Antihelmintic drugs

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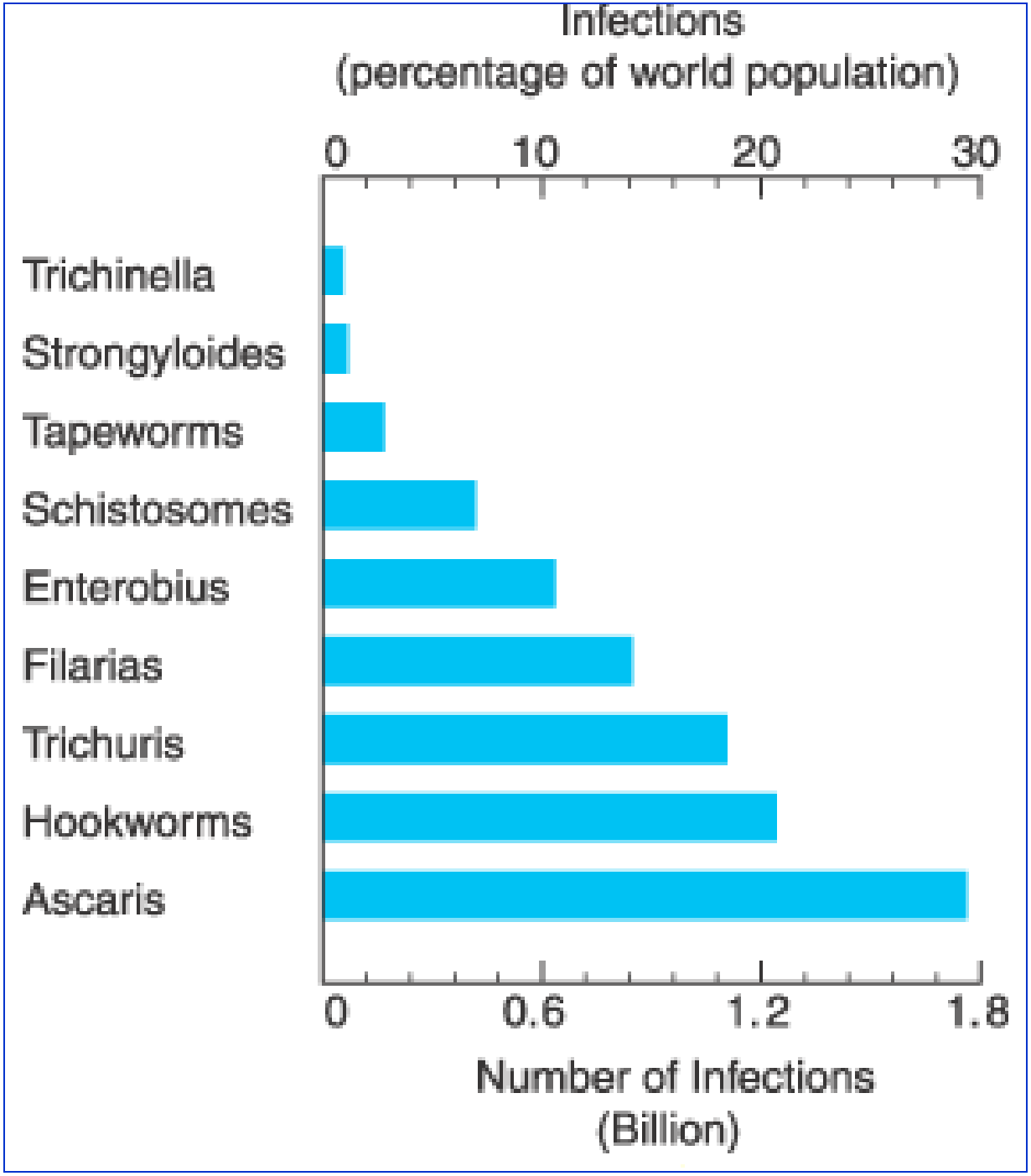
Helmintic infections

- Human is the primary host for most helminthic infections.
- Most worms produce eggs and larva
- These pass out of human body and infect secondary host
- Immature forms invade humans via skin or GIT

Relative incidence of helminth infections worldwide



Types (clinical)

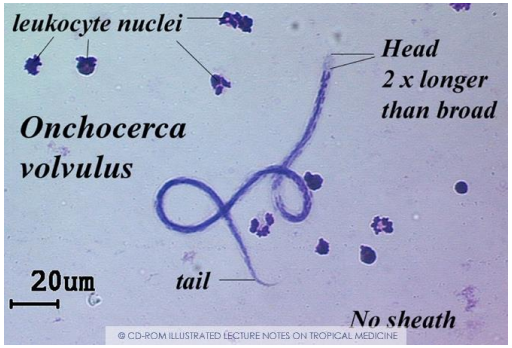
1. Worms live in hosts alimentary canal.

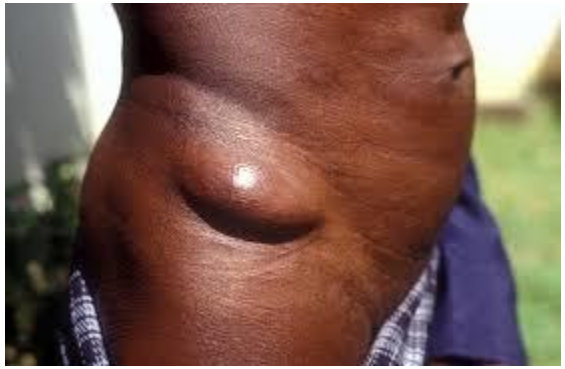
2. Worms or larvae live in other tissues of host body like muscles , viscera , menninges, lungs, subcutaneous tissues.

Nematode infections

ONCHOCERCIASIS (RIVER BLINDNESS)

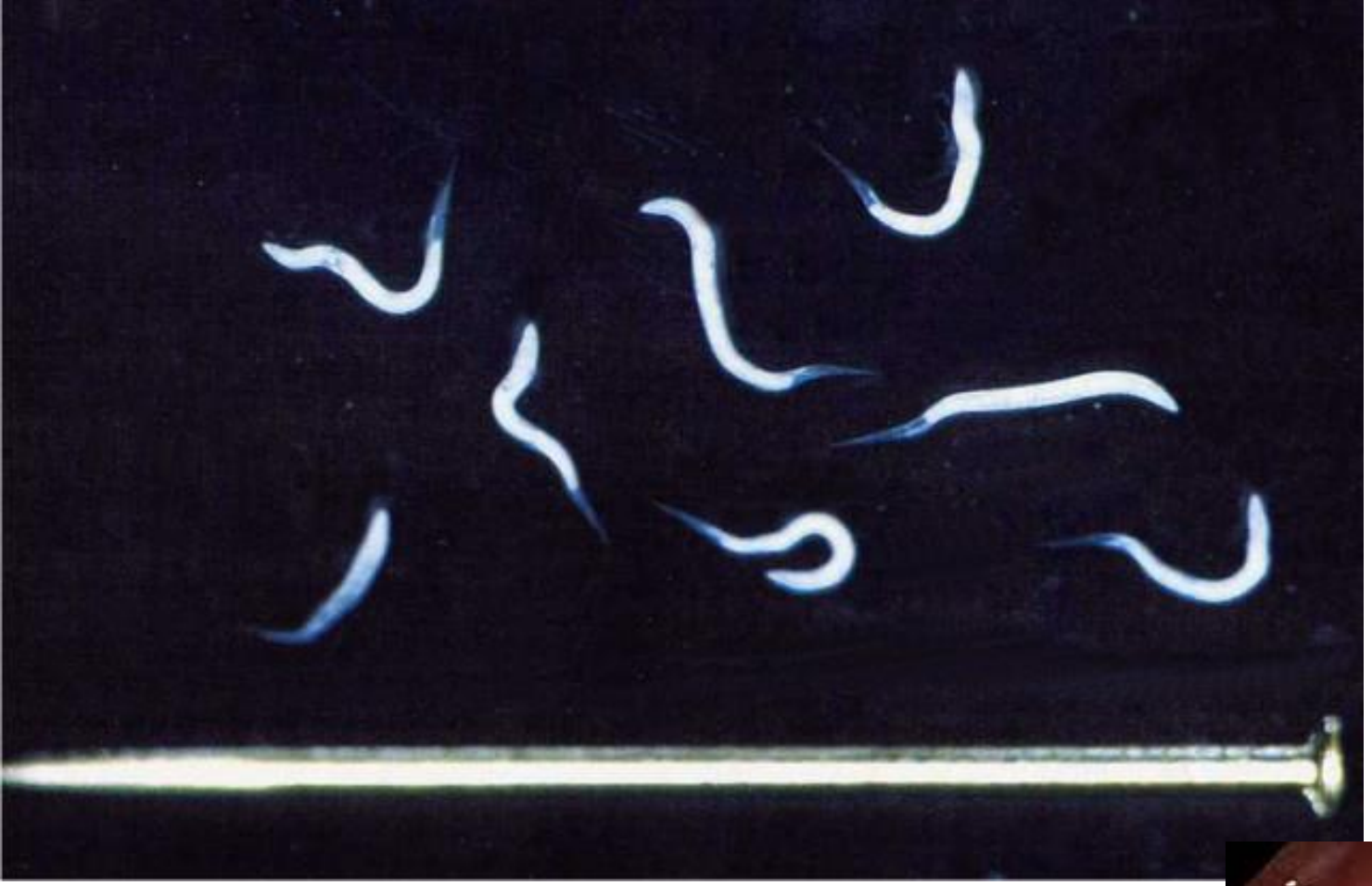
- Causative agent: Onchocerca volvulus.
- Common in areas of Mexico, South America, and tropical Africa.
- Characterized by subcutaneous nodules, a pruritic skin rash, and ocular lesions often resulting in blindness.
- Therapy: *Ivermectin*.

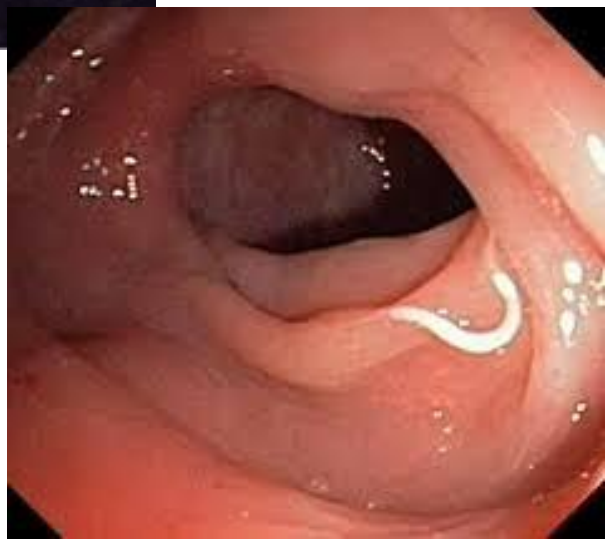

leukocyte nuclei
Head
2 x longer
than broad
Onchocerca
volvulus
20um
tail
No sheath
© CD-ROM ILLUSTRATED LECTURE NOTES ON TROPICAL MEDICINE



ENTEROBIASIS (PINWORM DISEASE)

- Causative agent: Enterobius vermicularis.
- Most commmon helminthic infection in the United States.
- Pruritus ani occurs, with white worms visible in stools or perianal region.
- Therapy: *Mebendazole* or *pyrantel pamoate*.

