Chapter 56 Antileprotic Drugs

Leprosy, caused by *Mycobacterium leprae*, has been considered incurable since ages and bears a social stigma. Due to availability of effective antileprotic drugs now, it is entirely curable, but deformities/defects already incurred may not reverse.

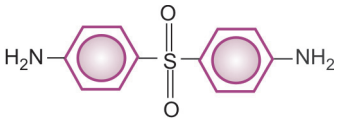
Chaulmoogra oil with weak antileprotic property was used in Indian medicine for centuries. Shortly after the demonstration of antibacterial property of sulfonamides, congeners were tested and dapsone, the parent sulfone, was found to be an active antileprotic. Demonstration of its efficacy in experimental tuberculosis and leprosy led to clinical trials in the 1940s, and since then it is the sheet-anchor of treatment of leprosy. Few other sulfones were added, but none could excel dapsone. Clofazimine was inducted in the early 1960s as a useful adjunct, and soon rifampin, developed for TB, was found to be a rapidly acting cidal drug for *M.leprae* as well. Lately good antileprotic activity has been detected in some fluoroquinolones, macrolides and minocycline.

CLASSIFICATION

1. *Sulfone*	Dapsone (DDS)
2. *Phenazine derivative*	Clofazimine
3. *Antitubercular drugs*	Rifampin, Ethionamide
4. *Other antibiotics*	Ofloxacin, Moxifloxacin, Minocycline, Clarithromycin

Dapsone (DDS)

It is diamino diphenyl sulfone (DDS), the simplest, oldest, cheapest, most active and most commonly used member of its class. All other sulfones have become obsolete.



DAPSONE

Activity and mechanism Dapsone is chemically related to sulfonamides and has the same mechanism of action, i.e. inhibition of PABA incorporation into folic acid by folate synthase. The antibacterial action of dapsone is antagonized by PABA. It is leprostatic at very low concentrations, while growth of many other bacteria sensitive to sulfonamides is arrested at relatively higher concentrations. Specificity for *M. leprae* may be due to difference in the affinity of its folate synthase. Doses of dapsone needed for treatment of acute pyogenic bacterial infections are too toxic, so not used.

Dapsone-resistance among *M. leprae*, first noted in 1964, has spread and has necessitated the use of multidrug therapy (MDT). When dapsone resistance is encountered in an untreated patient, it is called '*primary*', and indicates that the infection was contacted from a patient harbouring resistant bacilli. Resistance which develops during monotherapy in an individual patient with dapsone is called '*secondary*'.The incidence of primary dapsone resistance reported from different parts of the world, from time-to-time, has been variable; whereas secondary dapsone resistance occurred in upto 20% patients treated with monotherapy. The mechanism of secondary resistance appears to be the same as for *M. tuberculosis,* i.e. selective propagation of resistant bacilli over time. Dapsone resistant *M. leprae* have mutated folate synthase which has lower affinity for dapsone. However, the peak serum concentration of dapsone after 100 mg/day dose exceeds MIC for *M. leprae* by nearly 500 times; it continues to be active against low to moderately resistant bacilli, and the risk of relapse due to dapsone resistance is reported to be 2–3%. In addition to resistance, there is the problem of '*persisters*', that are drug

sensitive bacilli which become dormant, hide in some tissues and are not affected by any drug. They may stage a comeback after the drug is withdrawn.

Dapsone is active against certain protozoa as well. Combined with pyrimethamine, it is an alternative to sulfadoxine-pyrimethamine for *P. falciparum* and *Toxoplasma gondii* infections, as well as for the fungus *Pneumocystis jirovecii*. Antiinflammatory property has been detected in dapsone.

Pharmacokinetics Dapsone is completely absorbed after oral administration and is widely distributed in the body, though penetration in CSF is poor. It is 70% plasma protein bound, but more importantly it is concentrated in skin (especially lepromatous skin), muscle, liver and kidney.

Dapsone is acetylated as well as glucuronide and sulfate conjugated in liver. Metabolites are excreted in bile and reabsorbed from intestine, so that ultimate excretion occurs mostly in urine. The plasma t½ of dapsone is variable, though often > 24 hrs. The drug is cumulative due to retention in tissues and enterohepatic circulation. Elimination takes 1–2 weeks or longer.

DAPSONE 25, 50, 100 mg tab.

Adverse effects Dapsone is generally well tolerated at doses 100 mg/day or less.

Mild haemolytic anaemia is common. It is a dose-related toxicity—reflects oxidising property of the drug. Patients with G-6-PD deficiency are more susceptible; doses > 50 mg/day produce haemolysis in such subjects.

Gastric intolerance—nausea and anorexia are frequent in the beginning, decrease later.

Other side effects are methaemoglobinaemia, headache, paresthesias, mental symptoms and drug fever.

Cutaneous reactions include allergic rashes, fixed drug eruption, hypermelanosis, phototoxicity and rarely exfoliative dermatitis.

Hepatitis and agranulocytosis are rare complications.

Sulfone syndrome It is the reaction which develops 4–6 weeks after starting dapsone treatment: consists of fever, malaise, lymph node enlargement, desquamation of skin, jaundice and anaemia. It is generally seen in malnourished patients, and has become more frequent after the introduction of MDT. Some or all of the above symptoms may occur. Its treatment consists of stopping dapsone and instituting corticosteroid therapy along with supportive measures.

Contraindications Dapsone should not be used in patients with severe anaemia (Hb < 7 g/dl), G-6-PD deficiency and in those showing hypersensitivity reactions.

Other use In combination with pyrimethamine, dapsone can be used for chloroquine-resistant malaria, toxoplasmosis and *P. jirovecii* infection.

Clofazimine (Clo)

It is a dye with leprostatic and antiinflammatory properties. The putative mechanisms of antileprotic action of clofazimine are:

- Interference with template function of DNA in *M.leprae*
- Alteration of membrane stucture and its transport function.
- Disruption of mitochondrial electron transport chain.

When used alone, the clinical response to clofazimine is slower than that to dapsone, and resistance develops in 1–3 years. Dapsone-resistant *M. leprae* respond to clofazimine, but apparently after a lag period of about 2 months.

Clofazimine is orally active (40–70% absorbed). It accumulates in macrophages and gets deposited in many tissues including subcutaneous fat, as needle-shaped crystals. However, entry in CSF is poor. The t½ is 70 days so that intermittent therapy is possible.

CLOFOZINE, HANSEPRAN 50, 100 mg cap.

Clofazimine is used as a component of multidrug therapy (MDT) of leprosy. Because of its antiinflammatory property, it is valuable in lepra reaction.

Occasionally, it is used as a component of MDT for MAC infection.

Adverse effects In the doses employed for MDT, clofazimine is well tolerated.

Skin The major disadvantage is reddish-black discolouration of skin, especially on exposed parts. Discolouration of hair and body secretions may also occur. Dryness of skin and itching is often troublesome. Acneform eruptions and phototoxicity have been noted. Conjunctival pigmentation may create cosmetic problem.

GI symptoms Nausea, anorexia, abdominal pain, weight loss and enteritis with intermittent loose stools can occur, particularly when higher doses are used to control lepra reaction. The early syndrome is a reflection of irritant effect of the drug—subsides with dose adjustment and by taking the drug with meals. A late syndrome occurring after few months of therapy—is due to deposition of clofazimine crystals in the intestinal submucosa.

Clofazimine is to be avoided during early pregnancy and in patients with liver or kidney damage.

Rifampin (R)

This important tuberculocidal drug is also the most potent cidal drug for *M.leprae*; rapidly renders leprosy patients noncontagious. Upto 99.99% *M.leprae* are killed in 3–7 days by 600 mg/day dose. Clinical effects of rifampin are very rapid; nasal symptoms in lepromatous leprosy subside within 2–3 weeks and skin lesions start regressing by 2 months. However, nerve damage already incurred is little benefited. Moreover, it is not satisfactory if used alone; some bacilli persist even after prolonged treatment and resistance develops. Rifampin has been included in the MDT of leprosy whereby it shortens the duration of treatment, and no resistance develops. Persistence of dormant rifampin-sensitive bacilli, even after prolonged therapy has also been noted. However, relapse caused by such bacilli can be treated with the same MDT. Rifampin remains effective in leprosy even if given once a month. The 600 mg monthly dose used in MDT is practically nontoxic and does not cause enzyme induction to affect metabolism of other drugs. However, it should not be given to patients with hepatic or renal dysfunction, as well as during '*erythema nodosum leprosum*' (ENL) and '*reversal reaction*' in leprosy patients, because it can release large quantities of mycobacterial antigens by inducing rapid bacillary killing.

Ethionamide This antitubercular drug has significant antileprotic activity, but is poorly tolerated and causes hepatotoxicity in ~ 10% patients. It has been used as an alternative to clofazimine, but other substitutes are preferred. Ethionamide 250 mg/day may be used only when absolutely necessary.

Ofloxacin

Many fluoroquinolones like ofloxacin, pefloxacin, moxifloxacin, sparfloxacin are highly active against *M.leprae*, but ciprofloxacin has poor activity. Clinically, ofloxacin has been used to the largest extent. As a component of MDT, it has been found to hasten the bacteriological and clinical response. It is cidal to *M.leprae*, and in one study, over 99.9% bacilli were found to be killed by 22 daily doses of ofloxacin monotherapy. However, it is not yet included in the standard treatment protocols, but can be used in alternative regimens in case rifampin cannot be used, or to shorten the duration of treatment and reduce chances of drug resistance. Its safety during long-term use is not well documented. *Dose:* 400 mg/day.

Moxifloxacin is the most potent fluoroquinolone against *M. leprae*. Recently, it has been tried in some combination regimens with good clinical and bacteriological results.

Minocycline

Because of high lipophilicity, this tetracycline penetrates into *M.leprae* and is active against them. A dose of 100 mg/day produces peak blood levels that exceed MIC against *M. leprae* by 10–20 times. Its antileprotic activity is less marked than that of rifampin, but greater than that of clarithromycin. In one trial minocycline 100 mg daily monotherapy rendered all 8 patients of lepromatous leprosy negative for *M. leprae*

after 8 weeks. A good clinical response in terms of relief of lepromatous symptoms has also been reported. Vertigo is the only serious complication of its long-term use. It is being tried in alternative MDT regimens.

Clarithromycin

It is the only macrolide antibiotic with significant activity against *M. leprae*. However, it is less bactericidal than rifampin. Monotherapy with clarithromycin 500 mg daily caused 99.9% bacterial killing in 8 weeks. Rapid clinical improvement also occurred in lepromatous patients. A synergistic action with minocycline has been demonstrated. It is being included in alternative MDT regimens.

TREATMENT OF LEPROSY

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae*; primarily affecting skin, mucous membranes and nerves. It is more prevalent among the lowest socioeconomic strata. Many patients exploit it for begging and do not come forward for treatment. In India, the National Leprosy Control Programme was launched in 1955, and was changed to National Leprosy Eradication Programme (NLEP) in 1982. Following the initiative under WHO Action Programme for Elimination of Leprosy, India introduced multidrug therapy (MDT) for leprosy through NLEP in 1982 and achieved elimination of leprosy as a public health problem (prevalence rate < 1 case per 10,000 population) in Dec. 2005, though some states still had >1 case per 10,000.*

Though the burden of leprosy has fallen drastically after introduction of MDT, both globally and in India, WHO data (2010) show that 65% of all new leprosy cases worldover are from India. Brazil and Indonesia are the other major contributors.

Leprosy manifests in several clinical forms. The most widely used classification of leprosy is that of Ridley and Jopling (1966) who divided leprosy into Lepromatous (LL), Borderline lepromatous (BL), Borderline (BB), Borderline tuberculoid (BT), and Tuberculoid (TT). The important features of the two polar types are given in the box:

Tuberculoid leprosy	Lepromatous leprosy
Anaesthetic patch	Diffuse skin and mucous membrane infiltration, nodules
Cell mediated immunity (CMI) is normal	CMI is absent
Lepromin test—positive	Lepromin test—negative
Bacilli rarely found in biopsies	Skin and mucous membrane lesions teeming with bacilli
Prolonged remissions with periodic exacerbations	Progresses to anaesthesia of distal parts, atrophy, ulceration, absorption of digits, etc.

For operational purposes WHO divided leprosy into:

1. *Paucibacillary leprosy (PBL)* Patient has few bacilli and is noninfectious. It included the TT and BT types.
2. *Multibacillary leprosy (MBL)* Patient has large bacillary load and is infectious. It included the LL, BL and BB types.

To further simplify the classification so that it may be applied at the field level, WHO reclassified leprosy in 1998 into:

- *Single lesion paucibacillary leprosy (SL PB)*: With a solitary cutaneous lesion.
- *Paucibacillary leprosy (PB):* With 2–5 skin lesions. Both SLPB and PB cases are skin smear negative for *M.leprae*.
- *Multibacillary leprosy (MB):* With ≥ 6 skin lesions, as well as all smear positive cases.

The classification being followed by NLEP since 2009 is given in the box (*see* p. 884).

Conventionally, all forms of leprosy had been treated with dapsone alone (monotherapy: MT) 100–200 mg daily, 5 days a week; duration of treatment depending on the type: TT–4 to 5 years, LL–8 to 12 years or lifelong. With this monotherapy symptomatic relief occurred in few months, but bacteriological cure was delayed or

* India achieves National elimination of leprosy. *Ind. J. Leprosy* **2006;** *78(1):* 101.

NLEP (2009) Classification of Leprosy

Paucibacillary (PB)	*Multibacillary (MB)*
• 1-5 skin lesions • No nerve/only one nerve involvement, ± 1–5 skin lesions. • Skin smear negative at all sites	• 6 or more skin lesions • > 1 nerve involved irrespective of number of skin lesions • Skin smear positive at any one site

did not occur. Emergence of dapsone resistance since 1964 threatened the efficacy of monotherapy and upto 20% patients relapsed. Even primary dapsone resistance was increasingly encountered. Monotherapy is no longer given.

Multidrug therapy (MDT) of leprosy

To deal with dapsone resistant strains of *M. leprae* and to shorten the duration of treatment (as well as to eliminate microbial persisters, i.e. dormant forms, if possible), multidrug therapy with rifampin, dapsone and clofazimine was introduced by the WHO in 1981. This was implemented under the NLEP in 1982. The MDT is the regimen of choice for all cases of leprosy. Its advantages are:

- Effective in cases with primary dapsone resistance.
- Prevents emergence of dapsone resistance.
- Affords quick symptom relief and renders MBL cases noncontagious within few days.
- Reduces total duration of therapy.

Initially under standard MDT, the PBL cases were treated with dapsone + rifampin for 6 months, while the MBL cases were treated with dapsone + rifampin + clofazimine for a minimum of 2 years or till disease inactivity/skin smear negativity was achieved. The MBL cases were kept under surveillance without treatment for the next 5 years.

A WHO expert group (1994) reviewed the data collected over the past 12 years as well as results of clinical trials, and made observations which are summarized below:

- MDT had been highly successful, both in MBL and PBL. The estimated cases of leprosy fell from 10–12 million to 2.7 million.
- Relapse rate after MDT had been very low (0.77%) in MBL and 1.07% in PBL over a period of 9 years.
- The efficacy, safety and acceptability of MDT had been excellent.
- Some reports, mostly from India, had found that for uniformly satisfactory response, treatment of PBL had to be extended beyond the mandatory 6 months (mostly to 12 months). However, no difference in the relapse rate was found among 12000 Indian patients treated with MDT either for 6 months or for 1 year. As such, the WHO expert group recommended continuation of 6 months MDT for PBL.
- No resistance to rifampin developed with MDT. Nearly all *M. leprae* isolated from relapse cases remained fully sensitive to rifampin. No resistance to clofazimine had been reported. New cases of drug resistance were not reported after application of MDT. Retreatment of relapse cases with the same MDT had been successful, and was recommended.
- Drug toxicity had not been a major problem with MDT.
- Prevalence of lepra reaction had not increased due to use of MDT.
- No specific association of leprosy with HIV infection had been found. Leprosy in HIV-positive cases is to be treated in the same manner as in others.

Due to operational reasons, NLEP in India experimented with 'fixed duration therapy of 24 months' (FDT-24) for MBL cases without extending for smear negativity to be achieved (if needed), and found that relapse rates were similar to that with the standard protocol. As a result, FDT-24 was introduced by NLEP in selected areas for MBL cases in 1990. The WHO expert group (1994) recommended FDT-24 for all MBL cases whether disease inactivity or skin smear negativity was attained or not. The 6 months FDT continues for PBL cases.

