occurrence of systemic adverse reactions indicates that this is not the case. More than 65% of the drug dose can be recovered from the urine as colored metabolites. Omeprazole reduces the oral bioavailability of furazolidone.

Furazolidone is a monoamine oxidase (MAO) inhibitor; thus, caution should be used in its concomitant administration with other drugs (especially indirectly acting sympathomimetic amines) and in the consumption of food and drink containing tyramine during treatment. However, hypertensive crises have not been reported in patients receiving furazolidone, and it has been suggested that—because furazolidone inhibits MAOs gradually over several days—the risks are small if treatment is limited to a 5-day course. Because hemolytic anemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and glutathione instability, furazolidone treatment is contraindicated in mothers who are breast-feeding and in neonates.

Halofantrine This 9-phenanthrenemethanol is one of three classes of arylaminoalcohols first identified as potential antimalarial agents by the World War II Malaria Chemotherapy Program. Its activity is believed to be similar to that of chloroquine, although it is an oral alternative for the treatment of malaria due to chloroquine-resistant *P. falciparum*.

Although the mechanism of action is poorly understood, halofantrine is thought to share mechanism(s) with the 4-aminoquinolines, forming a complex with ferriprotoporphyrin IX and interfering with the degradation of hemoglobin.

Halofantrine exhibits erratic bioavailability, but its absorption is significantly enhanced when it is taken with a fatty meal. The elimination half-life of halofantrine is 1–2 days; it is excreted mainly in feces. Halofantrine is metabolized into *N*-debutyl-halofantrine by the cytochrome P450 enzyme CYP3A4. Grapefruit juice should be avoided during treatment because it increases both halofantrine's bioavailability and halofantrine-induced QT interval prolongation by inhibiting CYP3A4 at the enterocyte level.

Iodoquinol Iodoquinol (diiodohydroxyquin), a hydroxyquinoline, is an effective luminal agent for the treatment of amebiasis, balantidiasis, and infection with *Dientamoeba fragilis*. Its mechanism of action is unknown. It is poorly absorbed. Because the drug contains 64% organically bound iodine, it should be used with caution in patients with thyroid disease. Iodine dermatitis occurs occasionally during iodoquinol treatment. Protein-bound serum iodine levels may be increased during treatment and can interfere with certain tests of thyroid function. These effects may persist for as long as 6 months after discontinuation of therapy. Iodoquinol is contraindicated in patients with liver disease. Most serious are the reactions related to prolonged high-dose therapy (optic neuritis, peripheral neuropathy), which should not occur if the recommended dosage regimens are followed.

Ivermectin Ivermectin (22,23-dihydroavermectin) is a derivative of the macrocyclic lactone avermectin produced by the soil-dwelling actinomycete *Streptomyces avermitilis*. Ivermectin is active at low doses against a wide range of helminths and ectoparasites. It is the drug of choice for the treatment of onchocerciasis, strongyloidiasis, cutaneous larva migrans, and scabies. Ivermectin is highly active against microfilariae of the lymphatic filariases but has no macrofilaricidal activity. When ivermectin is used in combination with other agents such as DEC or albendazole for treatment of lymphatic filariasis, synergistic activity is seen. Although active against the intestinal helminths *Ascaris lumbricoides* and *Enterobius vermicularis*, ivermectin is only variably effective in trichuriasis and is ineffective against hookworms. Widespread use of ivermectin for treatment of intestinal nematode infections in sheep and goats has led to the emergence of drug resistance in veterinary practice; this development may portend problems in human medical use.

Data suggest that ivermectin acts by opening the neuromuscular membrane-associated, glutamate-dependent chloride channels. The influx of chloride ions results in hyperpolarization and muscle paralysis—particularly of the nematode pharynx, with consequent blockage of the oral ingestion of nutrients. As these chloride channels are present only in invertebrates, paralysis is seen only in the parasite.

Ivermectin is available for administration to humans only as an oral formulation. The drug is highly protein bound; it is almost completely excreted in feces. Both food and beer increase the bioavailability of ivermectin significantly. Ivermectin is distributed widely throughout the body; animal studies indicate that it accumulates at the highest concentration in adipose tissue and liver, with little accumulation in the brain. Few data exist to guide therapy in hosts with conditions that may influence drug pharmacokinetics.

Ivermectin is generally administered as a single dose of 150–200 μg/kg. In the absence of parasitic infection, the adverse effects of ivermectin in therapeutic doses are minimal. Adverse effects in patients with filarial infections include fever, myalgia, malaise, lightheadedness, and (occasionally) postural hypotension. The severity of such side effects is related to the intensity of parasite infection, with more symptoms in individuals with a heavy parasite burden. In onchocerciasis, skin edema, pruritus, and mild eye irritation may also occur. The adverse effects are generally self-limiting and only occasionally require symptom-based treatment with antipyretics or antihistamines. More severe complications of ivermectin therapy for onchocerciasis include encephalopathy in patients heavily infected with *Loa loa*.

Lumefantrine Lumefantrine (benflumetol), a fluorene arylaminoalcohol derivative synthesized in the 1970s by the Chinese Academy of Military Medical Sciences (Beijing), has marked blood schizonticidal activity against a wide range of plasmodia. This agent conforms structurally and in mode of action to other arylaminoalcohols (quinine, mefloquine, and halofantrine). Lumefantrine exerts its antimalarial effect as a consequence of its interaction with heme, a degradation product of hemoglobin metabolism. Although its antimalarial activity is slower than that of the artemisinin-based drugs, the recrudescence rate with the recommended lumefantrine regimen is lower. The pharmacokinetic properties of lumefantrine are reminiscent of those of halofantrine, with variable oral bioavailability, considerable augmentation of oral bioavailability by concomitant fat intake, and a terminal elimination half-life of ~4–5 days in patients with malaria.

Artemether and lumefantrine have synergistic activity, and the combined formulation of artemether and lumefantrine is effective for the treatment of falciparum malaria in areas where *P. falciparum* is resistant to chloroquine and antifolates.