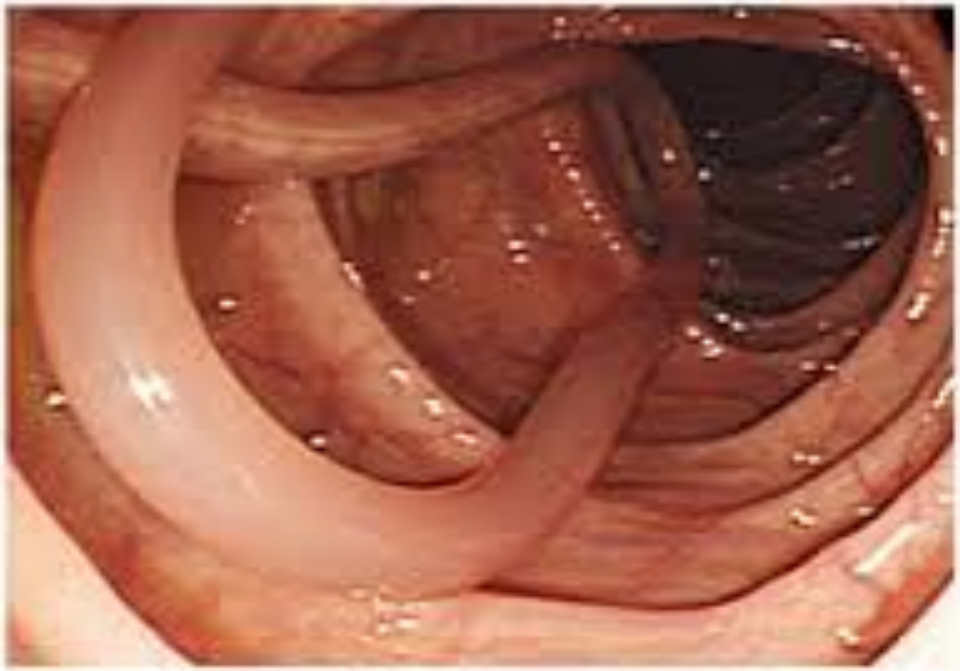




ASCARIASIS (ROUNDWORM DISEASE)

- Causative agent: Ascaris lumbricoides.
- Second only to pinworms as the most prevalent multicellular parasite in the United States; approximately one third of the world's population is infected with this worm.
- Ingested larvae grow in the intestine, causing abdominal symptoms, including intestinal obstruction; roundworms may pass to blood and infect the lungs.
- Therapy: *Pyrantel pamoate* or *mebendazole*.


Female
Male
A. lumbricoides Adult Worms
DMR 1999



TRICHURIASIS (WHIPWORM DISEASE)

- Causative agent: Trichuris trichiura.
- Infection is usually asymptomatic; however, abdominal pain, diarrhea, and flatulence can occur.
- Therapy: *Mebendazole*.

HOOKWORM DISEASE

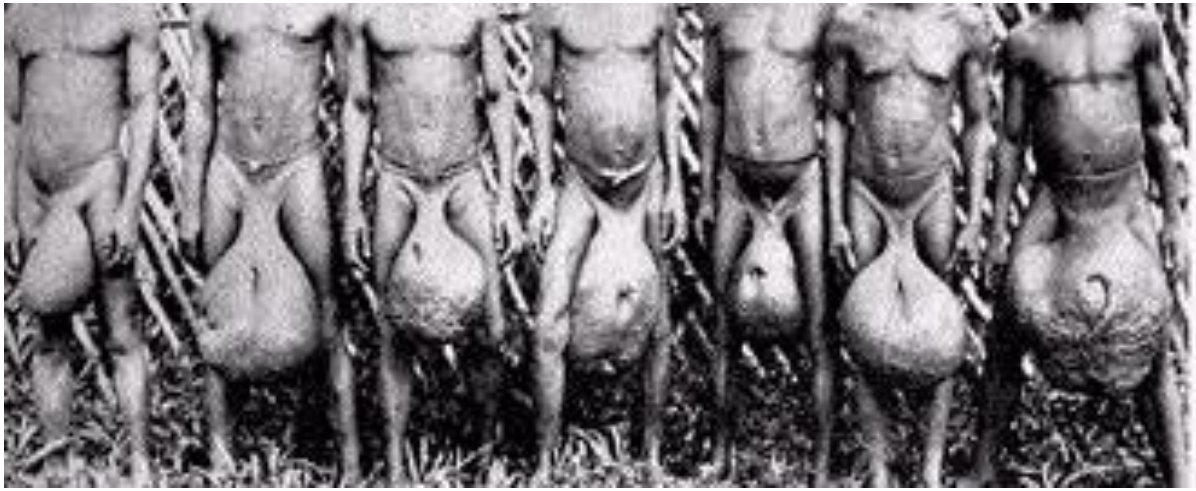
- Causative agents: Ancylostoma duodenale (Old World hookworm), Necator americanus (New World hookworm).
- Worm attaches to the intestinal mucosa, causing anorexia, ulcer-like symptoms, and chronic intestinal blood loss that leads to anemia.
- Treatment is unnecessary in asymptomatic individuals who are not anemic.
- Therapy: *Pyrantel pamoate* or *mebendazole*.

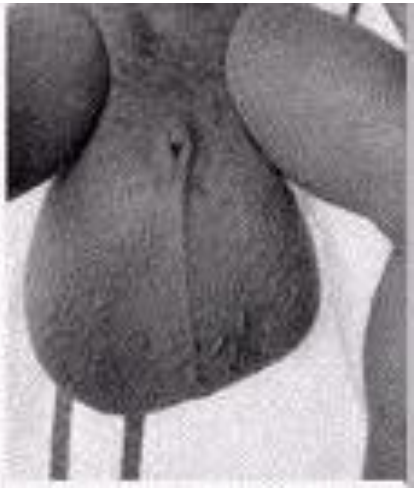
STRONGYLOIDIASIS (THREADWORM DISEASE)

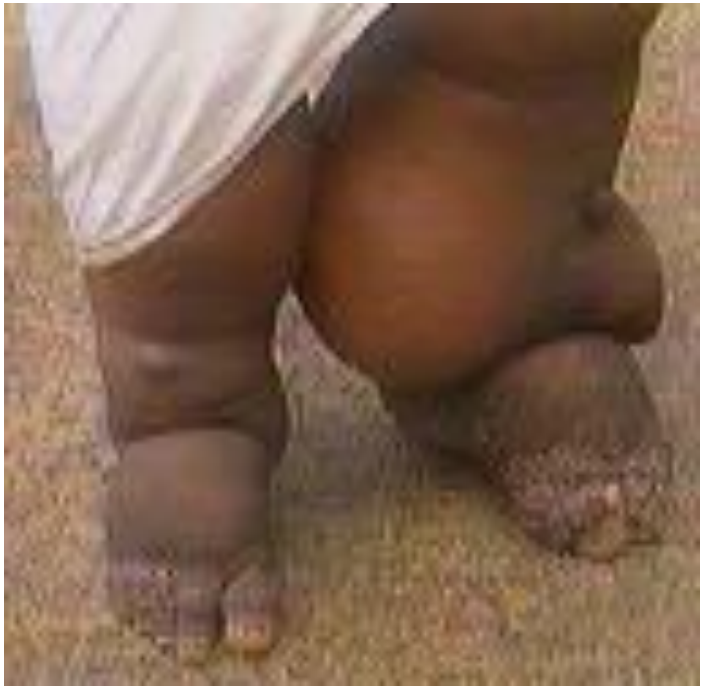
- **Causative agent: Strongyloides stercoralis.**
- **Relatively uncommon compared with other intestinal nematodes; a relatively benign disease in normal individuals that can progress to a fatal outcome in immuno-compromised patients.**
- **Therapy: *Thiabendazole* or *ivermectin*.**

FILARIASIS

- Causative agents: Wuchereria bancrofti, Brugia malayi.
- Worms cause blockage of lymph flow. Ultimately, local inflammation and fibrosis of the lymphatics occurs.
- After years of infestation, the arms, legs, and scrotum fill with fluid, causing elephantiasis.
- Therapy: A combination of *diethyl-carbamazine* and *albendazole*.

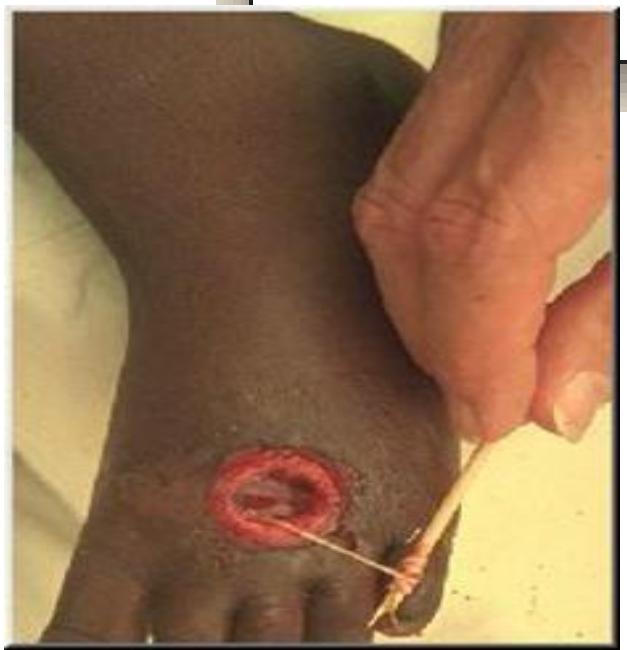






TRICHINOSIS

- Causative agent: Trichinella spiralis.
- Usually caused by consumption of insufficiently cooked meat, especially pork.
- Therapy: *Thiabendazole* (only in the early stages of disease).