MBL Encouraged by the very low relapse rates with 2 yrs FDT-24 and keeping in view operational constraints, studies were undertaken under the aegis of WHO to compare short-duration 12 months (FDT-12) with standard 24 months FDT-24. In the field situation the two were found to yield similar relapse rates over 3–5 yr follow

up. Accordingly, a WHO expert committee on leprosy (1997) recommended shortening of MDT to 12 months. This was implemented globally including India.* The currently used MDT (FDT-12) is given in the box:

Multidrug therapy (MDT) of leprosy

	Multibacillary	Paucibacillary
Rifampin	600 mg once a month supervised	600 mg once a month supervised
Dapsone	100 mg daily self administered	100 mg daily self administered
Clofazimine	300 mg once a month supervised and 50 mg daily self administered	—
Duration	12 months	6 months

Doses to be reduced suitably for children.

Blister packs of tablets for 28 day treatment are made available free of cost to all MBL cases, and 12 such blister packs have to be consumed by each MBL patient. Separate blister packs are given to PBL cases and 6 packs are to be taken by each patient.

A few studies, (mostly institutional) have shown that despite 2 yr MDT, some patients conti-\nue to harbour viable *M. leprae* (persisters). Relapse rates are higher in the later years of follow up and in the subgroup of patients with large bacillary load, i.e. bacillary index (BI) ≥ 4+. Thus, the length of MDT could depend on the aim of therapy, resources, and feasibility of follow up.

The primary purpose of mass programmes (WHO Action Programme for the Elimination of Leprosy, or NLEP-India) is to render patients non-contagious so as to cut down transmission. For this, 1 yr FDT may be considered adequate. Even if some patients relapse later, they can be treated by reinstituting MDT (dormant bacilli remain sensitive to the same drugs). This is more cost-effective than treating all patients with a longer MDT to prevent a few relapses. Moreover, case reports and prolonged follow ups show that some patients relapse upto 15 years after being cured of MBL by extended-MDT till smear negativity. Thus, few relapses cannot be prevented irrespective of the duration of regimen or the drugs used in the regimen, probably reflecting invincibility of the 'persister' bacilli.

On the other hand, in private or institutional care, the aim is cure of every individual patient. For this extended treatment is required till disease inactivity or skin smear negativity is achieved. Upto 4 years may be needed for this, particularly in highly bacillated patients (BI ≥ 4+). In the USA more intensive (daily) and longer lasting (3–10 years) regimens are used.

PBL For PBL, 6 month 2 drug therapy has now been used for > 25 yrs with very encouraging results. Field studies from various parts of the world suggest that this is adequate, provided that the patient is kept on follow up for the subsequent 1–2 years. However, institutional studies have found larger proportion of patients to have active disease after 6 month FDT. Some reports indicate that proportion of patients staying active can be reduced by 12 month MDT. Independent leprologists prefer to extend therapy of PBL for 12 months or longer till disease inactivity is achieved.

It may be concluded that, where feasible, treatment till cure of individual patient should be ensured both in MBL and in PBL, while in mass programmes FDT-12 may be the more practical approach to cover every leprosy patient.

Highlights of multidrug therapy (MDT) of leprosy*

- Worldover the case load of leprosy was ~ 12 million before introduction of MDT, whereas only 0.228 million new cases were detected during 2010.
- Globally 14.2 million patients of leprosy have been cured with very few relapses by MDT between 1985–2005, out of which 10.8 million cases were from India.
- In 1981 India recorded a total of 3.95 million leprosy cases. With institution of MDT in 1982, it has fallen to 0.127 million new cases detected during 2010-11.
- India achieved elimination of leprosy as a public health problem (prevalence rate < 1 case per 10,000 population) in Dec. 2005, by the use of MDT.
- The prevalence of leprosy in India was 57.6 cases per 10,000 population in 1981. It has fallen to 0.69 cases per 10,000 in 2010.

* The figures are based on WHO and NLEP data

* Short Course Treatment of Leprosy: present status; *ICMR Bulletin* **2002**; *32(2):* 13–19.

Alternative regimens Many alternative regimens incorporating newer antileprotic drugs have been investigated. However, these are used only in case of rifampin-resistance or when it is impossible/inadvisable to employ the standard MDT regimen. Some of these are:

- *Intermittent ROM*: Rifampin 600 mg + ofloxacin 400 mg + minocycline 100 mg are given once a month for 3–6 month for PBL and for 12 or 24 month for MBL cases, without any drug in between.
- *Single dose ROM*: A single dose of rifampin + ofloxacin + minocycline was given for single lesion PBL, but this has been discontinued.
- Cloflazimine 50 mg + any two of ofloxacin 400 mg/minocycline 100 mg/clarithromycin 500 mg daily for 6 month, followed by clofazimine 50 mg + any one of ofloxacin 400 mg/minocycline 100 mg daily for additional 18 months.
- Four drug regimen of rifampin 600 mg + sparfloxacin 200 mg + clarithromycin 500 mg + minocycline 100 mg daily for 12 weeks has yielded equivalent clinical improvement in MBL cases to standard 12 month MDT.
- In case of refusal to accept clofazimine: ofloxacin 400 mg or minocycline 100 mg daily can be substituted for it in the standard MDT. Use of ethionamide as a substitute is not recommended.
- *Intermitent RMMx*: Moxifloxacin 400 mg + minocycline 200 mg + rifampin 600 mg is administered once a month: 6 doses given for PBL and 12 doses given for MBL cases have produced rapid and marked clinical response.

Reactions in leprosy

Lepra reaction This occurs in LL, usually coincides with institution of chemotherapy and/or intercurrent infection. It is a Jarish Herxheimer (Arthus) type of reaction due to release of antigens from the killed bacilli, and may be mild, severe or life-threatening, i.e. erythema nodosum leprosum (ENL).

Lepra reaction is of abrupt onset; existing lesions enlarge, become red, swollen and painful; several new lesions may appear. Malaise, fever and other constitutional symptoms generally accompany and may be marked.

Temporary discontinuation of dapsone is recommended only in severe cases. Clofazimine (200 mg daily) is effective in controlling the reaction (except the severe one), probably because of its antiinflammatory property. For severe reaction, prednisolone 40–60 mg/day is started immediately and continued till the reaction subsides. The dose is then tapered over 2–3 months.

Thalidomide is an anxiolytic, antiemetic drug with antiinflammatory, cytokine (TNF_{α}, ILs, interferon) modulatory property. It can be used in ENL as an alternative to prednisolone. Thalidomide was introduced in 1958 for morning sickness and was found to be highly teratogenic (*see* p. 89), and withdrawn in 1961. It has been reintroduced for ENL as well as a variety of other conditions in which cytokines play an important role. It is also indicated in multiple myeloma.

Dose: For ENL 100–300 mg OD at bed time.

THAANGIO, THALODA 50, 100 mg cap.

Other drugs used are—analgesics, antipyretics, antibiotics, etc. according to symptoms and need. Chloroquine also suppresses lepra reaction.

Reversal reaction This is seen in TT and BL cases, and is a manifestation of delayed hypersensitivity to *M. leprae* antigens. Cutaneous ulceration, multiple nerve involvement with swollen, painful and tender nerves, occur suddenly even after completion of therapy. It is treated with clofazimine or corticosteroids in the same way as ENL, but thalidomide is ineffective.

☞ PROBLEM DIRECTED STUDY

56.1 A 50-year-old male attends the hospital OPD with multiple, diffusely raised nodules over the face and arms for the past 1 month. The skin over the lesions is reddish and glossy. Sensation over face and arms is diminished and the ulnar nerve is thickened. He informs that 6 years back he had suffered from similar lesions and had taken regular medication for the same for one year and was declared cured. The treatment records revealed that he was given the standard multidrug therapy with rifampin, clofazimine and dapsone and had successfully completed the one year course. The skin smear is positive for *M. leprae*.

(a) What could be the cause of relapse of leprosy in this case? What treatment should be prescribed?

(*see* Appendix-1 for solution)

Chapter 57 Antifungal Drugs

These are drugs used for superficial and deep (systemic) fungal infections.

A disquietening trend after 1950s is the rising prevalence of more sinister type of fungal infections which are, to a large extent, iatrogenic. Fungal infections are mostly associated with the use of broad-spectrum antibiotics, corticosteroids, anticancer/immunosuppressant drugs, dentures, indwelling catheters and implants, and emergence of AIDS. As a result of breakdown of host defence mechanisms by the above agents, saprophytic fungi easily invade living tissue.

Many topical antifungals have been available since the antiseptic era. Two important antibiotics *viz. amphotericin B*—to deal with systemic mycosis, and *griseofulvin*—to supplement attack on dermatophytes were introduced around 1960. Antifungal property of flucytosine was noted in 1970, but it could serve only as a companion drug to amphotericin. The development of *imidazoles* in the mid 1970s and *triazoles* in 1980s has been an advancement. *Terbinafine* is a novel antifungal. A group of potent semisynthetic antifungal antibiotics, the *Echinocandins* are the latest addition.

CLASSIFICATION

1. *Antibiotics*
   - A. *Polyenes:* Amphotericin B (AMB), Nystatin, Hamycin
   - B. *Echinocandins*: Caspofungin, Micafungin, Anidulafungin
   - C. *Heterocyclic benzofuran*: Griseofulvin
2. *Antimetabolite* Flucytosine (5-FC)
3. *Azoles*
   - A. *Imidazoles*
     - *Topical:* Clotrimazole, Econazole, Miconazole, Oxiconazole
     - *Systemic:* Ketoconazole
   - B. *Triazoles*: (systemic) Fluconazole, Itraconazole, Voriconazole, Posaconazole
4. *Allylamine* Terbinafine
5. *Other topical agents*

Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Butenafine, Sod. thiosulfate.

POLYENE ANTIBIOTICS

The name *polyene* is derived from their highly double-bonded structure. Amphotericin B is described as the prototype.

Amphotericin B (AMB)

It is obtained from *Streptomyces nodosus*.

Chemistry and mechanism of action The polyenes possess a macrocyclic ring, one side of which has several conjugated double bonds and is highly lipophilic, while the other side is hydrophilic with many OH groups. A polar aminosugar and a carboxylic acid group are present at one end in some. They are all insoluble in water and unstable in aqueous medium.

The polyenes have high affinity for ergosterol present in fungal cell membrane. They combine with it, get inserted into the membrane and several polyene molecules together orient themselves in such a way as to form a 'micropore'. The hydrophilic side forms the interior of the pore through which ions, amino acids and other water-soluble substances move out. The micropore is stabilized by membrane sterols which fill up the spaces between the AMB molecules on the lipophilic side—constituting the outer surface of the pore. Thus, cell permeability is markedly increased.

Cholesterol, present in host cell membranes, closely resembles ergosterol; the polyenes bind to it as well, though with lesser affinity. Thus, the selectivity of action of polyenes is low, and AMB is one of the most toxic systemically used antibiotics, though it is the least toxic polyene. Bacteria do not have sterols and are unaffected by polyenes.

It has been found that AMB enhances immunity in animals, and this action may aid immunocompromised individuals in handling fungal infection.

Antifungal spectrum AMB is active against a wide range of yeasts and fungi—*Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis, Torulopsis, Rhodotorula, Aspergillus, Sporothrix,* etc. Dermatophytes are inhibited *in vitro*, but concentrations of AMB attained in infected skin are low and ineffective. It is fungicidal at high and static at low concentrations.

Resistance to AMB during therapy has been rarely noted among *Candida* in a selected group of leucopenic cancer patients, but it is not a problem in the clinical use of the drug.

AMB is also active on various species of *Leishmania,* a protozoa.

Pharmacokinetics AMB is not absorbed orally; it can be given orally for intestinal candidiasis without systemic toxicity. Administered i.v. as a suspension made with the help of deoxycholate (DOC), it gets widely distributed in the body, but penetration in CSF is poor. It binds to sterols in tissues and to lipoproteins in plasma and stays in the body for long periods. The terminal elimination t½ is 15 days. About 60% of AMB is metabolized in the liver. Excretion occurs slowly both in urine and bile, but urinary concentration of active drug is low.

Administration and dose Amphotericin B can be administered orally (50–100 mg QID) for intestinal moniliasis; also topically for vaginitis, otomycosis, etc.:
FUNGIZONE OTIC 3% ear drops.

Conventional formulation of AMB (C-AMB) For systemic mycosis, C-AMB is available as dry powder along with deoxycholate (DOC) for extemporaneous dispersion before use:
FUNGIZONE INTRAVENOUS, MYCOL 50 mg vial.
It is first suspended in 10 ml water and then diluted to 500 ml with glucose solution (saline makes the suspension coarse, should be avoided). Initially 1 mg test dose is injected i.v. over 20 minutes. If no serious reaction follows, 0.3 mg/kg is infused over 4–8 hours. Daily dose may be gradually increased to 0.7 mg/kg depending on tolerance of the patient. The total dose of AMB for majority of cases is 3–4 g given over 2–3 months.

Intrathecal injection of 0.5 mg twice weekly has been given in fungal meningitis.

Liposomal amphotericin B (L-AMB) It has been produced to improve tolerability of i.v. infusion of AMB, reduce its toxicity and achieve targeted delivery. It consists of 10% AMB incorporated in uniform sized (60–80 nM) unilamellar liposomes made up of lecithin and other biodegradable phospholipids.
The special features of this preparation are:

- It produce milder acute reaction on i.v. infusion.
- It can be used in patients not tolerating infusion of conventional AMB formulation.
- It has lower nephrotoxicity.
- It causes minimal anaemia.
- It delivers AMB particularly to reticuloendothelial cells in liver and spleen—especially valuable for kala azar and in immunocompromised patients.

The *liposomal-AMB* produces equivalent blood levels, has similar clinical efficacy with less acute reaction and renal toxicity than conventional preparaton. It thus appears more satisfactory, can be infused at higher rates (3–5 mg/kg/day), but is many times costlier than conventional AMB. L-AMB is specifically indicated for empirical therapy in febrile neutropenic patients not responding to antibacterial antibiotics, critically ill deep mycosis cases and in kala azar.
FUNGISOME (liposomal AMB) 10 mg, 25 mg, 50 mg per vial inj., AMPHOLIP 10 mg/2 ml, 50 mg/10 ml, 100 mg/20 ml inj.

Another formulation amphotericin B colloidal dispersion (ABCD) containing 50% each of AMB and cholesteryl sulfate has been produced, but is not superior.

Adverse effects The toxicity of AMB is high.

(a) *Acute reaction* This occurs with each infusion and consists of chills, fever, aches and pain all over, nausea, vomiting and dyspnoea lasting for 2–5 hour, probably due to release of cytokines (IL, TNFα). When the reaction is severe—the dose should be increased gradually. Usually the intensity of reaction decreases with continued medication. Injection of hydrocortisone 0.6 mg/kg with the infusion may reduce the intensity of reaction.
Thrombophlebitis of the injected vein can occur.

(b) *Long-term toxicity* Nephrotoxicity is the most important. It occurs fairly uniformly and is dose-related. Manifestations are—azotemia, reduced g.f.r., acidosis, hypokalaemia and inability to concentrate urine. It reverses slowly and often incompletely after stoppage of therapy.
Anaemia: Most patients develop slowly progressing anaemia which is due to bone marrow depression. It is largely reversible.
CNS toxicity: occurs only on intrathecal injection—headache, vomiting, nerve palsies, etc.

Uses Amphotericin B can be applied topically for oral, vaginal and cutaneous candidiasis and otomycosis.

It is the most effective drug for various types of *systemic mycoses* and is the gold standard of antifungal therapy. However, because of higher toxicity of AMB, the azole antifungals are now preferred in conditions where their efficacy approaches that of AMB (*see* Table 57-1).

Febrile neutropenia: Empirical use of i.v. AMB is often made in neutropenic patients whose fever is not responding to i.v. bactericidal antibiotics.

Leishmaniasis: AMB is the most effective drug for resistant cases of kala azar and mucocutaneous leishmaniasis (*see* Ch. 60).

Interactions Flucytosine has supra-additive action with AMB in the case of fungi sensitive to both (AMB increases the penetration of 5-FC into the fungus).
Aminoglycosides, vancomycin, cyclosporine and other nephrotoxic drugs enhance the renal impairment caused by AMB.

Nystatin

Obtained from *S. noursei*, it is similar to AMB in antifungal action and other properties. However, because of higher systemic toxicity, it is used only locally in superficial candidiasis.
MYCOSTATIN 5 lakh U tab, 1 lakh U vaginal tab, 1 lakh U/g oint, NYSTIN EYE 1 lakh U/g ophthalmic oint.

Given orally, it is not absorbed; can be used for monilial diarrhoea (due to superinfection or otherwise), 5 lac U TDS (1 mg = 2000 U). Nausea and bad taste in mouth are the only side effects.