Trematode infections

SCHISTASOMIASIS (new world)

- **Schistosoma haematobium**
- The primary sites of infection are veins of the urinary bladder, where the organism's eggs can induce fibrosis, granulomas, and hematuria.
- The disease is transmitted by direct skin penetration
- This form of schistosomiasis is diagnosed by identifying characteristic eggs in the urine or bladder wall
- Therapy: Praziquantel

SCHISTASOMIASIS (old world)

- Schistosoma Japonicum, Schistosoma mansoni
- The primary site of infection is the gastrointestinal tract. Damage to the intestinal wall is caused by the host's inflammatory response to eggs deposited at that site. The eggs also secreted proteolytic enzymes.
- Clinical presentation includes GI bleeding, diarrhea, and liver damage.
- The disease is transmitted by direct skin penetration.
- This form of disease is diagnosed by identification of characteristic eggs in the stool.
- Therapy: Praziquantel

Paragonimiasis

- **Paragonimus westermani (lung fluke)**

  disease is caused by eating raw crab or fish , larvae move from intestine to blood and settle in lungs- bloody sputum

Therapy: Praziquantel

Clonorchiasis

- **Clonorchis sinensis (liver fluke)**

  disease is caused by eating raw freshwater fish and worm settle in the biliary tract, resulting inflammatory response can cause fibrosis and hyperplasia

Therapy: Praziquantel

Cestode infections

Echinococcosis (hydatid disease)

- Echinococcus granulosus (dog tapeworm)
- These are cestodes ,primary in canines (dogs) and sheep as intermediate host.
- humans can act intermediate host in which larvae develop to hydatid cyst with in the liver, lung, and brain.
- Anaphylactic reaction to worm antigens can occur if the cyst ruptures
- Therapy: Albendazole, surgical inc.of cysts
- Diagnosis: CT scan or biopsy

Cysticercosis

- Taenia solium larvae
- Infection produces cysterci in the brain

(causing seizures, headache, and vomiting) and in the eyes

- Diagnosis: CT scan or biopsy
- Therapy: praziquantel, albendazole, and/or surgery

Taeniasis

- Taenia saginata (beef tapeworm) or Taenia solium (pork tapeworm)
- The disease is transmitted by larvae in undercooked or raw meat.
- Intestines are primary site of infection, where the organism can cause diarrhea
- Therapy: niclosamide

Diphyllobothriasis

- Diphyllobothrium latum (fish tapeworm)
- The adult worm in a host’s intestine can be as long as 15 meters
- The disease is transmitted by larvae in raw or undercooked fish
- Therapy: Niclosamide

Drugs for the treatment of nematodes

Mebendazole *blocks glucose uptake* by nematodes. Mild GI disturbances may be Caused (abdominal pain and diarrhae), and it should not be used in pregnancy or in children under the age of 2.

In the treatment of infections by whipworm, pinworm, hookworm, and roundworm

Pyrantel ***depolarises neuromuscular junctions (roundworm, pinworms, hookworms)***

- of susceptible nematodes which are expelled in the faeces. It cures with a single dose.
- It may induce GI disturbance, headache, dizziness, drowsiness, and insomnia.
- Poorly absorbed orally and exert its effect in the GI tract.

Thiabendazole

- inhibits cellular enzymes of susceptible helminths.
- Gastrointestinal, neurological and hypersensitivity reactions (dizziness, anorexia, vomiting, nausea) liver damage,and crystalluria may be induced.
- Contrindicated during pregnancy

Diethylcarbamazine kills both microfilariae and adult worms. Fever, headache, anorexia, malaise, urticaria, vomiting, and asthmatic attacks following the first dose are due to products of destruction of the parasite, and reactions are minimised by slow increase in dosage over the first 3 days.

Ivermectin may cause immediate reactions due to the death of the *microfilaria (early stage in the life cycle of certain parasitic nematodes)* .
It can be effective in a single dose, but it works best if repeated at 6–12-month intervals.
Contraindicated in pregnancy and patients with meningitis

Drugs for the treatment of trematodes

Praziquantel paralyses both adult worms and larvae. It may cause nausea, headache, dizziness, and drowsiness; it cures with a single dose (or divided doses in one day).

Drugs for the treatment of cestodes

Niclosamide *blocks glucose uptake* by intestinal tapeworms. It may cause some mild GI symptoms.

Albendazole is similar to mebendazole.

Levamisole *paralyses the musculature* of sensitive nematodes which, unable to maintain their anchorage, are expelled by normal peristalsis. It may cause abdominal pain, nausea, vomiting, headache, and dizziness.

Worms (helminths)	Drug of choice
Tapeworms (cestodes)	**Niclosamide or Praziquantel or Albendazole**
Roundworms (nematodes) •***Enterobius vermicularis*** **(pinworm)** •***Ascaris lumbricoides*** •***Trichuris trichiura*** **(whipworm)** •***Trichinella spiralis*** **(trichinellosis)**	**Mebendazole or Pyrantel** **Mebendazole or Pyrantel** **Mebendazole or Albendazole** **Mebendazole and Thiabendazole**
•***Strongyloides stercoralis*** •***Necator americanus*** **(hookworm)** •***Ancylostoma duodenale***	**Thiabendazole** **Mebendazole or Pyrantel** **Mebendazole, Pyrantel, or Albendazole**
•***Onchocerca volvulus*** **(Onchocercosis)** •***Wuchereria bancrofti (Elephantiasis)***	**Ivermectin** **Diethylcarbamazine**
Flukes (trematodes) •***Schistzoma*** **(Schistozomes)**	**Praziquantel**

Antiprotozoal drugs

- ✓Protozoa are eukaryotes and unicellular organisms.
- ✓Most of the protozoal infections are due to unhygienic conditions.
- ✓Difficult to be treated than bacterial infections and antiprotozoal drugs are more toxic.

- ✓ Protozoal cells (Eukaryotes) have metabolic processes closer to human host than prokaryotic bacterial pathogens.

- ✓ Many of antiprotozoal drugs cause toxic effects in the host particularly on cells showing high metabolic activity, such as bone marrow stem, renal tubular cells, intestinal & neuronal cells.

- ✓ Antiprotozoal are not safe during pregnancy.

Protozoal infections

1. Amebiasis
2. Malaria
3. Giardiasis
4. Leshmaniasis
5. Toxoplasmosis
6. Trypanosomiasis

Chemotherapy for amebiasis

Amebiasis :

Is due to infection with *Entamoeba histolytica*

- Asymptomatic intestinal infection (90%)
- Mild to moderate colitis
- Severe intestinal infection (dysentery)
- Ameboma
- Liver abscess
- Other extraintestinal infections.

LIFE CYCLE

Entamoeba histolytica exists in two forms:

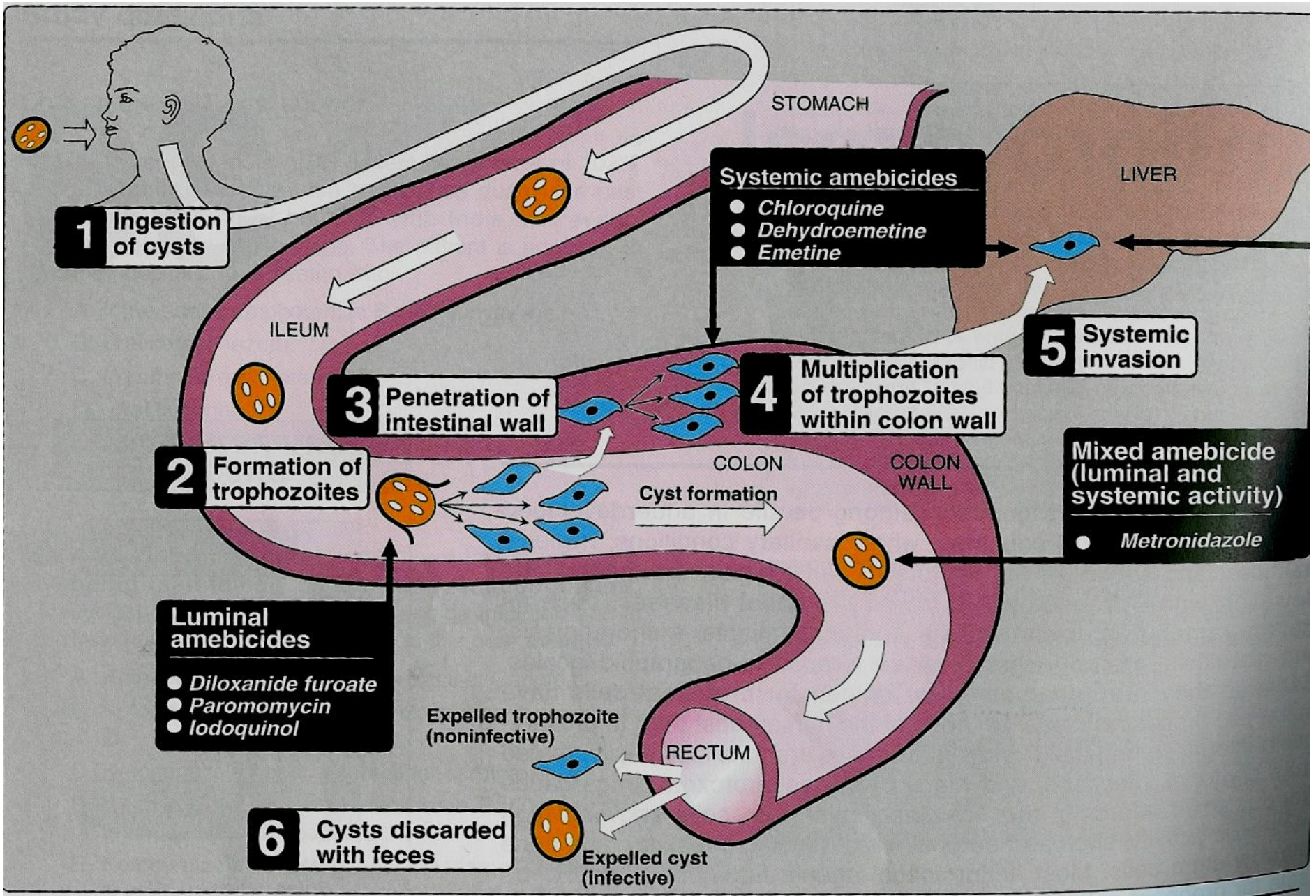
1. Cysts (infective):

- can survive outside the human body.
- transform to trophozoites.

2. Trophozoites (non-infective; invasive):

- Can reproduce
- They may feed on intestinal bacteria or invade and ulcerate wall of large intestine, and may migrate to liver or other tissues.
- transform to cysts which are excreted in feces.

LIFE CYCLE


STOMACH
LIVER
1 Ingestion of cysts
Systemic amebicides
Chloroquine
Dehydroemetine
Emetine
ILEUM
5 Systemic invasion
3 Penetration of intestinal wall
4 Multiplication of trophozoites within colon wall
2 Formation of trophozoites
COLON
COLON WALL
Cyst formation
Mixed amebicide (luminal and systemic activity)
Metronidazole
Luminal amebicides
Diloxanide furoate
Paromomycin
Iodoquinol
Expelled trophozoite (noninfective)
RECTUM
6 Cysts discarded with feces
Expelled cyst (infective)

Clinical presentations

- Asymptomatic Intestinal infection
  (Carriers, passing cysts)
- Mild to moderate intestinal disease
  (Nondysenteric Colitis)
- Severe Intestinal infection (Dysentery)
- Hepatic abscess, ameboma *(localized granulomatous lesion of colon)* and other extraintestinal disease

Classification of antiamebic drugs

- **Luminal Amebicides**
- **Tissue or systemic amebicides**
- **Mixed Amebicides**

LUMEN AMOEBICIDES

- Acts on the parasites in the lumen of the bowl.
- used for treatment of asymptomatic amebiasis.

Include

- Diloxanide Furoate
- Iodoquinol
- Antibiotics

  - Paromomycin
  - Tetracyclines
  - Erythromycin

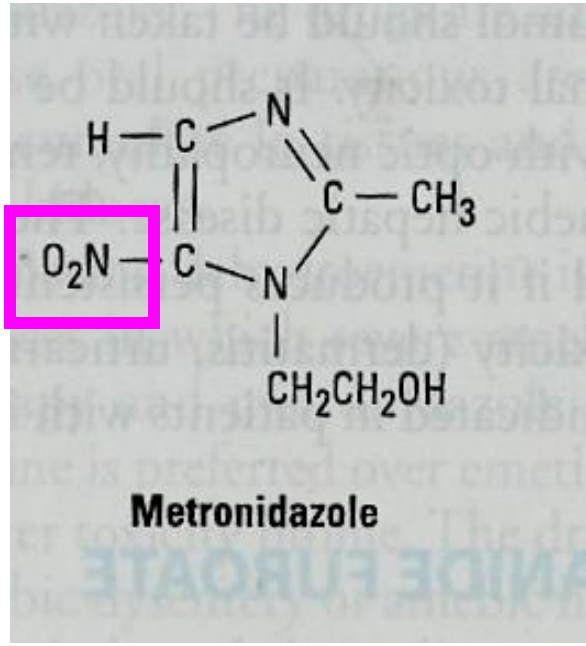
Mixed amoebicides

Effective against both luminal and systemic forms of the disease. Although luminal concentration is too low for single drug – treatment.

- **Metronidazol**
- **Tinidazole**

METRONIDAZOLE

- **Mixed ameobicide.**
- **Drug of choice for intestinal & extraintestinal ameobiasis.**
- **Acts on trophozoites.**
- **Has no effect on cysts.**
- **Nitro group of metronidazole is reduced by protozoan leading to cytotoxic reduced product that binds to DNA and proteins resulting into parasite death.**



Metronidazole

Pharmacokinetics

- **Given orally or IV.**
- **Absorption is rapid and complete.**
- **Due to rapid absorption from GIT, *not reliably effective against luminal parasites.***
- **Wide distribution to all tissues and body fluids (CSF, saliva, milk).**
- **Plasma protein binding is low (< 20%).**
- **Plasma half life is 8 h**

Pharmacokinetics

- **Metabolized in liver by mixed function oxidase followed by glucouroidation.**
- **Excreted in urine as unchanged drug plus metabolites.**
- **Clearance is decreased in liver impairment.**

Tinidazole has longer duration, simpler dosing regimen, less toxicity, than metronidazole, but is equally active.

Clinical Uses

- **Extraluminal amoebiasis (combined with luminal amebicide).**
- **Giardiasis**
- **Trichomoniasis**
- **Broad spectrum of Anaerobic bacteria e.g.,**
  - **Helicobacter pylori infection**
  - **Pseudomembranous colitis (Clostridium defficile).**

Adverse effects

1. GIT:

- **Nausea**
- **Vomiting**
- **Dry mouth**
- **Metallic taste**
- **Diarrhoea**
- **Oral Thrush (Moniliasis, yeast infection).**

Adverse effects

2. CNS: Neurotoxicological effect

- **Insomnia, dizziness**
- **peripheral neuropathy, paresthesia**
- **encphalopathy, convulsion (IV infusion, rare).**

3. Dysuria, dark urine.

4. Neutropenia

5. Disulfiram-like effect if taken with alcohol.

disulfiram like -effect

When metronidazole is given with alcohol abdominal distress, nausea, vomiting, flushing, or headache, tachycardia, hyperventilation

Drug interactions:

- **Enzyme inhibitors (cimetidine, ketoconazole)**
  increase duration of action of metronidazole
- **Inducers (phenytoin and phenobarbitone).**
- **inhibits CYP family 2C9 & 3A4**
- **potentiate anticoagulant effect of warfarin.**
- **potentiates lithium toxicity.**

CONTRAINDICATIONS / PRECAUTIONS:

- **Pregnancy**
- **Alcohol intake**
- **CNS diseases**
- **Severe hepatic disease**
- **Severe renal disease**

Tissue Amoebicides (systemic)

- acts on the intestinal wall and liver (or any other extra-intestinal tissue).
- **Used for treatment of systemic form of the disease (intestinal wall infection or liver abscesses).**
- **Emetine**
- **Dehydroemetine**
- **Chloroquine (liver only)**

EMETINE AND DEHYDROEMETINE

Chemistry:

- **Emetine hydrochloride is a plant alkaloid derived from ipeca.**
- **Dehydroemetine is a synthetic analogue**

Pharmacokinetics:

- **Erratic oral absorption.**
- **Given preferably subcutaneously but could be given by IM, NEVER I.V.**
- **Plasma half life is 5 days.**

EMETINE

- **Concentrated in Liver, Lungs, Spleen, Kidney, Cardiac muscle and Intestinal wall.**
- **Metabolized & Excreted slowly via kidney so it has a cumulative effect.**
- **Trace amounts could be detected in urine 1-2 month after last dose.**
- **Should not be used for more than 10 days (usually 3-5 days).**

Mechanism

- **Act on tissue trophozoites causing irreversible block of protein synthesis.**

Adverse Effects

- **Dehydroemetine is less toxic than emetine**
- **pain at site of injection, abcesses.**
- **GIT: nausea, vomiting, diarrhoea.**
- **Neuromuscular weakness**
- **Serious toxicities: cardiotoxicity**
  - **cardiac arrhythmias,**
  - **Hypotension**
  - **heart failure**

Clinical Uses

- **Amoebic liver abscess.**
- **Intestinal wall infections.**
- **Severe forms of amebiasis acute amoebic dysentery dehydroemetine is preferable due to less toxicity (3-5 days).**

Contraindications

- **Heart disease**
- **Kidney disease**
- **Pregnancy**
- **Children**

Chloroquine

- **Antiamebic drug**
- **Antimalarial drug**
- **Used in combination with metronidazole and diloxanide furoate to treat and prevent amebic liver abseses.**

Luminal amoebicides

- **acts on the luminal parasites**
- **used for treatment of asymptomatic amebiasis.**

Include

Diloxanide Furoate

- **Iodoquinol**
- **Antibiotics**
  - **Paromomycin**
  - **Tetracyclines**
  - **Erythromycin**

Diloxanide furoate

Chemistry

- **Ester of diloxanide + furoic acid .**

Pharmacokinetics

- **Given orally.**
- **Split in the intestine, most of diloxanide is absorbed, conjugated to form a glucoronide which is excreted in urine (90%).**
- **The unabsorbed diloxanide is the amoebicidal agent (10%).**

Pharmacodynamics:

- **Unkown mechanism of action**
- **Direct amoebicidal action against luminal forms.**
- **Not active against trophozoites intestinal wall or extraintestinal tissues.**

Therapeutic Uses

- **Drug of choice for asymptomatic intestinal infection.**
- **For eradication of infection given along with all forms of amebiasis.**
- **Dose: 500 mg three times/day for 10 days.**

Adverse Effects

- **Flatulence**
- **Nausea, vomiting, abdominal cramps.**
- **No serious adverse effects**

Contraindications:

- Pregnancy

- Children (less than 2 years).

Paromomycin Sulphate

- **Aminoglycoside, not absorbed from GItract.**
- **Effective against luminal forms of ameba**

Mechanism of action

- **Direct amebicidal action (causes leakage by its action on cell membrane of parasite).**
- **Indirect killing of bacterial flora essential for proliferation of pathogenic ameobae.**

Kinetics

- **Orally**
- **Not significantly absorbed from the GIT**
- **Small amount absorbed is excreted unchanged in urine (may accumulate with renal insufficiency).**

Adverse effects

- **Gastrointestinal distress and diarrhea.**

Precautions

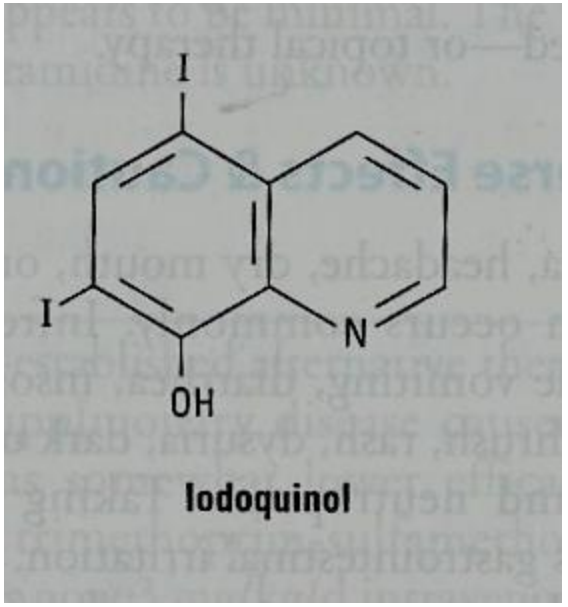
- **Severe renal disease**
- **patients with GIT ulceration**

Tetracyclines

- **Very weak direct amebicidal action.**
- **Mainly act indirectly on bacterial flora.**
- **Used in severe cases of amebic dysentery not responding to metronidazole combined with dehydroemetine.**

HALOGENATED HYDROXYQUINOLINES

- **Iodoquinol**



Iodoquinol

Mechanism of action

- **Unknown**
- **Effective against organisms in GIT only Not intestinal wall or liver.**

Pharmacokinetics

- **Absorption is poor (90%), excreted in feces.**
- **10% enter circulation, excreted as glucouronide in urine.**
- **Half life is 11-14 h**

Uses

- **lumen amebicide.**
- **For eradication of infection given along with tissue amoebicide (metronidazole).**

Adverse Effects

- **Peripheral neuropathy including optic neuritis**
- **GIT: Nausea, vomiting, diarrhoea.**
- **Enlargement of the thyroid gland.**
- **Agranulocytosis.**
- **Iodine sensitivity.**
- **interference with thyroid function tests (increase protein-bound serum iodine, decrease in measured ^{131}I uptake).**

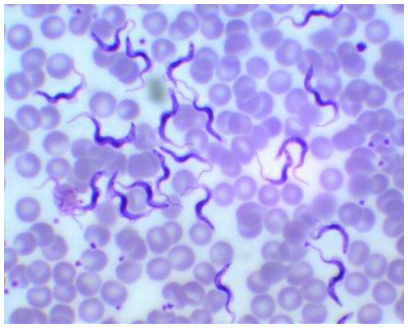
Contraindications

- **Optic neuropathy**
- **Thyroid disease**
- **Sensitivity to iodine**
- **Severe liver disease**
- **Severe kidney disease**
- **discontinued if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus, fever)**

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	*Iodoquinol* or *Paromycin* or *Diloxanide furoate*
Diarrhea/dysentery Extraintestinal	*Metronidazole* plus *Iodoquinol* or *Paromycin* or *Diloxanide furoate*
Amebic liver absess	*Chloroquine* plus *Metronidazole* or *Emetine*

Chemotherapy for trypanosomiasis

3. African trypanosomiasis (sleeping disease)



It is caused by the hemoflagellates *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. The organisms are transmitted by ***bites of tsetse flies*** (genus *Glossina*), which inhabit shaded areas along streams and rivers. The largest number of cases is in the Congo. Annual incidence estimates are about 100 000 cases and 48 000 deaths.