TABLE 57.1 Choice of drugs for systemic mycoses

Disease	Drugs	
	1st Choice	*2nd Choice*
1. Candidiasis		
oral / vaginal / cutaneous	FLU / NYS / CLO	ITR
deep / invasive	AMB / VORI	FLU / CAS / POSA
2. Cryptococcosis	AMB ± 5-FC	FLU
3. Histoplasmosis	ITR / AMB	FLU
4. Coccidioidomycosis	AMB / FLU	ITR / KTZ
5. Blastomycosis	ITR / AMB	KTZ / FLU
6. Sporotrichosis (disseminated)	AMB	ITR
7. Paracoccidioidomycosis	ITR	AMB
8. Aspergillosis	VORI / AMB	ITR / CAS / POSA
9. Mucormycosis	AMB	POSA
10. Chromomycosis	ITR	TER / POSA

AMB—Amphotericin B; 5-FC—Flucytosine; KTZ—Ketoconazole; FLU—Fluconazole; ITR—Itraconazole; NYS—Nystatin; CLO—Clotrimazole; VORI—Voriconazole; CAS—Caspofungin; POSA—Posaconazole; TER—Terbinafine

Nystatin is effective (but less than azoles) in monilial vaginitis—1 lac U tab inserted twice daily. For oral thrush, the vaginal tab may be crushed and suspended in glycerine for application in mouth. Corticosteroid aerosols (e.g. beclomethasone) can cause oral candidiasis: nystatin is effective in preventing as well as treating it.

Similarly, it is used for corneal, conjunctival and cutaneous candidiasis in the form of an ointment. No irritation or other side effect is ordinarily seen.

Candidal resistance to nystatin is not a clinical problem. It is ineffective in dermatophytosis.

Hamycin It was isolated from *S. pimprina* and developed by Hindustan Antibiotics at Pimpri. It is similar to nystatin, but more water soluble. A fraction of the orally administered dose is absorbed, but cannot be relied upon for the treatment of systemic mycosis: use is restricted to topical application for oral thrush, cutaneous candidiasis, monilial and trichomonas vaginitis and otomycosis by *Aspergillus*.

HAMYCIN, 5 lakh U/g oint, 2 lakh U/ ml susp for topical use, 4 lakh U vaginal ovules.

ECHINOCANDINS

These are a new class of potent semisynthetic antifungal antibiotics with a complex cyclic lipopeptide structure, which stand out due to their low toxicity compared to AMB.

Caspofungin

It is the first and the prototype member of the class, active mainly against *Candida* and *Aspergillus*. Strains of candida that have become resistant to azoles are susceptible to caspofungin. The mechanism of action is different from other antifungals, *viz.* it inhibits the synthesis of β-1, 3-glucan, which is a unique component of the fungal cell wall. Cross linking between chitin (a fibrillar polysaccharide) and β-1, 3-glucan gives toughness to the fungal cell wall. Weakening of the cell wall by caspofungin leads to osmotic susceptibility of fungal cell, which then succumbs.

Caspofungin is not absorbed orally; has to be infused i.v. It is distributed into tissues, but does not enter CSF. Metabolism is extensive and metabolites are excreted in urine as well as faeces with a plasma t½ of 10 hours. Caspofungin is approved for use in deep and invasive candidiasis, esophageal candidiasis and salvage therapy of nonresponsive invasive aspergillosis. Because of good tolerability, it is now increasingly used in neutropenic immunocompromised patients whose fever is not responding to antibacterial antibiotics.

Dose: 70 mg loading dose infused i.v. over 1 hour, followed by 50 mg i.v. daily.

CANCIDAS 70 mg in 10 ml and 50 mg in 10 ml inj.

An acute febrile reaction some times attends the i.v. infusion of caspofungin, as does phlebitis of the injected vein. Rash, vomiting, dyspnoea, hypokalemia and joint pain may occur. However, organ toxicity has not been noted.

Micafungin and *Anidulafungin* are the other echinocandins with similar properties.

HETEROCYCLIC BENZOFURAN

Griseofulvin

It was one of the early antibiotics extracted from *Penicillium griseofulvum*. However, because of lack of antibacterial activity, little attention was paid to it: clinical utility in dermatophytosis was demonstrated only around 1960.

Griseofulvin is fungistatic for most dermatophytes, including *Epidermophyton, Trichophyton, Microsporum,* etc., but not against *Candida* and other fungi causing deep mycosis. Bacteria are also insensitive. Dermatophytes actively concentrate it: this feature probably accounts for its selective toxicity. Resistance can be induced *in vitro* and this is associated with loss of concentrating ability. However, emergence of resistance during clinical use is rare.

Griseofulvin interferes with mitosis—multinucleated and stunted fungal hyphae are produced under its action. It also causes abnormal metaphase configurations. However, unlike the typical mitotic inhibitors (colchicine, vinca alkaloids), it does not cause metaphase arrest; rather the daughter nuclei fail to move apart or move only a short distance. It does not inhibit polymerization of tubulin (microtubular protein which pulls the chromosomes apart), but binds to polymerized microtubules and interferes with their function.

Pharmacokinetics The absorption of griseofulvin from g.i.t. is somewhat irregular because of its very low water solubility. Absorption is improved by taking it with fats and by microfining the drug particles; now ultramicrofine particle preparations from which absorption is still better are available.

Griseofulvin gets deposited in keratin forming cells of skin, hair and nails. It is especially concentrated and retained in tinea infected cells.

Griseofulvin is largely metabolized, primarily by methylation, and excreted in urine. Plasma t½ is 24 hrs, but it persists for weeks in skin and keratin.

Adverse effects Toxicity of griseofulvin is low and usually not serious. Headache is the commonest complaint, followed by g.i.t. disturbances. CNS symptoms and peripheral neuritis are occasional.

Rashes, photoallergy may warrant discontinuation. Gynaecomastia is reported.

Transient leukopenia and albuminuria (without renal damage) are infrequent.

Use Griseofulvin is used orally only for dermatophytosis. On getting deposited in the skin through circulation, it prevents fungal invasion of keratin. Because it is fungistatic and not cidal, the newly formed keratin is not invaded by the fungus, but the fungus persists in already infected keratin, till it is shed off. Thus, the duration of treatment is dependent upon the site of infection, thickness of infected keratin and its turnover rate. It is ineffective topically. Systemic azoles and terbinafine are equally or more efficacious, and are preferred now.

Dose: 125–250 mg QID with meals; duration depends on the site of infection (turnover rate of keratin).

Scalp	4 weeks
Palm, soles	6 to 8 weeks
Finger nails	6 to 8 months
Toe nails	10 to 12 months

Majority of localized tinea infections are treated with topical agents. Griseofulvin should be reserved for cases with nail, or large body surface involvement and tinea capitis. It is effective in athletes foot, but not in pityriasis versicolor.

GRISOVIN-FP, WALAVIN, GRISORAL 250 mg tab.

Interactions Griseofulvin induces CYP450 enzymes and hastens warfarin metabolism. Efficacy of oral contraceptives may be lost. Phenobarbitone reduces the oral absorption and induces the metabolism of griseofulvin—failure of therapy may occur.

Griseofulvin can cause intolerance to alcohol.

ANTIMETABOLITE

Flucytosine (5-FC)

It is a pyrimidine antimetabolite which is inactive as such. After uptake into fungal cells, it is converted into 5-fluorouracil and then to 5-fluorodeoxyuridylic acid which is an inhibitor of thymidylate synthesis. Thymidylic acid is a component of DNA. The fungal selectivity of 5-FC depends on the fact that mammalian cells (except some marrow cells) have low capacity to convert 5-FC into 5-fluorouracil, which is a potent anticancer drug.

5-FC is a narrow spectrum fungistatic, active against *Cryptococcus neoformans, Torula, Chromoblastomyces*; and a few strains of *Candida*. Other fungi and bacteria are insensitive.

Adverse effects Toxicity of 5-FC is lower than that of AMB; consists of dose-dependent bone marrow depression and gastrointestinal disturbances, particularly enteritis and diarrhoea.

Liver dysfunction is mild and reversible.

Use Flucytosine is not employed as the sole therapy except occasionally in chromoblastomycosis. Rapid development of resistance limits its utility in deep mycosis. In cryptococcosis (both meningeal and nonmeningeal) its synergistic action with AMB is utilized to reduce the total dose of the more toxic latter drug. Therapy with 5-FC is generally limited to first 2 weeks of AMB regimen to avoid its bone marrow toxicity.

IMIDAZOLES AND TRIAZOLES

These are presently the most extensively used antifungal drugs.

Four imidazoles are entirely topical, while ketoconazole is used both orally and topically. Two triazoles fluconazole and itraconazole have largely replaced ketoconazole for systemic mycosis because of greater efficacy, longer t½, as well as fewer side effects. Some newer triazoles have been added.

The imidazoles and triazoles have broad-spectrum antifungal activity covering dermatophytes, *Candida*, other fungi involved in deep mycosis (except mucor), *Nocardia* and *Leishmania*.

The mechanism of action of imidazoles and triazoles is the same. They inhibit the fungal cytochrome P450 enzyme 'lanosterol 14-demethylase' and thus impair ergosterol synthesis leading to a cascade of membrane abnormalities in the fungus. The lower host toxicity of triazoles compared to imidazoles has correlated with their lower affinity for mammalian CYP450 enzymes and lesser propensity to inhibit mammalian sterol synthesis.

Development of fungal resistance to azoles has been noted among *Candida* infecting advanced AIDS patients, but has not so far posed significant clinical problem in immunocompetent patients, except fluconazole resistance among *Candida* causing esophageal and other deep candidasis. Many of fluconazole-resistant *Candida* respond to itraconazole or to voriconazole. Mutation of the gene encoding for fungal 14-demethylase enzyme underlies azole resistance.

Clotrimazole It is effective in the topical treatment of tinea infections like ringworm: 60–100% cure rates are reported with 2–4 weeks application on a twice daily schedule. Athletes' foot, otomycosis and oral/cutaneous/vaginal candidiasis have responded in >80% cases. It is particularly favoured for vaginitis because of a long lasting residual effect after once daily application. A 7 day course is generally used. For oropharyngeal candidiasis 10 mg troche of clotrimazole is allowed to dissolve in the mouth 3–4 times a day, or the lotion/gel is applied/swirled in the mouth for as long as possible. It is also effective in skin infections caused by *Corynebacteria*, but like most topical antifungals, has poor efficacy in tinea capitis (scalp) and tinea unguium (nails).

Clotrimazole is well tolerated by most patients. Local irritation with stinging and burning sensation occurs in some. No systemic toxicity is seen after topical use.

SURFAZ, CLODERM 1% lotion, cream, powder; 100 mg vaginal tab. CANDID 1% cream, mouth paint, powder.

Econazole It is similar to clotrimazole; penetrates superficial layers of the skin and is highly effective in dermatophytosis, otomycosis, oral thrush, but is somewhat inferior to clotrimazole in vaginitis. No adverse effects, except local irritation in few is reported.

ECONAZOLE 1% oint, 150 mg vaginal tab; ECODERM 1% cream.

Miconazole It is a highly efficacious (>90% cure rate) drug for tinea, pityriasis versicolor, otomycosis, cutaneous and vulvovaginal candidiasis. Because of its good penetrating power, it has been found effective, though partially, even in onychomycosis; single application on skin acts for a few days.

Irritation after cutaneous application is infrequent. No systemic adverse effects are seen. However, a higher incidence of vaginal irritation is reported in comparison to clotrimazole; even pelvic cramps have been experienced.

DAKTARIN 2% gel, 2% powder and solution; GYNODAKTARIN 2% vaginal gel; ZOLE 2% oint, lotion, dusting powder and spray, 1% ear drops, 100 mg vaginal ovules.

Oxiconazole Another newer topical imidazole antifungal effective in tinea and other dermatophytic infection, as well as vaginal candidiasis. Local irritation can occur in some patients.

OXIZON, ZODERM: oxiconazole 1% with benzoic acid 0.25% cream/lotion; apply topically once or twice daily.

Ketoconazole (KTZ)

It is the first orally effective broad-spectrum antifungal drug, useful in both dermatophytosis and deep mycosis. The oral absorption of KTZ is facilitated by gastric acidity because it is more soluble at lower pH. Hepatic metabolism is extensive; metabolites are excreted in urine and faeces. Elimination of KTZ is dose dependent: t½ varies from 1½ to 6 hours. Penetration in CSF is poor; therefore not effective in fungal meningitis. However, therapeutic concentrations are attained in the skin and vaginal fluid.

In spite of relatively short t½, a single daily dose is satisfactory in less severe cases. The usual dose is 200 mg OD or BD.

FUNGICIDE, NIZRAL, FUNAZOLE, KETOVATE 200 mg tab. FUNGINOC 2% oint, 2% shampoo (for dandruff), KETOVATE 2% cream. NIZRAL 2% cream, 2% lotion; DANRUF 2% shampoo, HYPHORAL 2% lotion.

Adverse effects Ketoconazole is much less toxic than AMB, but more side effects occur than with itraconazole or fluconazole, that have largely replaced it for systemic use.

The most common side effects are nausea and vomiting; can be reduced by giving the drug with meals. Others are—loss of appetite, headache, paresthesia, rashes and hair loss.

The most important draw back of KTZ is its hormonal effects. It decreases androgen production from testes, and displaces testosterone from protein binding sites.

Gynaecomastia, loss of hair and libido, and oligozoospermia may occur when the drug is used for a few weeks. Menstrual irregularities occur in some women due to suppression of estradiol synthesis.

A dose-dependent decrease in serum hydrocortisone due to synthesis inhibition has also been noted, but without any clinical manifestations in normal individuals.

Mild and asymptomatic elevation of serum transaminases occurs in ~5% patients, but serious hepatotoxicity is infrequent.

It is contraindicated in pregnant and nursing women.

Interactions Ketoconazole (and most azoles) interact with several drugs. Due consideration must be given when they are coprescribed with other drugs.

H_2 blockers, proton pump inhibitors and antacids decrease oral absorption of KTZ by reducing gastric acidity.

Rifampin, phenobarbitone, carbamazepine and phenytoin induce KTZ metabolism and reduce its efficacy.

Ketoconazole inhibits CYP450 enzymes, especially CYP3A4, CYP2C9; CYP2C19 and raises the blood levels of several drugs including:

Phenytoin	Digoxin
Carbamazepine	Omeprazole
Diazepam	Cyclosporine
Haloperidol	Nifedipine and other DHPs
Warfarin	HIV protease inhibitors
Sulfonylureas	Statins

The dangerous interaction with terfenadine, astemizole and cisapride resulting in polymorphic ventricular tachycardia due to excessive rise in plasma levels of these drugs has resulted in their withdrawal (*see* p. 166).

Use Orally administered KTZ is effective in *dermatophytosis* because it is concentrated in the stratum corneum. It is an alternative to griseofulvin, but use is restricted due to potential adverse effects. Used as a lotion or shampoo, KTZ is quite effective in seborrhoea of scalp and dandruff.

Though effective in *monilial vaginitis*, oral therapy (for 5–7 days) with KTZ is reserved for recurrent cases or those not responding to topical agents.

Systemic mycosis: Administered orally, KTZ is effective in several types of systemic mycosis, but triazoles, being more active with fewer side effects, have largely replaced it for these indications.

KTZ is occasionally used in dermal leishmaniasis and in *kala azar*.

High-dose KTZ has been used in Cushing's syndrome to decrease corticosteroid production.

Fluconazole It is a water-soluble triazole having a wider range of activity than KTZ; indications include cryptococcal meningitis, systemic and mucosal candidiasis in both normal and immunocompromised patients, coccidioidal meningitis and some tinea infections.

Fluconazole is 94% absorbed; oral bioavailability is not affected by food or gastric pH. It is primarily excreted unchanged in urine with a t½ of 25–30 hr. Fungicidal concentrations are achieved in nails, vagina and saliva; penetration into brain and CSF is good. Dose reduction is needed in renal impairment.

Adverse effects Fluconazole produces fewer side effects: mostly nausea, vomiting, abdominal pain, rash and headache. Incidence and severity of these side effects increases with dose and duration of therapy.

Selectivity for fungal cytochrome P450 is higher; unlike KTZ, it does not inhibit steroid synthesis in man: antiandrogenic and other endocrine side effects have not occurred.

Elevation of hepatic transaminase has been noted in AIDS patients.

It is not recommended in pregnant and lactating mothers.

Interactions Though it affects hepatic drug metabolism to a lesser extent than KTZ, increased plasma levels of phenytoin, astemizole, cisapride, cyclosporine, warfarin, zidovudine and sulfonylureas have been observed. A few cases of ventricular tachycardia have been reported when fluconazole was given with cisapride. The same caution as with KTZ or itraconazole needs to be applied in coadministering other drugs. Proton pump inhibitors and H_2 blockers do not affect its absorption.

Use Fluconazole can be administered orally as well as i.v. (in severe infections).

A single 150 mg oral dose can cure vaginal candidiasis with few relapses.

Oral fluconazole (100 mg/day for 2 weeks) is highly effective in oropharyngeal candidiasis, but is reserved for cases not responding to topical antifungals. Fluconazole (100 mg/day) for 2–3 weeks is the first line treatment for candida esophagitis.

Most tinea infections and cutaneous candidiasis can be treated with 150 mg weekly fluconazole for 4 weeks.