American Trypanosomiasis (Chagas' Disease) is caused by *Trypanosoma cruzi*.

African trypanosomiasis – treatment:
Suramin or pentamidine is effective during the early stages but not for the later neurological manifestations for which **melarsoprol** should be used. ***Eflornithine*** *is effective for both early and late stages*.

American Trypanosomiasis – treatment:
Prolonged (1–3 months) treatment with **benznidazole or nifurtimox** may be effective.

Melarsoprol

- Melarsoprol is a derivative of mersalyl oxide, a trivalent arsenical.
- Its use is limited to the treatment of trypanosomal infections (usually in the late stage with CNS involvement)
- It is lethal to these parasites.
- Parenterally (slow injection i.v.)
- Penetrate the CSF

- Melarsoprol is, therefore, the agent of choice in the treatment of T. brucei rhodesiense, which rapidly invades the CNS, as well as for meningoencephalitis caused by T. brucei gambiense.
- A/E:

CNS toxicity- encephalopaty

Hypersensitivity reactions

GI disturbances- abdominal pain, vomiting

Pentamidine

- Active against trypanosomatid protozoans but toxicity is significant.
- Parentrally or inhalation
- Only trace amounts appear in the CNS, (not effective against CNS african trypanosomiasis.)
- The mechanism of action may interfere with synthesis of RNA, DNA and proteins.

Clinical Uses

- Pneumocystosis
- African Trypanosomiasis (Sleeping Sickness)
- Leishmaniasis

A/E: Highly toxic

- Rapid IV : Severe Hypotension, Tachycardia, Dizziness.
- IM : Pain at the injection site, Sterile abscesses.
- Inhaled : Cough, Dyspnea, Bronchospasm.

Suramin

- Introduced in the 1920s.
- Is the first-line therapy for early hemolymphatic East African trypanosomiasis .
- Does not enter the CNS .
- It acts by inhibiting enzymes of energy metabolism
- **A/E**: common.
- Immediate reactions : Fatigue, N/V
- Rarely: Seizures, Shock.
- Later reactions :Paresthesias, Renal Abnormalities, Hemolytic Anemia.

Nifurtimox

- Used for American trypanosomiasis (Chagas' disease).
- It acts by generating toxic radicals
- A/E: GI disturbance, fever, rash, neuropathies, and seizures.

Benznidazole

- It inhibits protein synthesis in T. Cruzi cells
- It is an alternative choice for treatment of acute and indeterminate phases of Chagas disease, but therapy with benznidazole does not offer any significant efficacy or toxicity advantages over that with nifurtimox.
- However, benznidazole is recommended as prophylaxis for preventing infections caused by T. cruzi among hematopoietic stem cell transplant recipients because treatment in potential donors is not always effective.

Chemotherapy for Leshmaniasis

- **Sodium stibogluconate**
- **Pentamidine**
- **Amphotericin**

Sodium Stibogluconate

- First-line agents for cutaneous and visceral leishmaniasis
- IV,IM
- MOA: It acts by inhibiting glycolysis and fatty acid oxidation
- A/E: Few but increases over the course of therapy.
- GI symptoms, fever, headache, myalgias, arthralgias,rash.
- IM: painful and lead to sterile abscesses.
- arrhythmias & nephrotoxicity

Chemotherapy for toxoplasmosis

- One of the most common infections in humans is caused by the protozoan Toxoplasma gondii, which is transmitted to humans when they consume raw or inadequately cooked infected meat.
- An infected pregnant woman can transmit the organism to her fetus.
- Cats are the only animals that shed oocysts, which can infect other animals as well as humans.
- The treatment of choice for this condition is a combination of sulfadiazine and pyrimethamine.
- Leucovorin is commonly administered to protect against folate deficiency.

Chemotherapy for giardiasis

- Giardia lamblia
- Ingestion, usually from contaminated drinking water, leads to infection.
- Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immune-suppressed patients
- The treatment of choice is met-ronidazole for 5 days.
- One alternative agent is tinidazole, which is equally effective as metronidazole in the treatment of giardiasis but with a much shorter course of therapy (2 grams given once).
- Nitazoxanide is equally efficacious as metronidazole and, in comparison, has a two-day-shorter course of therapy.

Antimalarial drugs

- Four species of plasmodium typically cause human malaria:

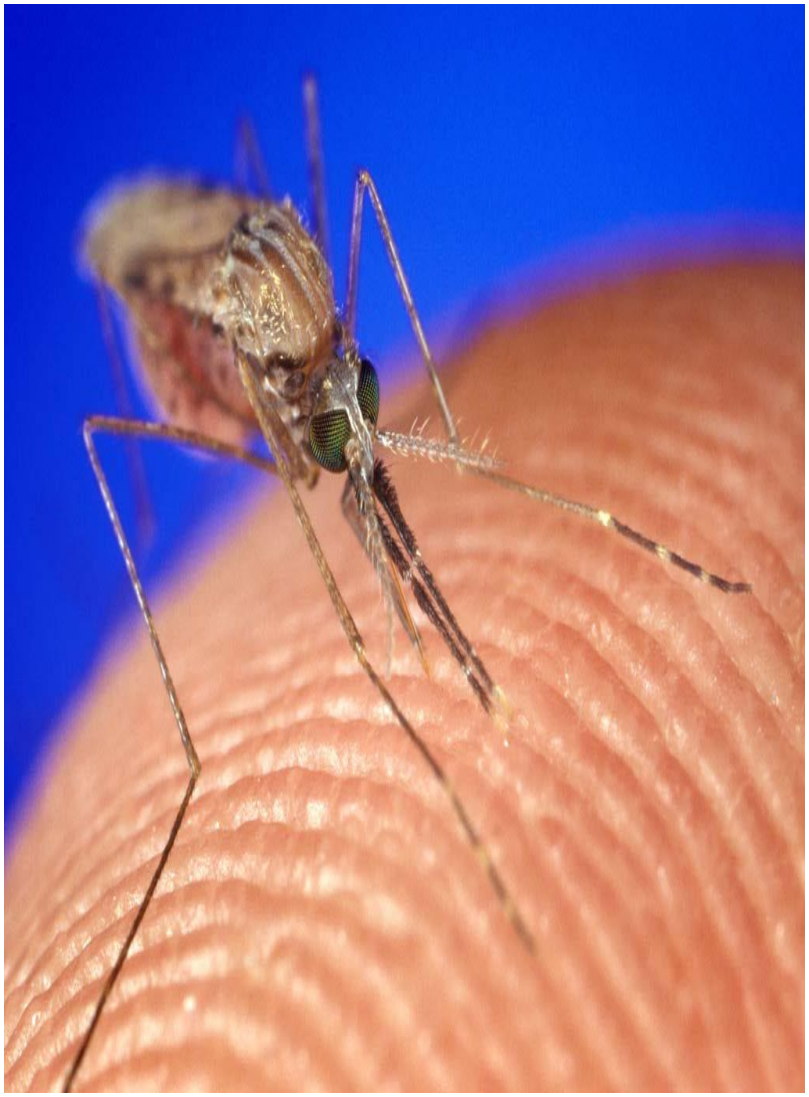
➢ ***Plasmodium falciparum***,

➢ *P vivax,*

➢ *P malariae,*

➢ *P ovale.*

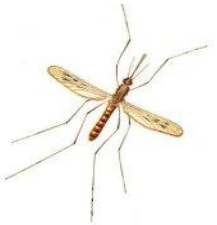
➢ *P knowlesi*, is primarily a pathogen of monkeys



The incubation period of malaria is 10–35 days.