For disseminated candidiasis, cryptococcal/coccidioidal meningitis and other systemic fungal infections the dose is 200–400 mg/day for 4–12 weeks or longer. It is the preferred drug for fungal meningitis, because of good CSF penetration. Long-term oral fluconazole maintenance therapy after initial treatment with i.v. fluconazole/AMB is used in AIDS patients with fungal meningitis.

An eye drop is useful in fungal keratitis.

Fluconazole is ineffective in aspergillosis and mucormycosis, and inferior to itraconazole for histoplasmosis, blastomycosis and sporotrichosis, as well as in tinea unguim.

SYSCAN, ZOCON, FORCAN, FLUZON 50, 100, 150, 200 mg caps, 200 mg/100 ml i.v. infusion.
SYSCAN 0.3% eye drops.

Itraconazole This orally active triazole antifungal has a broader spectrum of activity than KTZ or fluconazole; includes some moulds like *Aspergillus*. Some fluconazole resistant *Candida* are susceptible. It is fungistatic, but effective in immunocompromised patients. Steroid hormone synthesis inhibition is absent in itraconazole, and serious hepatotoxicity is rare.

Oral absorption of itraconazole is variable. It is enhanced by food and gastric acid. Itraconazole is highly protein bound, has a large volume of distribution (10 L/Kg), accumulates in vaginal mucosa, skin and nails, but penetration into CSF is poor. It is largely metabolized in liver by CYP3A4; an active metabolite is produced which is excreted in faeces; t½ varies from 30–64 hours.

Itraconazole is well tolerated in doses below 200 mg/day. Gastric intolerance is significant at > 400 mg/day. Dizziness, pruritus, headache and hypokalaemia are the other common side effects. Unsteadiness and impotence are infrequent. Plasma transaminase may rise transiently. However, antiandrogenic and other hormonal adverse effects are not seen. Impaired left ventricular function has been worsened in some patients.

Drug interactions Oral absorption of itraconazole is reduced by antacids, H_2 blockers and proton pump inhibitors.

TABLE 57.2 Properties of drugs used for systemic mycoses

Characteristic	*AMB*	*Caspo*	*5-FC*	*KTZ*	*FLU*	*ITR*	*VORI*
Antifungal spectrum	Broad	Narrow	Narrow	Broad	Broad	Broad	Broad
Absorbed orally	No	No	Yes	Yes	Yes	Yes	Yes
Administered i.v.	Yes	Yes	Yes	No	Yes	Yes	Yes
Resistance (*in vivo*)	No	No	Yes	Limited	Limited	No	No
Nephrotoxicity	Yes	No	No	No	No	No	No
Anaemia	Yes	No	Mild	No	No	No	No
Leucopenia	No	No	Yes	No	No	No	No
Gastrointestinal upset	Yes	Mild	Yes	Mild	Mild	Moderate	Mild
Overall toxicity	High	Low	Medium	Medium	Low	Low	Low

AMB—AmphotericinB; 5-FC—Flucytosine; KTZ—Ketoconazole; FLU—Fluconazole; ITR—Itraconazole
Caspo—Caspofungin, VORI—Voriconazole

Rifampin, phenobarbitone, phenytoin and carbamazepine induce itraconazole metabolism and reduce its efficacy.

On the other hand, clarithromycin and HIV protease inhibitors reduce the metabolism of itraconazole and raise its blood levels.

Itraconazole inhibits CYP3A4; drug interaction profile is similar to KTZ; ventricular arrhythmias have occurred with terfenadine, astemizole, cisapride and class III antiarrhythmics. Phenytoin, digoxin, sulfonylureas, statins, dihydropyridines, protease inhibitors, warfarin and cyclosporine levels are also increased.

Uses Itraconazole is the preferred azole antifungal for most systemic mycosis (*see* Table 57.1) that are not associated with meningitis. It is superior to fluconazole for histoplasmosis, blastomycosis, sporotrichosis and is the drug of choice for the rare fungal infections—paracoccidioidomycosis and chromomycosis. It also affords some relief in aspergillosis. A dose of 200 mg OD/BD with meals is used for 3 months or more.

Vaginal candidiasis: 200 mg OD oral for 3 days is as effective as intravaginal clotrimazole.

Dermatophytosis: 100–200 mg OD for 7–15 days: more effective than griseofulvin, but less effective than fluconazole.

Onychomycosis: 200 mg/day for 3 months. An intermittent pulse regimen of 200 mg BD for 1 week each month for 3 months is equally effective. Relapses have occurred after itraconazole therapy, though it remains in the nail for few months after completion of the course.

SPORANOX, CANDITRAL, CANDISTAT, ITASPOR, FLUCOVER 100 mg cap. ITASPOR 100 mg cap, 200 mg/20 ml vial.

Important features of drugs used for systemic mycosis are compared in Table 57.2.

Voriconazole It is a second generation broad-spectrum triazole introduced lately for difficult to treat fungal infections like invasive aspergillosis, disseminated infections caused by fluconazole resistant *Candida, Fusarium* infections, and febrile neutropenia not responding to antibacterial therapy. Serious cases are first treated i.v. followed by oral voriconazole. It is completely absorbed orally, except when taken with a fatty meal, widely distributed into tissues and metabolized extensively by CYP2C19, CYP3A4, CYP2C9. Metabolites are excreted in urine. The t½ is 6 hours. It also inhibits CYP isoenzymes and the drug interaction profile is similar to KTZ. Rashes, visual disturbances, QTc prolongation and an acute reaction on i.v. injection are the significant adverse effects.

Dose: 200 mg oral BD taken 1 hour before or 1 hour after meal. Begin i.v. infusion with 6 mg/kg 12 hourly infused over 2 hours twice followed by 3–4 mg/kg 12 hourly.

VFEND 50, 200 mg tabs, 40 mg/ml oral suspension; 200 mg/vial inj. , FUNGIVOR 200 mg tab.

Posaconazole This recently introduced broad-spectrum triazole has more potent antifungal activity and is the only azole which has shown efficacy in mucormycosis. It is indicated for salvage therapy of this difficult to treat fungal infection. Because of its high cost and limited experience, it is reserved for nonresponsive cases of aspergillosis and invasive candidiasis. Favourable results have been reported in febrile neutropenia and as a prophylactic in immunosuppressed patients. It has also been used as alternative to itraconazole for chromomycosis.

Side effects to posaconazole are common, but mostly limited to nausea, abdominal pain, loose motions, headache, dizziness and drowsiness. Anaemia, neutropenia, cardiac arrhythmias and visual disturbances are rare. Administered as an oral suspension, absorption of posaconazole is improved by low pH and fatty food. It is partly metabolized by CYP2C19 and glucuronidation, but excreted mostly unchanged in faeces. The t½ is > 24 hours. It can increase levels of drugs metabolized by CYP3A4.

Dose: 200 mg QID or 400 mg BD with meals.

NOXAFIL 200 mg/5 ml susp.

ALLYLAMINE

Terbinafine

This orally and topically active drug against dermatophytes and *Candida* belongs to a new allylamine class of antifungals. In contrast to azoles which are primarily fungistatic,

terbinafine is fungicidal. It acts as a non-competitive inhibitor of 'squalene epoxidase', an early step enzyme in ergosterol biosynthesis by fungi. Accumulation of squalene within fungal cells appears to be responsible for the fungicidal action. The mammalian enzyme is inhibited only by 1000-fold higher concentration of terbinafine.

Approximately 75% of oral terbinafine is absorbed, but only 5% or less from unbroken skin. First pass metabolism reduces oral bioavailability to < 50%. It is widely distributed in tissues, strongly plasma protein bound and has high affinity for keratin. Therefore, it is concentrated in sebum, stratum corneum of skin and into nail plates. Inactivation occurs by metabolism and it is excreted mainly in urine, but about 20% in faeces as well. Elimination t½ after single dose is 11–16 hours, but is prolonged to 10 days after repeated dosing.

Oral terbinafine is usually well tolerated. Side effects are gastric upset, rashes, taste disturbance. Some cases of hepatic dysfunction, haematological disorder and severe cutaneous reaction are reported. Enzyme inducers lower, and enzyme inhibitors raise its steady-state plasma levels. Terbinafine does not inhibit CYP450.

Topical terbinafine can cause erythema, itching, dryness, irritation, urticaria and rashes.

Use Terbinafine applied topically as 1% cream twice daily is indicated in localized tinea pedis/cruris/corporis and pityriasis versicolor; 2–4 weeks treatment is required according to the site, yielding high efficacy. Oral treatment with 250 mg OD is reserved for onychomycosis, tinea capitis and wide spread lesions. Duration of treatment varies from 3–6 months or more depending on the site. Efficacy in nail infection is ~80%, which is higher than griseofulvin and itraconazole.

Terbinafine is less effective against cutaneous and mucosal candidiasis: 2–4 weeks oral therapy may be used as an alternative to fluconazole.

LAMISIL, SEBIFIN, DASKIL 250 mg tab, 1% topical cream. EXIFINE 125, 250 mg tabs, 1% cream; TERBIDERM 1% cream.

OTHER TOPICAL ANTIFUNGALS

All these drugs are used for dermatophytosis.

1. Tolnaftate It is an effective drug for tinea cruris and tinea corporis, and most cases respond in 1–3 weeks. Because of poor penetrability, it is less effective in tinea pedis and other hyperkeratinized lesions. For the same reason, it is ineffective in tinea capitis (involving scalp) and tinea unguium (involving nails).

Symptomatic relief occurs early, but if applications are discontinued before the fungus bearing tissue is shed—relapses are common. Resistance does not occur. Salicylic acid can aid tolnaftate by keratolytic action.

Tolnaftate causes little irritation, but is inferior in efficacy to imidazoles. It is not effective in candidiasis or other types of superficial mycosis.

TINADERM, TINAVATE 1% lotion, TOLNADERM 1% cream.

2. Ciclopirox olamine It is a newer drug effective in tinea infections, pityriasis versicolor and dermal candidiasis. High cure rates are reported. It penetrates superficial layers and reaches hair roots but systemic absorption is negligible. Local tolerance without irritation is good. Sensitization occurs occasionally. Formulated as nail lacquer, it has been used in onychomycosis. Vaginal candidiasis can be treated by 1% ciclopirox vaginal cream.

BATRAFEN 1% cream, 1% topical solution, 1% vaginal cream, OLAMIN 1% cream.

3. Undecylenic acid It is fungistatic used topically, generally in combination with its zinc salt. It is inferior to the drugs described above; cure rates are low even after prolonged treatment. However, it is still used for tinea pedis, nappy rash and tinea cruris. Irritation and sensitization are infrequent.

TINEAFAX: Zinc undecenoate 8%, zinc naphthenate 8%, mesulphen 8%, methyl salicylate 2.5%, terpineol 2.5% oint.

4. Benzoic acid It has antifungal and antibacterial property in slightly acidic medium. Fungistatic action is weaker than tolnaftate;

eradication of the fungus needs prolonged application till infected keratin is totally shed.

On hyperkeratotic lesions, it is used in combination with salicylic acid (as Whitfield's ointment: benzoic acid 5%, salicylic acid 3%). The latter, by its keratolytic action, helps to remove the infected tissue and promotes the penetration of benzoic acid into the lesion. Irritation and burning sensation are experienced by many patients.

RINGCUTTER ointment.

5. Butenafine It is a benzylamine congener of terbinafine with the same mechanism of action. However, it is used only topically in dermatophytosis. Efficacy in tinea cruris/corporis/pedis is similar to that of topical terbinafine.

BUTOP, FINTOP 1% cream; apply locally once or twice daily.

6. Quiniodochlor By the oral route, it is used as a luminal amoebicide (Ch. 60). It also has weak antifungal and antibacterial activity. By external application, it has been used for dermatophytosis, mycosis barbae, seborrhoeic dermatitis, infected eczema, furunculosis and pityriasis versicolor.

Quiniodochlor is also used in vaginal creams for monilial and trichomonas vaginitis.

VIOFORM 3% cream; DERMOQUINOL 4%, 8% cream.

7. Sodium thiosulfate It is a weak fungistatic, active against *Malassezia furfur*. A 20% solution applied twice daily for 3–4 weeks is effective in pityriasis versicolor. However, normal pigmentation of the skin takes longer to return. It is not useful in other superficial mycosis.

in KARPIN LOTION 20%.

☞ PROBLEM DIRECTED STUDY

57.1 A 50-year-old woman presents with complaints of constant pain in the retrosternal region for the past 2 weeks. The pain is markedly aggravated during swallowing. The condition has progressively worsened, and now even drinking water hurts. There is difficulty in swallowing as well. She informs that she is a diabetic and takes Tab. Glibenclamide 5 mg twice a day for the past two years, but has not checked her blood glucose for the last few months. Endoscopy reveals diffuse streaks of creamy yellow mucosal plaques and a few erosions in the esophagus. Scrapings from the plaque are sent for microbiological examination. Fasting blood glucose is found to be 180 mg/dl. She is diagnosed as a case of esophageal candidiasis with poorly controlled diabetes mellitus.

(a) What drug/drugs should be prescribed to treat her esophageal condition? What should be the duration of therapy?

(b) What are the aspects to be considered in view of the fact that the patient is a poorly controlled diabetic taking a sulfonylurea medication?

(*see* Appendix-1 for solution)

Chapter 58 Antiviral Drugs

Viruses are the ultimate expression of parasitism. They not only take nutrition from the host cell but also direct its metabolic machinery to synthesize new virus particles. Viral chemotherapy, therefore was considered impossible, as it would require interference with cellular metabolism in the host. However, in the past 50 years virus directed enzymes have been identified in the infected cell and some viruses have few enzymes of their own which may have higher affinities for some antimetabolites or inhibitors than the regular cellular enzymes. In addition, drugs have been developed which target virus specific steps like cell penetration, uncoating, reverse transcription, virus assembly or maturation, etc. Another stumbling block is that in majority of acute infections viral replication is already at its peak when symptoms appear. To be effective, therefore, therapy has to be started in the incubation period, i.e. has to be prophylactic or preemptive.

CLASSIFICATION

1. *Anti-Herpes virus*
   Idoxuridine, Trifluridine, Acyclovir, Valacyclovir, Famciclovir, Ganciclovir, Valganciclovir, Cidofovir, Foscarnet, Fomivirsen
2. *Anti-Influenza virus*
   Amantadine, Rimantadine, Oseltamivir, Zanamivir
3. *Anti-Hepatitis virus/Nonselective antiviral drugs*
   Primarily for hepatitis B: Lamivudine, Adefovir dipivoxil, Tenofovir
   Primarily for hepatitis C: Ribavirin, Interferon α
4. *Anti-Retrovirus*
   (a) *Nucleoside reverse transcriptase inhibitors (NRTIs)*: Zidovudine (AZT), Didanosine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Tenofovir (Nt RTI)
   (b) *Nonnucleoside reverse transcriptase inhibitors (NNRTIs)*: Nevirapine, Efavirenz, Delavirdine
   (c) *Protease inhibitors*: Ritonavir, Atazanavir, Indinavir, Nelfinavir, Saquinavir, Amprenavir, Lopinavir
   (d) *Entry (Fusion) inhibitor*: Enfuvirtide
   (e) *CCR5 receptor inhibitor*: Maraviroc
   (f) *Integrase inhibitor*: Raltegravir

ANTI-HERPES VIRUS DRUGS

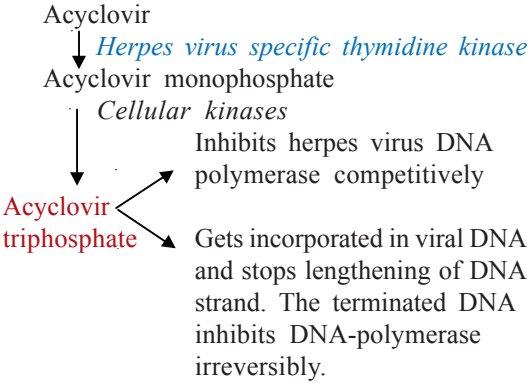
These are drugs active against the Herpes group of DNA viruses which include *Herpes simplex virus-1* (HSV-1), *Herpes simplex virus-2* (HSV2), *Varicella-Zoster virus* (VZV), *Epstein-Barr virus* (EBV), and *Cytomegalovirus* (CMV).

Idoxuridine It is 5-iodo-2-deoxyuridine (IUDR), which acts as a thymidine analogue. It was the first pyrimidine antimetabolite to be used as antiviral drug. It competes with thymidine, gets incorporated in DNA so that faulty DNA is formed which breaks down easily. It is effective only against DNA viruses and clinical utility is limited to topical treatment of *Herpes simplex* keratitis. Because of low virus selectivity, higher local toxicity and rapid development of viral resistance, use of idoxuridine is restricted to superficial dendritic keratitis when rapid action is required. Idoxuridine eye drops act faster than acyclovir eye ointment, which is more effective when there is stromal involvement of the cornea. Ocular irritation occurs with idoxuridine eye drops.
Dose: 0.1% eye drops to be instilled hourly, then 2 hourly and 4 hourly; apply 0.1% eye ointment at night.
IDURIN, TOXIL 0.1% eye drops and eye oint.