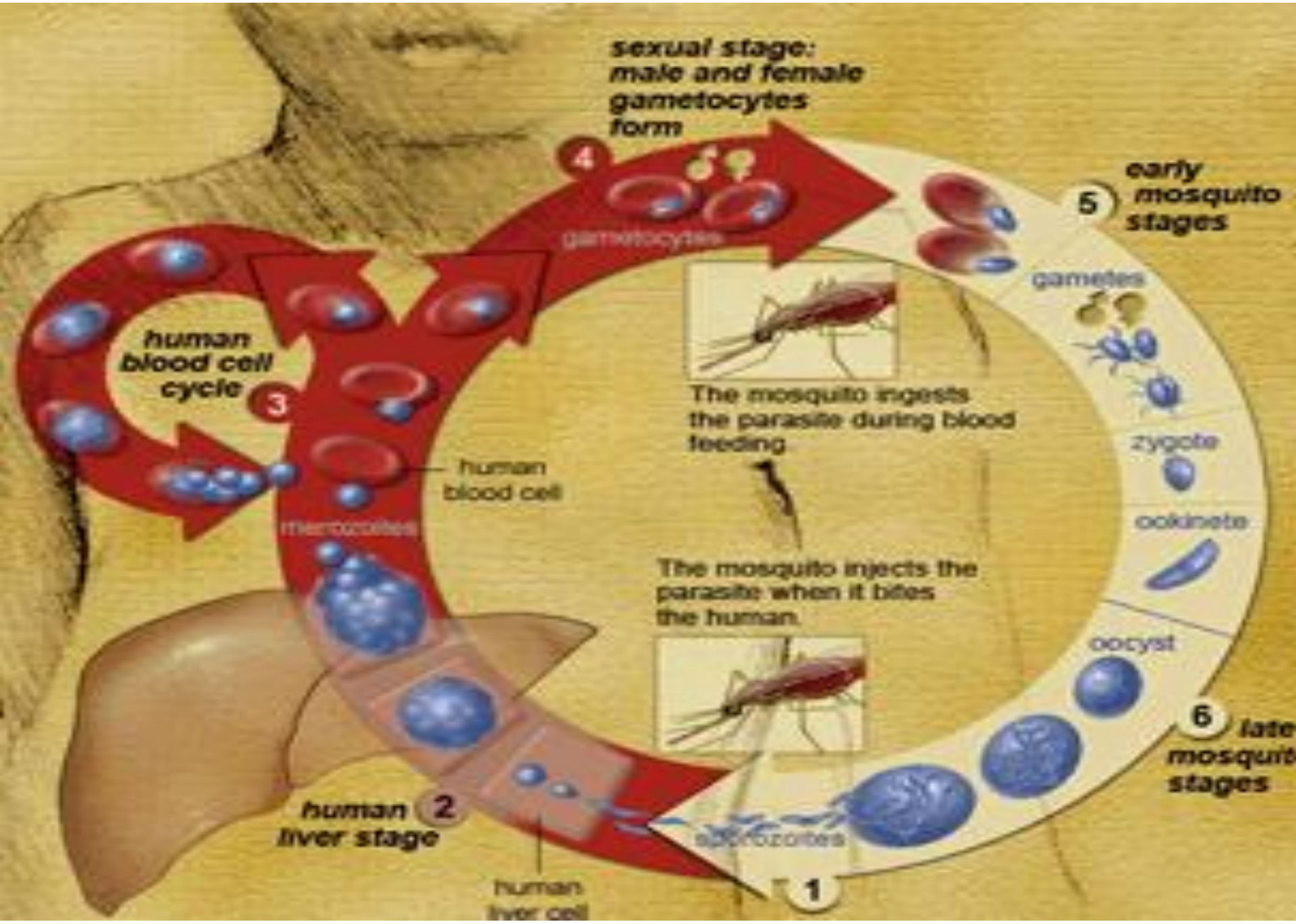
Female anopheles mosquitoes

require a blood meal for egg production and in the process of feeding they inject salivary fluid containing sporozoites into humans. Since no drugs are effective against sporozoites, *infection with the malaria parasite cannot be prevented*.



Hepatic cycle

Sporozoites enter liver cells where they develop into **tissue (liver) schizonts** which form large numbers of **merozoites** which, usually after 5–16 days but sometimes after months or years, are released into the circulation. Plasmodium falciparum differs in that it has no persistent hepatic cycle.


sexual stage:
male and female
gametocytes
form
4
gametocytes
5
early
mosquito
stages
gametes
zygote
ookinete
oocyst
6
late
mosquit
stages
human
blood cell
cycle
3
merozoites
human
blood cell
The mosquito ingests
the parasite during blood
feeding
The mosquito injects the
parasite when it bites
the human
human
liver stage
2
sporozoites
1
human
liver cell

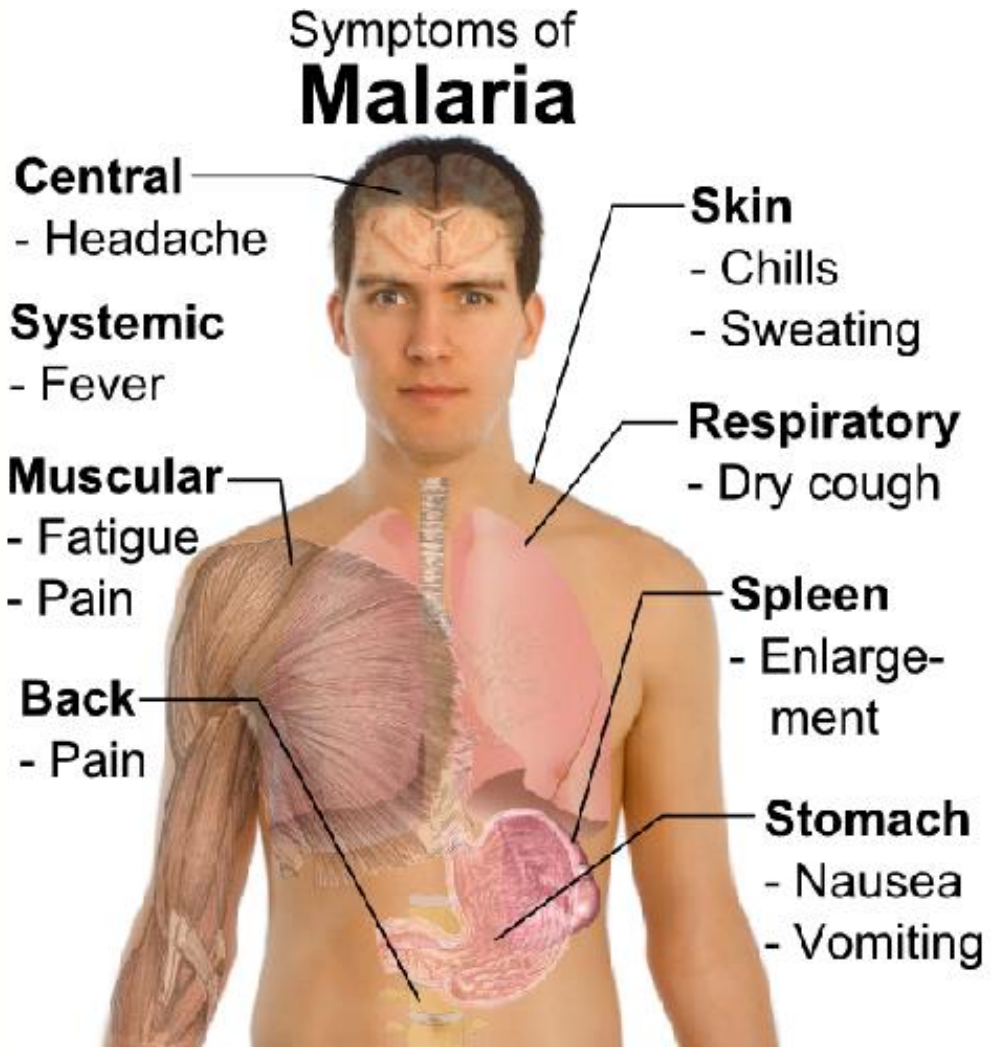
Parasite life cycle

An anopheline mosquito inoculates plasmodium **sporozoites** to initiate human infection. Circulating sporozoites rapidly invade liver cells, and exoerythrocytic stage tissue **schizonts** mature in the liver. **Merozoites** are subsequently released from the liver and invade erythrocytes.

Only erythrocytic parasites cause clinical illness. Sexual stage **gametocytes** also develop in erythrocytes before being taken up by mosquitoes, where they develop into infective **sporozoites.**

Treatment of malaria

- Type of malaria
- Knowledge of regional resistance
- Severity of illness (oral vs. intravenous)
- Age of patient



DRUG CLASSIFICATION

Tissue schizonticides: eliminate developing or dormant **liver** forms**;**

Blood schizonticides : act on **erythrocytic** parasites**;**

Gametocides : kill **sexual stages** and prevent transmission to mosquitoes**.**

**Radical cure: ** eliminate both hepatic and erythrocytic stages. Not available.

CHLOROQUINE

- For treatment and chemoprophylaxis since the 1940s,(drug resistance).

➢Oral use

Antimalarial Action:

❖Highly effective **blood** schizonticide.

❖ Moderately effective against **gametocytes** of *P vivax, P ovale,* and *P malariae* but not against those of *P falciparum.*

❖ Not active against liver stage parasites

Mechanism Of Action

Acts by :

concentrating in parasite **food vacuoles**, preventing the biocrystallization of the hemoglobin breakdown product, **heme**, into **hemozoin**, and thus eliciting parasite toxicity due to the buildup of free heme.

Clinical Uses

1.Treatment.
2.Chemoprophylaxis.

3.Amebic Liver Abscess.

- Drug of choice in the treatment of nonfalciparum and sensitive falciparum malaria.
- It is still used to treat falciparum : safety, low cost, antipyretic properties, and partial activity.
- Does not eliminate dormant liver forms of *P vivax* and *P ovale,* and for that reason **Primaquine** must be added for the radical cure of these species.

Adverse Effects

Usually very well tolerated

Pruritus, GI disturbance, headache, malaise, blurring of vision, and urticaria

Rare : hemolysis in G6PD-deficient persons, impaired hearing, agranulocytosis, alopecia, bleaching of hair, hypotension,

Large IM injections or rapid IV infusions : severe hypotension and respiratory and cardiac arrest.

QUININE & QUINIDINE

- First-line therapies for falciparum malaria.
- Oral administration.
- Higher plasma levels and half-life in infected persons than in healthy controls, but toxicity is not increased, apparently because of increased protein binding.
- MOA: is unknown, it may act like chloroquine

Antimalarial action

Quinine:

- Is rapid-acting, highly effective **blood** schizonticide against the 4 species of human malaria parasites.
- **Gametocidal** against *p vivax* and *p ovale* but not *p falciparum*
- Not active against liver stage parasites.

Clinical Uses:

Parenteral Treatment Of Severe Falciparum Malaria

Quinidine : parenteral treatment of severe falciparum malaria. continuous IV infusion; cardiac monitoring.

change to an effective oral agent as soon as the patient has improved and can tolerate oral medications.

Oral Treatment Of Falciparum Malaria

Quinine sulfate : uncomplicated falciparum malaria

± second drug (most often doxycycline or, in children, clindamycin) to shorten quinine's duration of use (usually to 3 days) and limit toxicity.

Adverse Effects

- **Cinchonism:**
  - Tinnitus,
  - Headache,
  - Nausea,
  - Dizziness,
  - Flushing,
  - Visual Disturbances
- **Black water fever**
  - rare severe illness
  - marked hemolysis
- **Hypersensitivity reactions**
- **Hypoglycemia**
- **Too-rapid IV infusions : Severe hypotension**
- **IV Quinidine : ECG abnormalities.**

MEFLOQUINE

Used in chloroquine-resistant strains of *P falciparum* and other species.

Is chemically related to quinine.

Can only be given **orally** because severe local irritation occurs with parenteral use.

Has strong **blood schizonticidal** activity against *P falciparum* and *P vivax,*

it is not active against hepatic stages or gametocytes.

MOA: is unknown.

Adverse Effects

- GI disturbance, Rash, Dizziness,
- Leukocytosis, Thrombocytopenia,
- Aminotransferase Elevations
- Arrhythmias , bradycardia.

Considered safe in young children and throughout pregnancy.

PRIMAQUINE

- **Hepatic stages** of all human malaria parasites.
- **Chemoprophylaxis** against all malarial species.
- It is the only available agent active against the **dormant stages** of *p vivax* and *p ovale.*
- **Gametocidal** against the 4 human malaria species.
- Acts against **erythrocytic** stage parasites, but this activity is too weak to play an important role.
- MOA: is unknown.

Adverse Effects

Generally well tolerated.

- GI disturbance, Headache
- Leukopenia, Agranulocytosis,
- Cardiac Arrhythmias, Hemolysis

It is never given **parenterally** because it may induce marked **hypotension**.

It should be avoided in pregnancy because the fetus is relatively G6PD-deficient and thus at risk of hemolysis.

ATOVAQUONE

For treatment and prevention of malaria.

Only administered orally.

MOA: disrupting mitochondrial electron transport.

It is active against tissue and erythrocytic schizonts,

A/E: GI disturbance, Fever, Rash, Headache

INHIBITORS OF FOLATE SYNTHESIS

Pyrimethamine ,Proguanil

•Used in combination regimens, in the treatment and prevention of malaria.

•Slowly but adequately absorbed from the GIT.

Fansidar, a fixed combination of the sulfonamide **sulfadoxine** and **pyrimethamine** .

➢Act slowly against **erythrocytic** forms of susceptible strains of all human malaria species.

➢**Proguanil** also has some activity against **hepatic** forms.

➢Neither drug is adequately gametocidal or effective against the persistent liver stages of *p vivax* or *p ovale*

Mechanism Of Action

Selectively inhibit **plasmodial dihydrofolate reductase,** a key enzyme in the pathway for synthesis of folate.

Sulfonamides and sulfones inhibit another enzyme in the folate pathway, **dihydropteroate synthase.**

A/E : GI Symptoms, Skin Rashes, Itching.

Proguanil: Mouth Ulcers, Alopecia .

Proguanil , Fansidar are considered safe in pregnancy

Antibiotics

Folate antagonists and **sulfonamides** ,**bacterial protein synthesis inhibitors**

❖None should be used as single agents because their action is much slower than that of standard antimalarials.

❖**Tetracycline** : erythrocytic schizonts , but not active against liver stages.

❖**Doxycycline** : falciparum malaria in conjunction with quinine, allowing a shorter and better-tolerated course of that drug, it has also become a standard chemoprophylactic drug,

❖**Clindamycin** , **Azithromycin** , **Fluoroquinolones**

HALOFANTRINE & LUMEFANTRINE

Against **erythrocytic** (but not other) stages of all four malaria species.

MOA: unknown.

A/E : GI disturbance, cough, rash, headache, pruritus, and elevated liver enzymes, dose-related prolongation of QT and PR intervals.

ARTEMISININ & ITS DERIVATIVES

Artemisinin: used orally.

Analogs are:

- **Artesunate** (water-soluble; oral, IM, IV and rectally),
- **Artemether** (lipid-soluble; oral, IM, and rectally),
- **Dihydroartemisinin** (water-soluble; oral).
- They are very rapidly acting **blood schizonticides** against all human malaria parasites, no effect on hepatic stages.

MOA

- The parasite when it infects a RBC, it consumes Hb within its digestive vacuole, liberating **free heme**, The iron in heme interacts with Artemisinin producing **reactive oxygen radicals** which damage the parasite leading to its death
- Or inhibition of a parasite calcium transporter.

Artemisinin-based combination therapy is now the standard for treatment of uncomplicated falciparum malaria in nearly all areas endemic for falciparum malaria.

A/E: GI disturbance, dizziness, neutropenia, anemia, hemolysis, elevated liver enzymes, allergic reactions.

Antiviral Agents

Overview of Viruses

- Obligate intracellular parasites
- Replication dependent on synthetic processes of host cell
- Smallest, most primitive living thing
- Viruses consist of genetic materials (DNA or RNA) surrounded by a protective coat of protein

- They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes.
- Viral reproduction uses much of the host's metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the host.
- Therapy for viral diseases is further complicated by the fact that the clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated.
- Some antiviral agents are useful as prophylactic agents.

Some human diseases caused by viruses

AIDS

Burkitt's lymphoma

chicken pox

colds

Colorado tick fever

dengue

encephalitis

fever blisters

genital warts

gastroenteritis

genital herpes

German measles

hepatitis

influenza

leukemia

liver cancer

measles

mononucleosis

mumps

oral herpes

polio

rabies

shingles

smallpox

virus hemorrhagic fever

warts

yellow fever

Antiviral Agents

General comments:

Restricted spectrum compared to antibiotics

No standardized *in vitro* susceptibility tests

Most inhibit viral replication; cure depends on host immune system to eradicate

Many need to be activated by viral and cellular enzymes before exerting antiviral effect

Current antiviral drugs do not eliminate non-replicating or latent virus

Single nucleotide mutations in target viral protein enough to cause drug resistance

Antiviral drug classification

A. Non-Retroviral Antiviral Agents

1. Anti-herpesvirus Agents
2. Anti-influenza Agents
3. Anti-hepatitis Agents

B. Antiretroviral Agents

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)
2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)
3. Protease Inhibitors (PI)
4. Entry Inhibitors
5. Integrase Strand Transfer Inhibitors

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A. Non-Retroviral Antiviral Agents

1. Anti-herpesvirus Agents

a. Nucleoside Analogs

General Mechanism of Action:

Taken up by host cells

Most converted by viral and cellular enzymes to the active triphosphate form

The triphosphate form inhibits:

- DNA polymerase
- Reverse transcriptase
- RNA polymerase

Additionally, some antivirals get incorporated into DNA leading to chain termination

Viral resistance

i. Acyclovir

Mechanism of action:

- inhibit viral DNA polymerase by competition with nucleosides
- incorporation and nascent DNA chain termination

Indications:

- treatment of HSV and VZV infections
- prophylactic for CMZ infections
- treatment of chickenpox (VZV) in children

Therapeutic Effects:

- for HSV: shortens healing time of lesions; reduces viral shedding
- for VZV: shortens acute pain; reduces severity of postherpetic neuralgia

Adverse effects:

- GI, headache, rash

ii. Valacyclovir

Mechanism of action:

- ester prodrug of acyclovir with better bioavailability (prodrug of a prodrug!)
- inhibit viral DNA polymerase by competition with nucleosides
- incorporation and nascent DNA chain termination

Indications:

- treatment of HSV and VZV infections
- prophylactic for CMZ infections

Therapeutic Effects:

- for HSV: shortens healing time of lesions; reduces viral shedding
- for VZV: shortens acute pain; reduces severity of postherpetic neuralgia

Adverse effects:

- GI, headache, rash

iii. Penciclovir

Mechanism of action:

inhibit viral DNA polymerase by competition with nucleosides

Indications:

treatment of HSV in topical formulation

Therapeutic Effects:

for HSV: shortens healing time of lesions; reduces viral shedding

Adverse effects:

rash

iv. Famciclovir

Mechanism of action:

ester prodrug of penciclovir with better bioavailability (prodrug of a prodrug)

inhibit viral DNA polymerase by competition with nucleosides

Indications:

treatment of HSV and VZV infections

Therapeutic Effects:

for HSV: shortens healing time of lesions; reduces viral shedding

for VZV: shortens acute pain; reduces severity of postherpetic neuralgia

Adverse effects:

GI, headache, rash

v. Ganciclovir

Mechanism of action:

inhibit viral DNA polymerase by competition with nucleosides

Indications:

drug of choice for CMV infections: retinitis, pneumonia, colitis

100X more active against CMV than acyclovir

Therapeutic Effects:

treat or prevent cytomegalovirus (CMV) infections

available in slow-release gel for intravitreous administration

Adverse effects:

leukopenia and thrombocytopenia

vi. Cidofovir

Mechanism of action:

inhibit viral DNA polymerase by competition with nucleosides

Indications:

i.v. only for CMV infections resistant to ganciclovir

Therapeutic Effects:

treat or prevent cytomegalovirus (CMV) infections

Adverse effects:

leukopenia and thrombocytopenia

vii. Trifluridine

Mechanism of action:

- irreversible inhibition of thymidylate synthetase
- inhibits viral DNA polymerase by competition with nucleosides

Indications:

- for HSV infections causing herpetic keratoconjunctivitis and epithelial keratitis

Therapeutic Effects:

- topical only formulation for treatment of ocular herpesvirus infections

Adverse effects:

- ocular irritation, redness, itching

Fomivirsen

An antisense oligonucleotide directed against CMV mRNA.

Its use is limited to those who cannot tolerate or have failed other therapies for CMV retinitis

A/E: iritis, vitritis, changes in vision

Vidarabine

It is one of the most effective of the nucleoside analogs.

It is active against HSV-1 and 2, VZV

Vidarabine is only available as an ophthalmic oinment.

b. Other agents

i. Foscarnet

Mechanism of action:

- an inorganic pyrophosphate analog
- blocks pyrophosphate-binding sites on viral DNA polymerase preventing attachment of nucleotide precursors
- only non-nucleoside drug for treatment of herpesvirus

Indications:

- i.v. only for use in CMV and HSV infections resistant to first-line drugs

Therapeutic Effects:

- treatment of CMV and HSV infections in immunocompromised ptx

Adverse effects:

- nephrotoxicity, hypocalcemia (chelates divalent cations)

Antiviral drug classification

A. Non-Retroviral Antiviral Agents
   1. Anti-herpesvirus Agents
   2. Anti-influenza Agents
   3. Anti-hepatitis Agents

Inhibitors of viral uncoating

i. Amantadine

Mechanism of action:

blocks M2 proton ion channel preventing acidification and fusion of virus

Indications:

prevention and treatment of influenza A (only) infections

Therapeutic Effects:

decrease in the severity and length of influenza A infections

Adverse effects:

GI, and CNS effects including nervousness, insomnia, and anorexia

ii. Rimantadine

Mechanism of action:

blocks M2 proton ion channel preventing acidification and fusion of virus

more potent than amantadine

Indications:

prevention and treatment of influenza A (only) infections

Therapeutic Effects:

decrease in the severity and length of influenza A infections

Adverse effects:

GI, and CNS effects including nervousness, insomnia, and anorexia

Less incidence of adverse effects than amantadine

-Neurominidase inhibitors

i Oseltamivir

Mechanism of action:

- inhibits neuroaminidases of both influenza A and B viruses preventing release of virions from infected cells
- neuroaminidase inhibition also prevents spreading of virions in respiratory tract by leaving mucus intact

Indications:

- prevention and treatment of influenza A and B

Therapeutic Effects:

- decrease in the severity and length of influenza A and B infections

Adverse effects:

- minor GI complaints

ii. Zanamivir

Mechanism of action:

- inhibits neuroaminidases of both influenza A and B viruses preventing release of virions from infected cells
- neuroaminidase inhibition also prevents spreading of virions in respiratory tract by leaving mucus intact

Indications:

- prevention and treatment of influenza A and B

Therapeutic Effects:

- nasal spray only formulation; decreases in the severity and length of influenza A and B infections

Adverse effects:

- minor respiratory complaints

Ribavirin

- Ribavirin is a synthetic guanosine analog. It is effective against a broad spectrum of RNA and DNA viruses.
- For example, ribavirin is used in treating infants and young children with severe ReSV infections. [It is not indicated for use in adults with RSV.]
- Ribavirin is also effective in chronic hepatitis C infections when used in combination with interferon-α.
- Ribavirin may reduce the mortality and viremia of Lassa fever.