Trifluridine It is a fluorinated nucleoside which acts in the same way as idoxuridine, and inhibits HSV-1, HSV-2, CMV and related viruses. However, virus selectivity is low and DNA synthesis in host cells is also affected. In India trifluridine eye drop is approved for use in *H. simplex* keratitis. Higher efficacy than idoxuridine eye drops is reported. Ocular irritation and lid edema can occur.

Acyclovir

This deoxiguanosine analogue antiviral drug requires a virus specific enzyme for conversion to the active metabolite that inhibits DNA synthesis and viral replication.



Acyclovir is preferentially taken up by the virus infected cells. Because of selective generation of the active inhibitor in the virus infected cell and its greater inhibitory effect on viral DNA synthesis, acyclovir has low toxicity for host cells: a several hundred-fold chemotherapeutic index has been noted.

Acyclovir is active only against herpes group of viruses; HSV-1 is most sensitive followed by HSV-2 > VZV=EBV, while CMV is practically not affected. HSV and VZV have been found to develop resistance to acyclovir during therapy; the former primarily due to mutants deficient in thymidine kinase activity and the latter primarily by change in specificity of virus directed enzyme so that its affinity for acyclovir is decreased.

Pharmacokinetics Only about 20% of an oral dose of acyclovir is absorbed. It is little plasma protein bound and is widely distributed attaining CSF concentration that is 50% of plasma concentration. After topical application, it penetrates cornea well. Acyclovir is primarily excreted unchanged in urine, both by glomerular filtration and tubular secretion; plasma t½ is 2–3 hours. Renal impairment necessitates dose reduction. ZOVIRAX 200 mg tab, 250 mg/vial for i.v. inj; CYCLOVIR 200 mg tab, 5% skin cream; HERPEX 200 mg tab, 3% eye oint, 5% skin cream; OCUVIR 200, 400, 800 mg tab, 3% eye oint, ACIVIR-DT 200, 400, 800 mg tab. ACIVIR EYE 3% oint.

Use Acyclovir is effective in patients with normal as well as deficient immune status.

1. *Genital Herpes simplex* Generally caused by type-2 virus; can be treated by topical, oral or parenteral acyclovir depending on stage and severity of disease.

Primary disease: Topical treatment has low efficacy; 5% ointment is applied locally 6 times a day for 10 days. This is useful only if started early and in mild cases. Late and more severe cases should receive oral therapy (1 g/day in 5 divided doses or 400 mg TDS for 10 days) in addition to local therapy. Both local and oral therapies afford symptomatic relief and rapid healing of lesions, but do not prevent recurrences.

Recurrent disease: Topical therapy is totally ineffective. Response to oral treatment is slow and incomplete; severe cases may be treated parenterally—5 mg/kg i.v. infused over 1 hr, repeated 8 hourly for 10 days. Suppressive oral therapy with 400 mg BD has been shown to prevent recurrences as long as given. It is recommended to stop treatment after 1 yr and ascertain whether the patient is still having recurrences; if so restart treatment. After prolonged therapy frequency of recurrences is reduced. Continuous acyclovir prophylaxis is generally advocated in patients with > 8 recurrences per year. However, suppressive therapy reduces, but does not toally prevent, disease transmission to sexual partner.

2. *Mucocutaneous H. simplex* It is a type-1 virus disease, remains localized to lips and gums; does not usually require specific treatment, but acyclovir skin cream may provide some relief. Spreading lesions may be treated with 10 day oral acyclovir. Prophylactic oral therapy may prevent sun exposure related recurrences. The disease often gets disseminated in immunocompromised individuals and may be treated with oral or i.v. acyclovir (15 mg/kg/day) for 7 days, but recurrences are not prevented.

3. *H. simplex encephalitis* (type-1 virus): Acyclovir 10 to 20 mg/kg/8 hr i.v. for ≥10 days is the drug of choice. Treatment is effective only if started early: delay precludes salutary effect on mortality and neurological complications.

4. *H. simplex (type I) keratitis*: Acyclovir is equally effective as idoxuridine in superficial dendritic corneal ulcer, and may be better for deep stromal infections because of good corneal penetration. Though acyclovir eye ointment acts slower than idoxuridine eye drops, blindness can be prevented. The eye ointment should be applied 5 times daily till 3 days after healing.

5. *Herpes zoster*: The varicella-zoster virus is less susceptible to acyclovir. As such, higher doses are needed and it should be used only in immunodeficient individuals or in severe cases: 10 mg/kg/8 hr i.v. for 7 days. Oral therapy with 800 mg 5 times daily is beneficial only if started early. It affords symptomatic relief and faster healing of lesions. Postherpetic neuralgia is not prevented, though its duration may be shortened. Acyclovir skin cream may be applied on herpetic ulcers.

6. *Chickenpox*: in patients with immunodeficiency and in neonates only calls for specific therapy. Acyclovir (15 mg/kg/day i.v. × 7 days) is the drug of choice: reduces fever, eruptions, hastens healing and prevents visceral complications.

Oral acyclovir 400 mg 4 times a day for 7 days given during the incubation period may abort chickenpox in susceptible contacts.

Adverse effects

Topical: Stinging and burning sensation after each application.

Oral: The drug is well tolerated; headache, nausea, malaise and some CNS effects are reported.

Intravenous: Rashes, sweating, emesis and fall in BP occur only in few patients.

Dose-dependent decrease in g.f.r. is the most important toxicity; occurs especially in those with kidney disease; normalises on discontinuation of the drug.

Reversible neurological manifestations (tremors, lethargy, disorientation, hallucinations, convulsions and coma) have been ascribed to higher doses.

No teratogenic potential has been noted.

Valacyclovir It is an ester prodrug of acyclovir with improved oral bioavailability (55–70%) due to active transport by peptide transporters in the intestine. During passage through intestine and liver, it is completely converted to acyclovir in the first passage by esterases. Thus, higher plasma levels of acyclovir are obtained improving clinical efficacy in certain conditions; e.g. it is the drug of choice in herpes zoster. Valaciclovir is excreted in urine as acyclovir with a t½ of 3 hours.

Dose: For genital herpes simplex—first episode 0.5–1.0 g BD × 10 days; recurrent episode 0.5 g BD × 3 days; suppressive treatment 0.5 g OD × 6–12 months.

For orolabial herpes 2 g BD × 1 day; in immunocompromised patient 1 g BD × 5 days.

For herpes zoster 1 g TDS × 7 days.

VALCIVIR 0.5 g, 1.0 g tabs.

Famciclovir It is an ester prodrug of a guanine nucleoside analogue *penciclovir*, which has good oral bioavailability and prolonged intracellular t½ of the active triphosphate metabolite. Like acyclovir, it needs viral thymidine kinase for generation of the active DNA polymerase inhibitor. Famciclovir inhibits *H. simplex, H. zoster* but not acyclovir-resistant strains. Some activity against hepatitis B virus (HBV) has been noted. It is used as an alternative to acyclovir for genital or orolabial herpes and herpes zoster. Early treatment of herpes zoster reduces the duration of post herpetic neuralgia, but not its incidence.

Dose: Genital herpes (1st episode) 250 mg TDS × 5 days; recurrent cases 250 mg BD for up to 1 year. Herpes zoster and orolabial herpes 500 mg TDS for 7–10 days.

FAMTREX 250, 500 mg tabs.

Famciclovir is a less active alternative to lamivudine in chronic hepatitis B, but not in resistant cases. Side effects are headache, nausea, loose motions, itching, rashes and mental confusion.

Penciclovir, the active metabolite of famciclovir is available for i.v. use in some countries.

Ganciclovir It is an analogue of acyclovir which is active against all herpes viruses including *H. simplex*, *H. zoster,* EBV and CMV against which it is most active. Ganciclovir is also activated intracellularly by virus specific thymidine kinase and its triphosphate nucleotide preferentially inhibits viral DNA polymerase. This active metabolite attains much higher concentration inside CMV infected cells. The precursor cells in bone marrow are also quite sensitive to ganciclovir, and this may account for its bone marrow toxicity. Due to poor oral absorption, bioavailability of ganciclovir is low (<10%). *Valganciclovir*, the valyl prodrug, has ~ 8 times higher bioavailability, and is preferred, where available. Ganciclovir and its active metabolite are mostly excreted unchanged in urine. The plasma t½ of ganciclovir is 2–4 hrs, but that of its triphosphate inside CMV infected cells is > 24 hrs. These factors account for its high activity against CMV infections. CMV can develop ganciclovir resistance by mutation of viral phosphokinase and/or viral DNA polymerase.

Systemic toxicity of ganciclovir is high (bone marrow depression, rash, fever, vomiting, neuropsychiatric disturbances). Therefore, use is restricted to prophylaxis and treatment of severe CMV infections (pneumonia/colitis/retinitis) in immunocompromised (AIDS, transplant recipient) patients. Treatment may be initiated with i.v. infusion of ganciclovir 10 mg/kg/day which can prevent blindness in AIDS patients with CMV retinitis. Oral valganciclovir has replaced i.v. ganciclovir for long-term therapy. After control of retinitis, oral suppressant therapy is indicated.

Dose: Prophylaxis and treatment of CMV infections in immunocompromised patients: 5 mg/kg twice daily for 1–3 weeks, followed by 5 mg/kg once daily.

GANGUARD 250, 500 mg tabs.

Cidofovir It is a monophosphate nucleotide analogue of cytidine which inhibits most DNA viruses including HSV, CMV, pox and adenoviruses. Many HSV resistant to acyclovir and many CMV resistant to ganciclovir are susceptible. Because it is a monophosphate, it does not require viral phosphokinase and is converted to the active diphosphate by cellular enzymes. Cidofovir diphosphate does not preferentially accumulate in virus infected cells, but remains intracellularly for long periods to inhibit viral DNA polymerase, as well as acts as its alternative substrate. Weekly therapy is, therefore, possible despite short plasma t½ (2–3 hours) of cidofovir itself. CMV develops cidofovir resistance by mutation of its DNA polymerase.

Very little cidofovir is absorbed orally. It is administered by infusion with pre and post dose oral probenecid which inhibits its tubular secretion and improves its availability for entering into cells, as well as reduces nephrotoxicity. Cidofovir 5 mg/kg i.v. weekly and then every 15 dyas is used for CMV retinitis in AIDS patients, particularly those who have failed ganciclovir therapy. It can also be used for acyclovir-resistant mucocutaneous herpes simplex in immunosuppressed patients. It can be applied topically on anogenital warts. The primary toxicity of cidofovir is dose related kidney damage. Gastric disturbances, constitutional symptoms, hypersensitivity reactions, neutropenia and uveitis are the other adverse effects.

Foscarnet It is a simple straight chain phosphonate unrelated to any nucleic acid precursor which inhibits viral DNA polymerase and reverse transcriptase. It is active against *H. simplex* (including strains resistant to acyclovir), CMV (including ganciclovir-resistant ones), other herpes group viruses and HIV. Viral resistance to foscarnet is minimal. However, viral selectivity of foscarnet is low. Oral absorption is poor. Its t½ is 4–8 hours, and it is not metabolised.

Toxicity of foscarnet is high: damages kidney— produces a renal diabetes like condition, acute renal failure can also occur. Anaemia, phlebitis, tremor, convulsions and other neurological as well as constitutional symptoms due to hypocalcaemia are frequent. Administered by i.v. infusion, foscarnet has been used for:

1. CMV retinitis and other CMV infections in AIDS patients; efficacy is similar to ganciclovir, includes resistant cases, but produces more adverse effects.
2. Acyclovir-resistant mucocutaneous *H. simplex* type 2 and varicella-zoster infections in AIDS patients.

When used to treat associated CMV/*H. simplex*/VZV infection in AIDS patient, it decreases HIV viral titre, and may improve outcome in patients receiving highly active antiretroviral therapy (HAART).

Fomivirsen It is an antisense oligonucleotide which binds to the mRNA of CMV and interferes with transcription of early peptides in viral replication. CMV that has become resistant to ganciclovir, cidofovir and foscarnet is inhibited by fomivirsen. For CMV retinitis it has been injected weekly-to-monthly into the vitreous humor. Ocular complications are common and it has been discontinued in USA.

ANTI-INFLUENZA VIRUS DRUGS

Amantadine

Chemically, it is a unique tricyclic amine unrelated to any nucleic acid precursor, but inhibits replication of influenza A virus (a myxovirus). The antiviral activity of amantadine is strain specific; influenza B is not affected. Moreover, H5N1 (avian influenza/bird flu) and H1N1 (swine flu) strains of influenza A are resistant in most areas. It appears to act at an early step (possibly uncoating) as well as at a late step (viral assembly) in viral replication. A protein designated 'M2' which acts as an ion channel has been identified as one of its targets of action. Resistance to amantadine develops by mutation causing amino acid substitutions in the M2 protein. Amantadine is well absorbed orally and excreted unchanged in urine over 2–3 days (t½ 16 hr).

Adverse effects Generally well tolerated; nausea, anorexia, insomnia, dizziness, nightmares, lack of mental concentration, rarely hallucinations have been reported. Ankle edema occurs due to local vasoconstriction.

Uses

1. Prophylaxis of influenza A_2 during an epidemic or seasonal influenza, especially in high risk patients. Influenza season and epidemics generally last ~ 2 months, and only this period needs to be covered by prophylaxis. Only when the epidemic causing strain of virus is known to be sensitive to amantadine, should prophylactic use be considered. For seasonal prophylaxis success rate is variable, but often substantial. Amantadine does not interfere with antibody response to influenza vaccination; both may be given together. If the vaccine is given, amantadine can be stopped after 2 weeks. However, amantadine is no longer recommended in UK, either for prophylaxis or for treatment of influenza.
2. Treatment of influenzal (A_2) illness: a modest therapeutic effect (reduction in fever, congestion, cough and quicker recovery) occurs if the drug is given immediately after the symptoms appear. A 5 day treatment is advised.
3. Parkinsonism (*see* Ch. 31)

Dose: 100 mg BD, elderly—half dose, children 5 mg/kg/day; 100 mg OD may be used for prophylaxis.
AMANTREL, NEAMAN 100 mg tab.

Contraindications: epilepsy and other CNS disease; gastric ulcer, pregnancy.

Rimantadine This methyl derivative of amantadine is more potent, longer acting (t½ 30 hours) and better tolerated than the parent drug. Incidence of side effects is lower. Oral bioavailability of rimantadine is higher and it is largely metabolized by hydroxylation followed by glucuronide conjugation. The metabolites are excreted in urine. Dose and clinical application in influenza A is similar to amantadine and it is being preferred over the latter. However, amantadine resistant virus is resistant to rimantadine as well.

Dose: 100 mg BD; elderly and renal insufficiency patients 100 OD; children 5 mg/kg/day.
FLUMADINE 100 mg tab.

Oseltamivir This newer anti-influenza virus drug is a sialic acid analogue with broad spectrum activity covering influenza A (amantadine sensitive as well as resistant), H5N1 (bird flu), nH1N1 (swine flu) strains and influenza B. It is an ester prodrug that is rapidly and nearly completely hydrolysed during absorption in intestine and by liver to the active form *oseltamivir carboxylate* with an oral bioavailability of ~ 80%. The active metabolite is not further metabolized and is excreted by the kidney with a t½ of 6–10 hours. It acts by inhibiting influenza virus neuraminidase enzyme which is needed for release of progeny virions from the infected cell. Spread of the virus in the body is thus checked. Resistance can develop by mutation of the viral neuraminidase enzyme. In many areas oseltamivir-resistant H1N1 (seasonal influenza) and H5N1 have been encountered, though swine flu (nH1N1) is still mostly sensitive. Some oseltamivir-resistant strains remain susceptible to zanamivir and *vice versa*.

Oseltamivir is indicated both for prophylaxis as well as treatment of influenza A, swine flu, bird flu and influenza B. Started at the onset of symptoms, it is the most effective drug; reduces the severity, duration and complications of the illness. Prophylactic use for 5–10 days prevents illness in contacts of influenza patients.

Dose: therapeutic 75 mg oral BD for 5 days; prophylactic 75 mg OD.
TAMIFLU, ANTIFLU 75 mg cap, 12 mg/ml susp., FLUVIR 75 mg cap.

Side effects are nausea and abdominal pain due to gastric irritation (reduced by taking the drug with food), headache, weakness, sadness, diarrhoea, cough and insomnia. Skin reactions have been reported.

Zanamivir Another influenza A (including amantadine-resistant, nH1N1, H5N1 strains) and influenza B virus neuraminidase inhibitor that is administered by inhalation as a powder due to very low oral bioavailability. Small amount

that is absorbed after inhalation is excreted by the kidney with a t½ of 2–5 hours. The mechanism of action, clinical utility and efficacy of zanamivir are similar to that of oseltamivir. Some variant strains resistant to oseltamivir remain sensitive to zanamivir and *vice versa.* It can be used as an alternative to oseltamivir, and is equally effective in reducing severity, duration and complications of the disease. Prophylactic use may be made for 7–10 days in household contacts.

Dose: 10 mg through breath actuated inhaler, BD × 5 days for treatment, and OD for prophylaxis.

RELENZA 5 mg/actuation powder inhaler.

The inhaled powder can induce bronchospasm in some individuals. This may be severe in asthmatics; contraindicated in them. Headache, dizziness, nausea and rashes are mild and infrequent side effects.

ANTI-HEPATITIS VIRUS/NONSELECTIVE ANTIVIRAL DRUGS

Several antiviral drugs are relatively virus nonselective and inhibit viruses belonging to different classes; even cover both DNA and RNA viruses. While hepatitis B virus (HBV) is a DNA virus which, like retroviruses, can integrate into host chromosomal DNA to establish permanent infection, the hepatitis C virus (HCV) is a RNA virus, which does not integrate into chromosomal DNA, does not establish noncurable infection, but frequently causes chronic hepatitis.

Lamivudine, a nucleoside analogue, is active against HVB as well as HIV, and is described with antiretroviral drugs on p. 807–08.

Adefovir dipivoxil *Adefovir* is a monophosphate analogue of AMP which is active against HBV and some other DNA as well as RNA viruses, but is used only for hepatitis caused by HBV. Esterases in the intestine and liver release the active drug during absorption to attain oral bioavailability of ~60% in terms of adefovir, which is then distributed in whole body water. On entering cells, adefovir is phosphorylated to the diphosphate which has high affinity for HBV DNA polymerase compared to host cell DNA polymerase. This enzyme is inhibited and adefovir itself gets incorporated in the viral DNA resulting in termination of the DNA chain. Adefovir is primarily excreted by the kidney. While its plasma t½ is 7 hours, intracellular t½ of the diphosphate is upto 18 hours.

Adefovir is indicated in chronic hepatitis B, including lamivudine-resistant cases and those having concurrent HIV infection. There is no cross resistance between adefovir and lamivudine. Clinical, biochemical (liver function tests), histological, serological and virological response occurs in nearly 50% patients within 1 year. More cases respond with continued treatment. The optimum duration of treatment is uncertain. Ocurrence of adefovir resistance is infrequent.

Dose: 10 mg/day; ADESERA, ADFOVIR 10 mg tab.

At 10 mg/day dose adefovir is well tolerated. Side effects are sore throat, headache, weakness, abdominal pain and flu syndrome. Nephrotoxicity occurs at higher doses and in those with preexisting renal insufficiency. Lactic acidosis is a risk in patients receiving anti-HIV drugs.

Tenofovir It is a monophosphate nucleotide related to AMP, which is active against HBV as well as HIV. Due to very low oral absorption, it is used as the disoproxil ester prodrug, which not only improves bioavailability, but also intracellular passage of the active form. Tenofovir released from hydrolysis of the prodrug is diphosphorylated by cellular kinases into tenofovir diphosphate which preferentially inhibits HBV-DNA polymerase and HIV-reverse transcriptase. Affinity for host DNA-polymerase is very low. It also gets incorporated in the viral DNA to cause chain termination.

Tenofovir disoproxil is incompletely, but adequately absorbed after oral intake, and is largery excreted by the kidney with a plasma t½ of ~ 16 hours. It produces few side effects, which are mostly limited to the g.i. tract: nausea, flatulence, abdominal discomfort, loose motions and headache. Remarkably, renal toxicity is quite rare, though slight increase in serum creatinine occurs. Drug interactions are also not significant.

Administered in a dose of 300 mg daily, tenofovir disoproxil has produced good clinical and virological response in chronic hepatitis B. In a comparative study, higher percentage of patients responded within one year of use than with adefovir. A response rate of > 90% has been reported among HBe antigen negative patients. Tenofovir-resistance has not developed during treatment of chronic hepatitis B, and it is effective in lamivudine-resistant cases. Due to its high efficacy, good tolerability and low risk of resistance, tenofovir is being preferred for HBV infection, especially lamivudine resistant cases.
TENTIDE, TENOF 300 mg tab; 1 tab OD.

Ribavirin This purine nucleoside analogue has broad-spectrum antiviral activity, including that against influenza A and B, respiratory syncytial virus and many other DNA and double stranded RNA viruses. Its mono- and triphosphate derivatives generated intracellularly inhibit GTP and viral RNA synthesis and have other sites of action as well. Viral resistance to ribavirin is rare.

Oral bioavailability of ribavirin is ~50%. It is partly metabolized and eliminated in a multi-exponential manner; accumulates in the body on daily dosing and persists months after discontinuation; long term t½ is > 10 days.

Administered orally or i.v. ribavirin has been used in severe influenza A/B and measles in immunosuppressed patients as well as for herpes virus infections, acute hepatitis, but is not a first line drug for any of these. The most common therapeutic use of oral ribavirin is in chronic hepatitis C. Though ribavirin monotherapy may produce a response, it is incomplete. As per current recommendation, the first line treatment of chronic hepatitis C is oral ribavirin combined with injected peginterferon for 6–12 months. Recurrent cases are treated in the same way. Nebulized ribavirin is used for respiratory syncytial virus bronchiolitis in infants and children, particularly those with congenital heart disease, prematurity or other high risk conditions. It has also shown efficacy in some rare viral infections.
Dose: 200 mg QID; 400 mg TDS for body weight ≥ 75 kg (children 15 mg/kg/day).
VIRAZIDE, RIBAVIN 100, 200 mg caps, 50 mg/5 ml syr.

Prominent toxic effects are anaemia, bone marrow depression, haemolysis, CNS and g.i. symptoms. It is also teratogenic. The aerosol can cause irritation of mucosae and bronchospasm.

Interferon α

Interferons (IFNs)are low molecular weight glycoprotein cytokines produced by host cells in response to viral infections, TNFα, IL-1 and some other inducers. They have nonspecific antiviral as well as other complex effects on immunity and cell proliferation. Interferons bind to specific cell surface receptors and affect viral replication at multiple steps, *viz.* viral penetration, synthesis of viral mRNA, assembly of viral particles and their release, but the most widespread effect is direct or indirect suppression of viral protein synthesis, i.e. inhibition of translation. Interferon receptors are JAK-STAT tyrosine protein kinase receptors which on activation phosphorylate cellular proteins. These then migrate to the nucleus and induce transcription of 'interferon-induced-proteins' which exert antiviral effects.

Interferons inhibit many RNA and DNA viruses, but they are host specific: those produced by another species have poor activity in man. Three types of human IFNs (α, β and γ) are known to have antiviral activity. Only IFNα_{2A} and IFNα_{2B} produced by recombinant technology are available and are clinically used. Both are nonglycosylated low MW proteins administered by i.m. or s.c. injection. Their pegylated forms are meant for s.c. injection at weekly intervals. Plasma levels of pegIFNα_{2A} are sustained twice longer than those of pegIFNα_{2B}.

After i.m./s.c. injection, interferon is distributed to tissues. It is degraded mainly in liver and kidney, and remains detectable in plasma for 24 hours. However, cellular effects are longer lasting because the interferon induced proteins persist, so that IFN is generally administered thrice weekly. Complexed with polyethylene glycol (*peginterferon*), it is absorbed more slowly—exerts more sustained effects, permiting weekly administration and improving clinical efficacy.

PegIFN has replaced IFN, except for consideration of cost.

ALFERON: Interferon α_{2A} 3MU/vial inj, ZAVINEX 3MU, 5MU vials for inj.

REALFA-2B, SHANFERON, VIRAFERON: Interferon α_{2B} 3MU, 5MU vials for inj.

Uses

1. *Chronic hepatitis B:* IFNα_{2A} 2.5–5 MU/m^2 or IFNα_{2B} 5–10 MU given 3 times per week for 4–6 months causes disappearance of HBV-DNA from plasma and improvement in liver function tests/histology in nearly half of the patients. High doses (10 MU) injected thrice weekly for 6 months often produce prolonged remission, but relapses do occur. The pegIFNs 180 µg s.c. once weekly for 24–48 weeks produce better and more sustained responses.
2. *Chronic hepatitis C:* IFNα_{2B} 3MU 3 times weekly for 6–12 months has produced remission in 50–70% patients. Viral RNA becomes undetectable and liver function tests return to normal. Histology improves if response is sustained. However, relapses occur in majority of patients. PegIFNs 180 µg/week are more effective and induce longer lasting remissions. Combination with oral ribavirin increases number of responders, and decreases chances of relapse. Combination therapy with IFN/pegIFN + ribavirin is particularly indicated in patients who do not respond to IFN alone.
3. *AIDS-related Kaposi's sarcoma:* IFN is used to treat AIDS related Kaposi's sarcoma, but not to treat HIV as such. However, interferon accentuates haematological toxicity of zidovudine.
4. *Condyloma acuminata:* caused by papilloma virus is usually treated with topical podophyllin. Intralesional interferon injection may be used in refractory cases.
5. *H. simplex, H. zoster* and CMV: For these infections in immunocompromised patients, interferon is inferior to acyclovir/ganciclovir. It may be used as second line/adjuvant drug.
6. Interferons are also used in chronic myeloid leukaemia, follicular lymphoma, cutaneous T-cell lymphoma and multiple myeloma.

Interferon is not effective orally. Clinical utility of s.c. or i.m. injected interferon is limited by substantial adverse effects.

Adverse effects

- Flu-like symptoms—fatigue, aches and pains, malaise, fever, dizziness, anorexia, nausea, taste and visual disturbances develop few hours after each injection, but become milder later.
- Neurotoxicity—numbness, neuropathy, altered behaviour, mental depression, tremor, sleepiness, rarely convulsions.
- Myelosuppression: dose dependent neutropenia, thrombocytopenia.
- Thyroid dysfunction (hypo as well as hyper).
- Hypotension, transient arrhythmias, alopecia and liver dysfunction.

ANTI-RETROVIRUS DRUGS

These are drugs active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging and improving the quality of life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC), but do not cure the infection. The clinical efficacy of antiretrovirus drugs is monitored primarily by plasma HIV-RNA assays and CD4 lymphocyte count carried out at regular intervals.

HIV is a single stranded RNA retrovirus which uniquely carries out reverse transcription of proviral DNA from viral RNA (normally RNA is transcripted from DNA) with the help of a viral RNA-dependent DNA polymerase (reverse transcriptase). The primary cell type attacked by HIV is the CD4+ helper T-lymphocyte, but later macrophages and some other cell types may also be infected. When population of CD4 cells declines markedly (<200 cells/µL), cell mediated immunity (CMI) is lost and opportunistic infections abound, to which the victim ultimately succumbs, unless treated. Because the HIV genome integrates with the host DNA, eradication of the virus from the body of the victim appears impossible at present.

Over the past 30 years, a number of virus specific targets have been identified and drugs for these developed. We now have drugs which effectively suppress HIV replication and restore

CMI for variable periods of time. The two established targets for anti-HIV attack are:
(a) *HIV reverse transcriptase*: Which transcripts HIV-RNA into proviral DNA.
(b) *HIV protease*: Which cleaves the large virus directed polyprotein into functional viral proteins.

In addition, some newer targets being exploited are:

- Fusion of viral envelope with plasma membrane of CD4 cells through which HIV-RNA enters the cell.
- Chemokine coreceptor (CCR5) on host cells which provide anchorage for the surface proteins of the virus.
- HIV-integrase: Viral enzyme which integrates the proviral DNA into host DNA.

The first anti-retrovirus (ARV) drug *zidovudine* was made available for use in 1987. Over the past 25 years a large number of drugs belonging to 3 classes *viz.* Nucleoside or Non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs) and HIV-protease inhibitors (PIs) have been produced and extensively used. Recently few drugs for the newer targets have also become available for use in patients who have failed several regimens employing the 3 major groups of drugs, and have viral multiplication despite optimized background therapy.

The aim of anti-HIV therapy is to cause maximal suppression of viral replication for the maximal period of time that is possible. For this, ARV drugs are always used in combination of at least 3 drugs and regimens have to be changed over time due to development of resistance. Life long therapy is required.

Over the past 35 years, HIV infection has emerged as a major global health problem. Though, with the use of effective antiretroviral therapy (ART) the prevalence is declining in the present century, WHO estimate in 2009 showed that 33.3 million people world wide were living with HIV, and HIV/AIDS killed 1.8 million people in 2010, most of them in subsaharan Africa. India is a relatively low HIV prevalence country, but it has the 3rd largest number of people living with HIV, which was 2.4 million in 2009, concentrated mostly among female sex workers, injection drug abusers, transgenders, etc. India launched its National AIDS Control Programme (NACP) in 1992, but the prevalence and annual death rate has declined steadily only after 2004 when the National AIDS Control Organization (NACO) rolled-out free combination ART to eligible registered patients. Currently ~ 5 lac patients are alive on ART*, and new infections have declined by > 50% during the last decade, which in a large measure, is due to effective use of combination ART.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Zidovudine It is a thymidine analogue (azido-thymidine, AZT), the prototype NRTI. After phosphorylation in the host cell—zidovudine triphosphate selectively inhibits viral reverse transcriptase in preference to cellular DNA polymerase.

Single-stranded viral RNA
↓ Virus directed reverse transcriptase (*inhibited by zidovudine triphosphate*)
Double-stranded proviral DNA

On the template of single-stranded RNA genome of HIV, a double-stranded DNA copy is produced by viral reverse transcriptase. This proviral DNA translocates to the nucleus and is integrated with chromosomal DNA of the host cell (by viral integrase enzyme) which then starts transcribing viral genomic RNA as well as viral mRNA. Under the direction of viral mRNA, viral regulatory and structural proteins are produced in the form of a polyprotein. Finally, viral particles are assembled and matured after fractionation of the polyprotein by viral protease. Zidovudine thus prevents infection of new cells by HIV, but has no effect on proviral DNA that has already integrated into the host chromosome. It is effective only against retroviruses. Zidovudine itself gets incorporated into the proviral DNA and terminates chain elongation. Resistance to AZT occurs by point mutations which alter reverse transcriptase enzyme. In the past, when AZT was used alone, >50% patients became nonresponsive to AZT within 1–2 years therapy due to growth of resistant mutants.

Pharmacokinetics The oral absorption of AZT is rapid, but bioavailability is ~65%. It is quickly

* NACO Annual report 2011-12 [http/www.nacoonline.org]

cleared by hepatic glucuronidation (t½ 1 hr); 15–20% of the unchanged drug along with the metabolite is excreted in urine. Plasma protein binding is 30% and CSF level is ~50% of that in plasma. It crosses placenta and is found in milk.

Dose Adults 300 mg BD; Children 180 mg/m^2 (max 200 mg) 6–8 hourly.

RETROVIR, ZIDOVIR 100 mg cap, 300 mg tab, 50 mg/5 ml syr VIRO-Z, ZIDOMAX, ZYDOWIN 100 mg cap, 300 mg tab. (to be taken with plenty of water).

Adverse effects Toxicity is mainly due to partial inhibition of cellular mitochondrial DNA polymerase γ which has higher affinity for zidovudine triphosphate than chromosomal DNA polymerase. Anaemia and neutropenia are the most important and dose-related adverse effects. Nausea, anorexia, abdominal pain, headache, insomnia and myalgia are common at the start of therapy, but diminish later.

Myopathy, pigmentation of nails, lactic acidosis, hepatomegaly, convulsions and encephalopathy are infrequent.

Interactions Paracetamol increases AZT toxicity, probably by competing for glucuronidation. Azole antifungals also inhibit AZT metabolism. Other nephrotoxic and myelosuppressive drugs and probenecid enhance toxicity. Stavudine and zidovudine exhibit mutual antagonism by competing for the same activation pathway.

Use Zidovudine is used in HIV infected patients only in combination with at least 2 other ARV drugs. It is one of the two optional NRTIs used by NACO for its first line triple drug ARV regimen. Its efficacy as monotherapy in AIDS was confirmed in the past. HIV-RNA titer is reduced to undetectable levels and CD4 count increases progressively. Immune status is improved and opportunistic infections become less common. There is a sense of well-being and patients gain weight. AZT also reduces neurological manifestations of AIDS and new Kaposi's lesions do not appear. Mortality among AIDS patients is reduced. However, beneficial effects are limited from a few months to a couple of years after which progressively non-responsiveness develops.

AZT, along with two other ARV drugs is the standard choice for post-exposure prophylaxis of HIV, as well as for mother to offspring transmission (*see* p. 814-15).