- It is effective orally and intravenously
- Absorbtion is increased if the drug is taken with a fatty meal
- A/E: dose-dependent transient anemia, elevated bilirubin, contraindicated in pregnancy,
- Aerosol formulations of it may be safer

Antiviral drug classification

A. Non-Retroviral Antiviral Agents
   1. Anti-herpesvirus Agents
   2. Anti-influenza Agents
   3. Anti-hepatitis Agents

A. Non-Retroviral Antiviral Agents

3. Anti-hepatitis Agents

a. Ribavirin

b. Adefovir dipivoxil

Mechanism of action:

ester prodrug of adefovir, a nucleotide analog of adenosine

converted to active diphosphate form which inhibits RT and vDNA pol

selectivity for HBV DNA polymerase over host cell polymerase

Indications:

treatment of chronic hepatitis B (HBV) infections

Therapeutic Effects:

reduces viral load of serum HBV by 100-fold

normalizes liver histology and enzymes by 48 weeks

Adverse effects:

nephrotoxicity

c. Lamivudine

Mechanism of action:

nucleoside analog that inhibits both HIV RT and HBV DNA polymerase

host cell kinases convert to active triphosphate form

Indications:

treatment of chronic hepatitis B (HBV) infections

(also used in antiretroviral therapy)

Therapeutic Effects:

reduces viral load of serum HBV

normalizes liver histology and enzymes

Adverse effects:

mild: neutropenia, headache and nausea

d. Interferons (pegIFN alfa 2a, 2b)

Mechanism of action:

antiviral, anticancer and immunomodulating endogenous chemokines
several sites of action in viral cycle; inhibit translation of viral proteins
inhibits both hepatitis B and C viruses

Indications:

treatment of chronic HBV and HCV infections
treatment of condylomata acuminata (genital warts) due to HPV
(also for Kaposi's sarcoma in HIV ptx; malignancies, and multiple sclerosis)

Therapeutic Effects:

in combination with ribavarin, reduces viral load of serum HBV and HCV
intralesion injections for genital warts effective in 50% of ptx

Adverse effects:

flu-like syndrome, bone marrow suppression; CNS

Antiviral drug classification

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B. Antiretroviral Agents

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)

a. Zidovudine (azidothymidine:AZT)

Mechanism of action:

nucleoside analog activated to triphosphate form by host cell kinases

inhibits HIV RT function

incorporation by HIV RT into proviral DNA causes chain termination

Indications:

treatment of HIV infections

prevention of maternal to infant HIV transmission

Therapeutic Effects:

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

…. granulocytopenia and anemia; headache, nausea, insomnia, ……..myalgias

B. Antiretroviral Agents

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)

b. Lamivudine

Mechanism of action:

nucleoside analog that inhibits both HIV RT and HBV DNA polymerase

host cell kinases convert to active triphosphate form

Indications:

treatment of HIV infections in combination with other antiretroviral agents

(also used in treatment of chronic hepatitis B (HBV) infections)

Therapeutic Effects:

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

Adverse effects:

mild: neutropenia, headache and nausea

B. Antiretroviral Agents

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)

c. Stavudine and d. Didanosine

Mechanism of action:

nucleoside analogs activated to triphosphate form by host cell kinases

inhibits HIV RT function

incorporation by HIV RT into proviral DNA causes chain termination

Indications:

treatment of HIV infections

Therapeutic Effects:

usually not first-line treatment

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

……..peripheral neuropathy; HIV lipodystrophy syndrome (fat wasting)

……didanosine also pancreatitis

B. Antiretroviral Agents

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)

e. Abacavir

Mechanism of action:

nucleoside analogs activated to triphosphate form by host cell kinases

inhibits HIV RT function

incorporation by HIV RT into proviral DNA causes chain termination

Indications:

treatment of HIV infections

Therapeutic Effects:

usually not first-line treatment

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

…….hypersenstivity rx; repeat exposure often fatal

B. Antiretroviral Agents

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)

f. Emtricitabine

Mechanism of action:

nucleoside analogs activated to triphosphate form by host cell kinases
inhibits HIV RT function
incorporation by HIV RT into proviral DNA causes chain termination
antiviral activity 10-fold greater than lamivudine

Indications:

treatment of HIV infections in combinations with other agents

Therapeutic Effects:

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

……mild; pigmentation of skin

B. Antiretroviral Agents

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)

g. Tenofovir

Mechanism of action:

nucleoside analogs activated to triphosphate form by host cell kinases
inhibits HIV RT function
incorporation by HIV RT into proviral DNA causes chain termination

Indications:

treatment of HIV infections in combinations with other agents

Therapeutic Effects:

usually not first-line treatment

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

……..mild; flatulence

Antiviral drug classification

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   3. Protease Inhibitors (PI)
   4. Entry Inhibitors
   5. Integrase Strand Transfer Inhibitors

B. Antiretroviral Agents

2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

a. Nevirapine

Mechanism of action:

non-competitively binds to allosteric site on HIV RT enzyme
causes conformational change which inhibits HIV RT function
no host cell activation required as in NRTIs

Indications:

treatment of HIV infections

Therapeutic Effects:

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

…….rash; Stevens-Johnson syndrome rarely

B. Antiretroviral Agents

2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

b. Efavirenz

Mechanism of action:

non-competitively binds to allosteric site on HIV RT enzyme
causes conformational change which inhibits HIV RT function
no host cell activation required as in NRTIs

Indications:

treatment of HIV infections

Therapeutic Effects:

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

CNS: dizziness, insomnia, impaired concentration, psychotic episodes

Antiviral drug classification

A. Non-Retroviral Antiviral Agents
   1. Anti-herpesvirus Agents
   2. Anti-influenza Agents
   3. Anti-hepatitis Agents

B. Antiretroviral Agents
   1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)
   2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)
   3. **Protease Inhibitors (PI)**
   4. Entry Inhibitors
   5. Integrase Strand Transfer Inhibitors

B. Antiretroviral Agents

3. Protease Inhibitors (PI)

a. Saquinavir

Mechanism of action:

first approved peptide-like agent that inhibits HIV protease

selective for homodimer of HIV protease; homolog in host are monomer

blocks cleavage of gag-pol precursor proteins and prevents maturation

Indications:

treatment of HIV infections

Therapeutic Effects:

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

GI including N/V, diarrhea, anorexia and taste perversion

…….HIV lipodystrophy syndrome

B. Antiretroviral Agents

3. Protease Inhibitors (PI)

b. Atazanivir

Mechanism of action:

peptide-like agent that inhibits HIV protease

selective for homodimer of HIV protease; homolog in host are monomer

blocks cleavage of gag-pol precursor proteins and prevents maturation

Indications:

treatment of HIV infections

Therapeutic Effects:

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

hyperbilirubinemia not associated with other hepatotoxicity

less likely to cause HIV lipodystrophy syndrome

B. Antiretroviral Agents

3. Protease Inhibitors (PI)

c. Ritonavir

Mechanism of action:

peptide-like agent that inhibits HIV protease

selective for homodimer of HIV protease; homolog in host are monomer

blocks cleavage of gag-pol precursor proteins and prevents maturation

Indications:

treatment of HIV infections

most potent inhibitor of CYP3A4 so used in *boosted therapy* with other PI

Therapeutic Effects:

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

GI including N/V, diarrhea, anorexia and taste perversion

HIV lipodystrophy syndrome

B. Antiretroviral Agents

3. Protease Inhibitors (PI)

d. Lopinavir

Mechanism of action:

peptide-like agent that inhibits HIV protease

selective for homodimer of HIV protease; protease in host cell is monomer

blocks cleavage of gag-pol precursor proteins and prevents maturation

similar to Ritonavir but 10-fold more potent

Indications:

treatment of HIV infections

Therapeutic Effects:

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

GI including N/V, diarrhea, anorexia and taste perversion

……..HIV lipodystrophy syndrome

Indinavir

It has the shortest half-life of the protease inhibitors

It characteristically causes nephrolithiasis and hyperbilirubinemia

Nelfinavir

Fosamprenavir

Lopinavir

Tipranavir

Darunavir

Antiviral drug classification

A. Non-Retroviral Antiviral Agents
   1. Anti-herpesvirus Agents
   2. Anti-influenza Agents
   3. Anti-hepatitis Agents

B. Antiretroviral Agents
   1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)
   2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)
   3. Protease Inhibitors (PI)
   4. **Entry Inhibitors**
   5. Integrase Strand Transfer Inhibitors

B. Antiretroviral Agents

4. Entry Inhibitors

a. Enfuvirtide

Mechanism of action:

large peptide that binds to HIV gp 41 and blocks fusion

i.v. route of administration

Indications:

treatment of HIV infections in combination with other antiretroviral drugs

Therapeutic Effects:

usually not first-line treatment, used when other drugs ineffective

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

injection site irritation

B. Antiretroviral Agents

4. Entry Inhibitors

b. Maraviroc

Mechanism of action:

antagonist of CCR5 co-receptor on CD4 cells

prevents binding of HIV glycoproetin 120 (gp120) to CCR5 co-receptor

inhibits CCR5-tropic HIV entry (HIV can also use CXCR4 co-receptor)

Indications:

treatment of HIV infections in combination with other antiretroviral drugs

Therapeutic Effects:

usually not first-line treatment

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

↓mortality and opportunistic infections, gain weight, better quality of life, delays signs and symptoms of AIDS

Adverse effects:

……Hepatotoxicity; may be preceded by systemic allergic reaction

Antiviral drug classification

A. Non-Retroviral Antiviral Agents
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B. Antiretroviral Agents
   1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)
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   3. Protease Inhibitors (PI)
   4. Entry Inhibitors
   5. **Integrase Strand Transfer Inhibitors**

B. Antiretroviral Agents

5. Integrase Strand Transfer Inhibitors

a. Raltegravir

Mechanism of action:

recruits divalent cation binding to core area of HIV integrase

prevents HIV integrase from integrating viral DNA into host DNA

Indications:

treatment of HIV infections

Therapeutic Effects:

usually not first-line treatment

in combination with other antiretroviral drugs, reduces viral load of HIV and increases CD4 cells

Adverse effects:

headache, GI and N/V

Antiviral vaccines

Measles
Mumps
Rubella
Polio
Hepatitis A and B
Herpes zoster
Human papillomavirus
Influenza A and B
Rotavirus
Rabies
Monkeypox
Smallpox
Japanese encephalitis
Yellow fever