Didanosine (ddI) It is a purine nucleoside analogue which after intracellular conversion to didanosine triphosphate competes with ATP for incorporation into viral DNA, inhibits HIV reverse transcriptase and terminates proviral DNA. Antiretroviral activity of didanosine is equivalent to AZT. Mutational resistance develops, but only few AZT resistant mutants are non-responsive to didanosine also. Its use has declined due to higher toxicity than other NRTIs.

Dose: 400 mg/day (for ≥ 60 kg BW), 250 mg/day (< 50 kg BW) 1 hour before or 2 hour after meals.

DINEX EC, DDRETRO, VIROSINE DR 250 mg, 400 mg tabs.

Oral absorption of didanosine is somewhat erratic due to acid lability. It is metabolized as well as excreted unchanged; t½ 1 to 1.5 hr. In contrast to AZT, it does not cause myelosuppression. The major dose-related toxicity is peripheral (stocking and glove) neuropathy, which may be irreversible, and rarely acute pancreatitis. Diarrhoea, abdominal pain, dry mouth and nausea are the side effects.

Stavudine (d4T) It is also a thymidine analogue which acts in the same way as AZT. By utilizing the same thymidine kinase for activation, AZT antagonises the effect of stavudine and the two should not be used together. It should also not be combined with didanosine, because both cause peripheral neuropathy. Resistance to stavudine develops as for other NRTIs.

It is well absorbed orally and rapidly metabolized (t½ 1.5 hr). The anti-HIV efficacy of stavudine is comparable to AZT, and it is used in combination regimens. Frequent peripheral neuropathy, lipodystrophy, lactic acidosis, and rarely pancreatitis are the serious adverse effects which have restricted its use. However for operational and cost considerations, stavudine is one of the optional components of first line regimen used by NACO.

Dose: 30 mg BD irrespective of body weight (WHO and NACO guidelines 2007)

STAG , STAVIR, VIROSTAV 30, 40 mg caps.

Lamivudine (3TC) This deoxycytidine analogue is phosphorylated intracellularly and

inhibits HIV reverse transcriptase as well as HBV DNA polymerase. Its incorporation into DNA results in chain termination. Most human DNA polymerases are not affected and systemic toxicity of 3TC is low. Point mutation in HIV-reverse transcriptase and HBV-DNA polymerase gives rise to rapid lamivudine resistance. However, certain lamivudine-resistant mutants become slow growing and have lower virulence. Some cross-resistance with didanosine has been noted among HIV.

Oral bioavailability of 3TC is high and plasma t½ longer (6–8 hours). Intracellular t½ is still longer (> 12 hr). It is mainly excreted unchanged in urine.

Lamivudine is used in combination with other anti-HIV drugs, and appears to be as effective as AZT. It synergises with most other NRTIs for HIV, and is an essential component of all first line triple drug NACO regimens for AIDS. It is also a first line drug for chronic hepatitis B. HBV-DNA titre is markedly reduced and biochemical as well as histological indices of liver function improve. However, viral titres rise again after discontinuation. Even with continued medication HBV viraemia tends to return after 1–4 years due to emergence of resistant mutants.

Dose: For chronic hepatitis B—100 mg OD
For HIV infection— 150 mg BD, or 300 mg OD.
LAMIVIR 150 mg tab, 150 mg/ 5 ml soln; LAMIVIR-HBV 100 mg tab; HEPTAVIR, LAMIDAC, LAMUVID, VIROLAM 100, 150 mg tabs;

Lamivudine is generally well tolerated and has low toxicity, because of which it is accorded high priority in use. Side effects are few—headache, fatigue, rashes nausea, anorexia, abdominal pain. Pancreatitis and neuropathy are rare. Hematological toxicity does not occur.

Abacavir (ABC) This guanosine analogue is a clinically potent ARV drug that acts after intracellular conversion to carbovir triphosphate, which gets incorporated in proviral DNA and terminates chain elongation. Rapid reduction in plasma HIV-RNA count and rapid rise in CD4 cell count has been noted when abacavir was given to AIDS patients. Resistance to ABC develops slowly, and it exhibits little cross resistance with other NRTIs. Its oral bioavailability is 80% and it is mainly eliminated by metabolism. The plasma t½ is 1–1.5 hour, but intracellular t½ of the active metabolite is >12 hours. Hypersensitivity reactions such as rashes, fever, abdominal pain, bowel, upset, flu-like respiratory and constitutional symptoms, which occur in 2–5% adult patients, are the major problems. Abacavir must be promptly stopped when the reaction occurs, because fatalities have occurred when patients developing the reaction were given further doses of ABC. A genetic basis and massive release of TNFα have been related to this reaction. Abacavir should never be given again to a patient who has developed this reaction. Other side effects are not serious. Lypodystrophy is least likely. Avoidance of alcohol is advised. Combination regimens including abacavir are frequently used.

Dose: 300 mg BD or 600 mg OD.
ABAVIR, ABAMUNE 300 mg tab.

Tenofovir This is the only nucleotide (not nucleoside) analogue that is a relatively newer addition to the clinically used anti-HIV drugs. It is also active against HBV, and its pharmacology is described on p. 803. Tenofovir was initially used only in previously treated patients, but because of good tolerability profile, it is now being included in first line regimens as well. Tenofovir containing regimens have been found at least as effective and less toxic as other first line regimens. NACO includes tenofovir in its first line 3 drug regimen as an alternative when either zidovudine or nevirapine/efavirenz cannot be used due to toxicity/contraindication.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Nevirapine (NVP) and Efavirenz (EFV) These are nucleoside unrelated compounds which directly inhibit HIV reverse transcriptase without the need for intracellular phosphorylation. Their locus of action on the enzyme is also different, and they are non-competitive inhibitors. They are more potent than AZT on HIV-1, but do not inhibit HIV-2. Accordingly, they are not indicated in infections caused by HIV-2. If used alone, viral resistance to NNRTIs develops rapidly by

point mutation of the enzyme; they should always be combined with 2 other effective drugs. Cross-resistance between NVP and EFV is common, but not with NRTIs or PIs. A patient failing any NNRTI regimen should not be treated with another NNRTI.

NVP is well absorbed orally; is extensively metabolized, mainly by CYP3A4 and to a lesser extent by CYP2B6, with a t½ of ~ 30 hours. Oral absorption of EFV is ~ 50%, but the t½ is longer (48 hours). It is completely metabolized, mainly by CYP2B6 and a smaller fraction by CYP3A4. Both are enzyme inducers, and cause auto-induction of their own metabolism. However, EFV inhibits CYP3A4 as well. Nevirapine is started at a lower dose (200 mg/day); the dose is doubled after 2 weeks when its blood levels go down due to autoinduction. Such dose escalation is not required for EFV. Rifampin induces NVP metabolism and makes it ineffective, but has little effect on EFV levels. If a patient being treated with NVP develops TB and is put on rifampin, NVP should be replaced by EFV.

The NNRTIs are indicated in combination regimens for HIV. Either NVP or EFV is included in the first line triple drug regimen used by NACO. These drugs have also succeeded in reducing HIV-RNA levels when an earlier regimen (not including an NNRTI) has failed.

Nevirapine (NVP)

Dose: Initially 200 mg/day, to be increased after 2 weeks to 200 mg twice daily (because autoinduction reduces levels).

NEVIMUNE, NEVIVIR, NEVIPAN, NEVIRETRO 200 mg tab.

Rashes are the commonest adverse effect, followed by nausea and headache. Occasionally skin reactions are severe. Fever and rise in transaminases occurs dose dependently. NVP is potentially hepatotoxic. In patients developing NVP toxicity, it should be replaced by EFV which has low hepatotoxicity. NVP should not be used in patients with hepatic dysfunction.

Efavirenz (EFV) Its side effects are headache, rashes, dizziness, insomnia and a variety of neuropsychiatric symptoms. However, these symptoms decrease over time and discontinuation rate (due to adverse effect) is low. EFV is contraindicated in pregnancy and in women likely to get pregnant, since it is teratogenic. Because of its longer plasma t½, occasional missed doses of EFV are less damaging.

Dose: 600 mg OD on empty stomach.

EFFERVEN, VIRANZ, EVIRENZ 200 mg cap, 600 mg tab.

Retroviral protease inhibitors (PIs)

An aspartic protease enzyme encoded by HIV is involved in the production of structural proteins and enzymes (including reverse transcriptase and integrase) of the virus from the large viral polyprotein synthesized in the infected cell. The polyprotein is broken into various functional components by this protease enzyme. It acts at a late step in HIV replication, i.e. maturation of the new virus particles when the RNA genome acquires the core proteins and enzymes. Six protease inhibitors—*Atazanavir (ATV), Indinavir (IDV), Nelfinavir (NFV), Saquinavir (SQV), Ritonavir (RTV)* and *Lopinavir* (in combination with ritonavir *LPV/r*) have been marketed in India for use against HIV. They bind to the active site of protease molecule, interfere with its cleaving function, and are more effective viral inhibitors than AZT. Because they act at a late step of viral cycle, they are effective in both newly as well as chronically infected cells. Under their influence, HIV-infected cells produce immature noninfectious viral progeny—hence prevent further rounds of infection.

Oral bioavailability of PIs is variable (IDV and RTV ~65%, NFV >20%, SQV 15%) and their plasma t½ ranges from 2–8 hours. All are extensively metabolized mainly by CYP3A4, except NFV which is mainly a substrate of CYP2C19. All PIs (especially ritonavir and lopinavir) are potent inhibitors of CYP3A4, while some other CYP isoenzymes are induced. The PIs interact with many drugs. Nelfinavir, lopinavir and ritonavir induce their own metabolism.

In the past monotherapy with one of these drugs in previously AZT treated patients reduced HIV viral levels, increased CD4 cell count and

improved the clinical condition. However, viral resistance developed against the PIs over months due to selection of resistant mutants in a stepwise manner. Combination of NRTIs with PIs has been found more effective than either drug given alone, and triple therapy is more effective than double therapy. Current recommendations are to use a PI in combination with either two NRTIs or one NRTI + one NNRTI. However, PIs are avoided in 1st line regimens, because their use in initial regimens markedly restricts second line regimen options. Most guidelines, including that of NACO, reserve them for failure cases.

Because different PIs inhibit as well as induce specific CYP isoenzymes to different extents, drug interactions with them are common and often unpredictable. Manufacturer's package inserts should be consulted while coprescribing any other drug. Specifically, metabolism of PIs is induced by rifampin and other enzyme inducers rendering them ineffective. Another problem in their use is the large tablet load. In case of different PIs, 6–18 tablets are to be taken daily, some on empty stomach, but others with meals; and this has to go on for months and years. Therefore, patient acceptability and compliance are often low. One of the strategies adopted to reduce the dose of ATV, IDV, LPV and SQV is to combine them with a low and subtherapeutic dose (100 mg) of ritonavir. By reducing first pass metabolism, ritonavir increases the bioavailability and by slowing systemic metabolism decreases clearance of the companion PI. This 'boosted PI regimen' permits reduction in the number/frequency of tablets to be taken each day. Lopinavir is marketed only in combination with ritonavir. Nelfinavir is not to be combined with ritonavir because it is metabolized mainly by CYP2C19 that is not inhibited.

The most prominent adverse effects of PIs are gastrointestinal intolerance, asthenia, headache, dizziness, limb and facial tingling, numbness and rashes. Of particular concern are lipodystrophy (abdominal obesity, buffalo hump with wasting of limbs and face), dyslipidaemia (raised triglycerides and cholesterol) which may necessitate hypolipidaemic drugs, and insulin resistance. Diabetes may be exacerbated. Indinavir crystalises in urine and increases risk of urinary calculi.

Atazanavir (ATV) This PI is administered with light meal which improves absorption, while acid suppressant drugs decrease its absorption. ATV is primarily metabolized by CYP3A4, which is also moderately inhibited by it. Bioavailability and efficacy of ATV is improved by combining with RTV. The t½ is 6–8 hours. Dyslipidaemia and other metabolic complications are minimal with ATV, but jaundice occurs in some patients without liver damage due to inhibition of hepatic glucuronyl transferase.

Dose: 300 mg OD with ritonavir 100 mg taken at meal time.
ATAZOR 100, 150, 200, 300 mg caps.

Indinavir (IDV) It is to be taken on empty stomach; g.i. intolerance is common; excess fluids must be consumed to avoid nephrolithiasis. Hyperbilirubinaemia occurs. It is less frequently used now.

Dose: 800 mg TDS (BD if taken with 100 mg RTV).
INDIVAN, INDIVIR, VIRODIN 400 mg cap.

Nelfinavir (NFV) It is to be taken with meals, since food increases absorption, but bioavailability is erratic. NFV is mainly metabolized by CYP2C19. Often produces diarrhoea and flatulence; clinical efficacy may be somewhat lower than other PIs; less popular now.

Dose: 750 mg TDS; NELFIN, NELVIR, NEIVEX 250 mg tab.

Ritonavir (RTV) It is a potent PI; also a potent CYP3A4 inhibitor. Drug interactions, nausea, diarrhoea, paresthesias, fatigue and lipid abnormalities are prominent. Though RTV (600 mg twice daily) can be used as an antiretroviral drug, it is more commonly employed in a low dose (100 mg BD) to boost other PIs like LPV, ATV, SQV, IND, but not NFV.

RITOMUNE, RITOMAX 100 mg cap; RITOVIR 250 mg tab.

Saquinavir (SQV) Two types of formulations (hard gel and soft gel capsules) with differing, but low oral bioavailability have been produced. The tablet load is large and side effects are

frequent; photosensitivity can occur. Importantly, it is a weak inhibitor of CYP3A4.

Dose: 1200 mg TDS on full stomach; 1000 mg BD (with RTV 100 mg).

SAQUIN 200 mg tab.

Lopinavir It is available only in combination with RTV to improve bioavailability, though it is itself a CYP3A4 inhibitor. Diarrhoea, abdominal pain, nausea and dyslipidaemias are more common. Its dose needs to be increased by 1/3rd if either NVP or EFV is used concurrently.

Dose: 400 mg (with ritonavir 100 mg) BD with food.

RITOMAX-L: V-LETRA: lopinavir 133.3 mg + ritonavir 33.3 mg cap.

Entry (fusion) inhibitor

Enfuvirtide This HIV-derived synthetic peptide acts by binding to HIV-1 envelope transmembrane glycoprotein (gp41) which is involved in fusion of viral and cellular membranes. Fusion of the two membrances is thus prevented and entry of the virus into the cell is blocked. It is not active against HIV-2. No cross resistance with other classes of ARV drugs occurs. Administered s.c. twice daily, it is used as add on drug to an optimized regimen in selected patients who have failed many earlier regimens and for whom there is no other treatment option. The injections are painful and cause local nodules/cysts. The cost and inconvenience are prohibitive.

CCR5 receptor inhibitor

Maraviroc The globular glycoprotein gp120 of the HIV envelope anchors to the CD4 site of host cell by binding to a cell membrane receptor, which mostly is the CCR5 chemokine receptor (most HIV are CCR5-tropic). Maraviroc is a novel anti-HIV drug which targets the host cell CCR5 receptor and blocks it. Attachment of the virus and subsequent entry of viral genome into the cell is thus interfered. It has no effect on HIV strains that are CXCR4 receptor tropic (CXCR4 is an alternative chemokine receptor which also can bind gp 120), or dual CCR5/CXCR4 tropic.

Added to optimized background therapy in patients who have already been treated with several regimens and who have CCR5-tropic HIV infection, maraviroc has resulted in marked reduction in HIV-RNA load, and improvement in CD4 count. It is active orally and there is no cross resistance with any other ARV drug. However, CCR5-tropism must be proven before using it.

Though a number of side effects are reported, tolerability in general is satisfactory. Since it blocks one of the human chemokine receptor, there is concern about impaired immune surveillance and increased risk of infection/malignancy.

Integrase inhibitor

Raltegravir The HIV-proviral DNA transcripted in the cytoplasm of host cell translocates to the nucleus along with an integrase enzyme. The HIV-integrase nicks host chromosomal DNA and integrates the proviral DNA with it. Raltegravir is an orally active drug that blocks this step by inhibiting the integrase enzyme. It is active against both HIV-1 and HIV-2. Because of its unique mechanism of action, there is no cross resistance between it and any other ARV drug. Addition of raltegravir to optimized background therapy in repeatedly treated patients caused disappearance of HIV-RNA from circulation in a higher percentage of cases and improved the CD4 cell count. It has also shown good efficacy in untreated patients as a component of initial triple drug regimen along with two NRTIs. Side effects are nonspecific; myopathy is a potential toxicity. It is otherwise well tolerated. However, raltegravir is a new drug; efficacy and safety need to be established.

Some antiretroviral combinations

1. Lamivudine 150 mg + Zidovudine 300 mg tab (1 tab BD); COMBIVIR, CYTOCOM, DUOVIR, LAMUZID tab.
2. Lamivudine 150 mg + Stavudine 30 mg or 40 mg tab (1 tab BD); LAMIVIR-S, LAMOSTAD, VIROLIS tab.
3. Lamivudine 150 mg + Zidovudine 300 mg + Nevirapine 200 mg tab (1 tab BD); DUOVIR-N, CYTOCOM-N, NEXIVIR-Z.
4. Lamivudine 150 mg + Stavudine 30 mg or 40 mg + Nevirapine 200 mg tab (1 tab BD); LAMOSTAD-N, TROMUNE, VIROLANS.
5. Lamivudine 150 mg + Zidovudine 300 mg 2 tab and Efavirenz 600 mg 1 tab kit; CYTOCOM-E kit.

HIV TREATMENT PRINCIPLES AND GUIDELINES

The treatment of HIV infection and its complications is complex, prolonged, needs expertise, strong motivation and commitment of the patient, resources and is expensive. Antiretroviral therapy (ART) is only 25 years old, and is still evolving. Initially, anti-HIV drugs were used singly one after the other as each failed in a patient due to emergence of resistance. Understanding the biology of HIV infection and availability of several potent drugs belonging to different classes has mandated 'highly active antiretroviral therapy' (HAART) with combination of 3 or more drugs whenever indicated. Monotherapy is contraindicated.

It has been realized that even with HAART, which rapidly kills > 99% virions, a small number survive within the resting CD4 lymphocytes and invariably give rise to relapse when treatment is discontinued despite complete absence of detectable viraemia and normal CD4 cell count for years. Relapses occur even if the same ART is continued after disappearance of viraemia and immune reconstitution. This is because HIV-reverse transcriptase is highly copying error prone,

implying that viral replication produces changes at some base pairs (and codons) with high frequency—rate of mutation is high. Some mutations confer resistance to one or the other antiretroviral drugs. The resistant mutants are selected by anti-HIV therapy and in time an apparently sensitive population is replaced by resistant virions. As the disease progresses in the individual (and several anti-HIV drugs are used) the HIV population becomes genetically complex and diverse with respect to susceptibility to drugs. Each failing regimen limits future treatment options. Even primary drug resistance (i.e. in untreated patients) is being detected in 5–20% HIV patients. In developed countries, drug resistance studies are being recommended before initiating ART.

Since none of the currently available regimens can eradicate HIV from the body of the patient, the goal of therapy is to maximally and durably inhibit viral replication so that the patient can attain and maintain effective immune response towards potential microbial pathogens. Greater the suppression of viral replication, lesser is the chance of emergence of drug resistant virus. Effective ART reduces infectivity of the patient for other persons, thus serves to limit transmission.

Initiating antiretroviral therapy Although it is attractive to treat all symptomatic and asymptomatic HIV positive patients, little long-term clinical benefit has been demonstrated in asymptomatic cases with reasonable immune competence (CD4 cell count > 350/µl). Arguments against early treatment in asymptomatic stable patients include:

- Deleterious effect of anti-HIV drugs on quality of life, their side effects and toxicity, especially lipid abnormalities and drug interactions.
- Risk of drug resistance limiting future treatment options.
- Limited durability of available regimens.
- Risk of dissemination of resistant virus.
- High cost.

The best time to initiate anti-HIV therapy remains uncertain. Various professional bodies and health authorities have framed treatment guidelines from time-to-time. Highlights of the same are:

CD4 cell count is the major determinant of initiating therapy in asymptomatic cases. ART should be started before the immune system is precariously damaged and the patient becomes ill or develops opportunistic infection. Increased mortality occurs when treatment is begun after CD4 count has fallen below 200/µl, and response to anti-HIV drugs is suboptimal.

The US Department of Health and Human Services guidelines (2010) recommend instituting ART to:

(a) All symptomatic HIV disease patients.
(b) Asymptomatic patients when the CD4 cell count falls to 350/µl or less.
(c) All HIV patients coinfected with HBV/HCV requiring treatment.
(d) All pregnant HIV positive women.
(e) All patients with HIV-nephropathy.

In addition to above, the current NACO guidelines give priority in treatment to:

- All HIV-positive persons in WHO-clinical stage 3 and 4.
- All persons who tested HIV positive 6–8 years ago.
- Patients with history of pulmonary TB and/or Herpes zoster.
- HIV infected partners of AIDS patients.
- All HIV positive children < 15 years of age.

In developed countries some authorities now recommend initiating ART in asymptomatic subjects at CD4 count ≤ 500/µL, and not wait till it falls below 350/µL.Greater potency and better tolerability of newer anti-HIV drugs has prompted such recommendation in the hope of offering life expectancy approaching that of noninfected persons.

Therapeutic regimens Whenever treatment is instituted, it should be aggressive (HAART) with at least 3 anti-HIV drugs. The optimum response to any regimen is reduction of plasma HIV-RNA to undetectable levels (<50 copies/µl) within 6 months. In treatment-naive patients, therapy with 3 drugs is considered optimal. Addition of a fourth drug affords no additional benefit; may be tried in failed patients only. Due to availability of multiple drugs, a variety of combination regimens are possible and have been employed. However, no specific combination can be considered optimal initial regimen for all patients. Choice has to be made on the basis of efficacy, durability, tolerability, convenience,

drug interactions, impact on future options and cost.

Taking into consideration the above factors and the experience gained so far, the first line regimens universally include 2 NRTIs + 1 NNRTI. In developed countries, placing emphasis on tolerability and efficacy over cost and other constraints, preferred NRTIs are lamivudine, abacavir, tenofovir and sometimes emtricitabine. Efavirenz is preferred over nevirapine as the NNRTI. However, NACO selects first line regimens for untreated patients on the following principles:

- All regimens should have 2 NRTI+1NNRTI.
- Include lamivudine in all regimens.
- The other NRTI can be zidovudine or stavudine.
- Choose one NNRTI from nevirapine or efavirenz.
- Choose efavirenz in patients with hepatic dysfunction and in those concurrently receiving rifampin. Do not use efavirenz in pregnant women or in those likely to get pregnant.

The first-line NACO recommended regimens are listed in the box.

The other important general points are:

- The 3 drugs in the regimen should belong to at least 2 different classes. Single class regimens are inferior. There is convincing evidence that 3 NRTI regimens are clinically less effective than those which include 2 NRTI + 1 NNRTI.
- The 3 NRTI regimen is employed only when a NNRTI cannot be used.
- For treatment-naive patients, only PI sparing regimens (2 NRTI + NNRTI) are chosen. They are more convenient with lower pill burden, simpler dosing schedules, more acceptable, better tolerated and produce less metabolic complications.
- The PI containing regimens (2 NRTI + PI or NRTI + NNRTI + PI) are reserved for advanced cases who have failed earlier regimens.
- Low dose ritonavir boosted PIs are preferred over higher dose single PI due to lower pill burden and better tolerability.
- If drug toxicity develops, either the entire regimen should be interrupted or the offending drug should be changed. No dose reduction should be tried.
- 'Drug holidays' or 'structured treatment interruptions' may briefly improve well being (by absence of side effects), but allow viral replication and increase risk of drug resistance; are not recommended.
- Treatment is life-long.
- Institution of HAART in patients with latent or partially treated opportunistic infection may produce '*immune reconstitution syndrome*' characterized by marked inflammatory reaction against residual organisms and constitutional symptoms due to 'reestablishment of immune function.
- Pregnancy in women does not contraindicate ART. Drugs considered relatively safe during pregnancy are: zidovudine, lamivudine, nevirapine, nelfinavir, saquinavir.
- The ARV drug combinations that should not be employed are given in the box on p. 814.

Durability of the regimens depends mainly on adherence of the patient to it. Compliance is a major determinant of outcome. Use of combined drug formulations greatly improves convenience and adherence, and are

First-line antiretroviral regimens*

Preferred regimen

1. Lamivudine + Zidovudine + Nevirapine

Alternative regimens

1. Lamivudine + Zidovudine + Efavirenz
2. Lamivudine + Stavudine[1] + Efavirenz
3. Lamivudine + Stavudine + Nevirapine

Other options

1. Lamivudine + Tenofovir[2] + Nevirapine
2. Lamivudine + Tenofovir[2] + Efavirenz
3. Lamivudine[3] + Zidovudine + Tenofovir

* Recommended by NACO

1. Stavudine is substituted for zidovudine if patient is anaemic
2. Tenofovir is included when there is toxicity or other contraindication to both zidovudine and stavudine
3. 3NRTI regimen is only for patients unable to tolerate both nevirapine and efavirenz.

Antiretroviral drug combinations to be avoided

1. Zidovudine + stavudine:	Pharmacodynamic antagonism
2. Stavudine + didanosine:	Increased toxicity (neuropathy, lactic acidosis)
3. Lamivudine + didanosine:	Clinically not additive

recommended, unless doses have to be individualized for specific reasons. Therapy should not be discontinued during an acute opportunistic infection, except in case of intolerance, interactions or toxicity. Since multiple antiretroviral, anti-*P. jiroveci*, antitoxoplasma, anti-CMV/herpes virus, antitubercular, antifungal or other drugs may have to be used in a patient, careful attention to drug interactions and toxicities has to be paid.

Changing a failing regimen An ART regimen is considered to have failed when:

- Plasma HIV-RNA count is not rendered undetectable (<50 copies/µl) within 6 months therapy.
- Repeated detection of virus in plasma after initial suppression to undetectable levels despite continuation of the drug regimen.
- Clinical deterioration, fall in CD4 cell count, serious opportunistic infection while continuing drug therapy.

Failure is due to development of resistance to one or more components of the regimen. Treatment failures are to be anticipated and occur invariably after one to few years. The failed regimen should be changed entirely (all 3 drugs changed) to drugs that have not been administered earlier. A single drug should not be changed or added to a failed regimen.

In designing second line regimens, drugs with known overlapping viral resistance should be avoided, e.g. indinavir should not be substituted for nelfinavir or saquinavir; efavirenz should not be replaced by nevirapine. Viral resistance testing is recommended for selecting the salvage regimen. A boosted PI is nearly always included in 2nd line regimens. Because an NNRTI is nearly always used in 1st line regimens, and resistance to one NNRTI means resistance to all NNRTIs, this class is practically out for 2nd line regimens. With repeated failures it may become more difficult to construct an active combination. The integrase inhibitor, CCR5 inhibitor or fusion inhibitor may be considered at this stage. The 2nd line regimens suggested by NACO are listed in the box.

List of second line regimens*
(in order of preference)

NRTI components	PI component
Standard regimens	
1. Tenofovir + Abacavir	1. Lopinavir/r£
2. Didanosine + Abacavir	2. Atazanavir/r
3. Tenofovir + Zidovudine	3. Saquinavir/r
4. Tenofovir + Lamivudine	4. Indinavir/r
Special circumstances	5. Nelfinavir
1. Didanosine + Zidovudine	
2. Didanosine + Lamivudine	

* Suggested by NACO
£ r-low dose ritonavir boosted

Prophylaxis of HIV infection

Post-exposure prophylaxis (PEP) Health care workers and others who get accidentally exposed to the risk of HIV infection by needle-stick or other sharp injury or contact with blood/biological fluid of HIV patients or blood transfusion should be considered for PEP. The aim of PEP is to suppress local viral replication prior to dissemination, so that the infection is aborted. However, PEP is not necessary when the contact is only with intact skin, or with mucous membrane by only a few drops for short duration. It is also not indicated when the source is known to be HIV negative. The NACO recommends 2 types of regimens (*see* box) for PEP depending on the magnitude of risk of HIV transmission.

In developed countries, where a large number of source HIV patients have received one or more anti-HIV regimens and may be harbouring drug-resistant virus, alternative prophylactic regimens using stavudine, didanosine, abacavir, efavirenz have also been used. If the drugs received by the source person is known, prophylactic regimen may be individualized to include at least 2 drugs that the source has not received.

Post-exposure prophylaxis of HIV

Basic (2 drug) regimen* (for low risk)

Zidovudine 300 mg + Lamivudine 150 mg	Twice daily for 4 weeks

***Expanded (3 drug) regimen* (for high risk)$**

Zidovudine 300 mg + Lamivudine 150 mg	Twice daily
+	
Indinavir 800 mg (or another PI)	Thrice daily All for 4 weeks

**Low risk*

- When the source is HIV positive, but asymptomatic with low HIV-RNA titre and high CD4 cell count.
- Exposure is through mucous membrane, or superficial scratch, or through thin and solid needle.

$High risk

- When the source is symptomatic AIDS patient with high HIV-RNA titre or low CD4 count.
- Exposure is through major splash or large area contact of longer duration with mucous membrane or abraded skin or through large bore hollow needle, deep puncture, visible patient's blood on the needle.

Nevirapine is not recommended for PEP due to its hepatotoxic potential.

When indicated, PEP should be started as soon as possible, preferably within 1–2 hours of exposure. The likelihood of preventing infection declines with the delay; some guidelines do not recommend starting it beyond 72 hours of exposure. According to others, in case of default, PEP may be started even 1–2 weeks later. Though HIV infection may not be prevented, onset of AIDS may be delayed by the late-start PEP.

Prophylaxis after sexual exposure Though there is no data to evaluate the value of prophylaxis after sexual exposure, the same regimen as for needle stick may be used.

Perinatal HIV prophylaxis HIV may be transmitted from the mother to the child either through the placenta, or during delivery, or by breastfeeding. The highest risk (>2/3rd) of transmission is during the birth process. As per current recommendation, all HIV positive women, who are not on ART, should be put on the standard 3 drug ART. This should be continued through delivery and into the postnatal period, and has been shown to prevent vertical transmission of HIV to the neonate, as well as benefit mother's own health. The first line NACO regimen for pregnant women is:

Zidovudine + Lamivudine + Nevirapine

However, women with CD4 count > 250 cells/μL face a higher risk of hepatotoxicity due to NVP and should be closely watched. EFV is teratogenic, and not used, particularly in the first trimester. In HIV-positive women who are not taking ART, Zidovudine (300 mg BD) started during 2nd trimester and continued through delivery to postnatal period, with treatment of the neonate for 6 weeks has been found to reduce mother-to-child transmission by 2/3rd. Combination therapy is even more effective. Even if not started earlier, AZT administered during labour and then to the infant is also substantially protective. Breastfeeding by HIV-positive mother is contraindicated, because it carrys substantial risk of transmission to the infant.

☞ PROBLEM DIRECTED STUDY

58.1 A dental surgeon consults you with the following problem:

During a dental procedure he got exposed to a 26-year-old female patient's blood and saliva through a piercing injury on the finger. A needle had penetrated across his gloves and skin to a depth of 2–3 mm, but was withdrawn immediately and the area washed under running water. On enquiry, the patient revealed that one year back she had tested HIV positive, but was asymptomatic and not taking any anti-HIV medication.

(a) Should the dental surgeon be advised to take post-exposure prophylactic medication for HIV, or no medication is indicated under the circumstances?

(b) If medication is advised, which drug/drugs, doses and duration of use would be appropriate?

(*see* Appendix-1 for solution)

Chapter 59 Antimalarial Drugs

These are drugs used for prophylaxis, treatment and prevention of relapses of malaria.

Malaria, caused by 4 species of the protozoal parasite *Plasmodium*, is endemic in most parts of India and other tropical countries. It is one of the major health problems. As per latest WHO estimates (2011)* between 149–274 (median 216) million clinical cases and ~ 0.655 million deaths occur globally due to malaria each year, 90% of which are in Africa. This amounts to one malaria death every minute. In India the National Malaria Eradication Programme (NMEP), started in 1958, achieved near complete disappearance of the disease in 1960s (from 75 million cases in 1950s to 0.1 million cases in 1960s). However, due to the development of insecticide resistance among mosquitoes and other factors, it staged a comeback in the mid 1970s (6.47 million cases in 1976), and continues to prevail in endemic/subendemic proportions, so that 80% indian population lives in malaria risk areas. Conceding that eradication of malaria is not possible, NMEP was renamed National Antimalaria Programme (NAMP), which now is 'National vector borne diseases control programme' (NVBDCP) with a wider disease coverage. For the year 2010, the NVBDCP has reported 1.49 million slide proven malaria cases in India, out of which 0.78 million (52%) were falciparum malaria with 767 recorded deaths. The WHO estimates that actual number of malaria cases in India is much higher, and an expert committee has estimated that about 40,000 malaria deaths occur annually.

The bark of *Cinchona* tree, growing in Peru, was introduced in Europe in the early 17th century as a cure for fevers. Later it was realized to be a specific remedy for malaria. *Quinine*, isolated from *Cinchona* bark in 1820, replaced the crude preparation and continued to be the major antimalarial drug till 1942. The world's supply of *Cinchona* bark for producing quinine was met by Java and neighbouring countries. This was cut off from the Germans during World War I and from the Allies during World War II. Due to enormous military importance of malaria and its treatment, intense activity was initiated for the development of antimalarial drugs. *Mepacrine* was produced in Germany in 1926 and extensively field tested by the Allies during World War II. *Chloroquine* was produced in USA soon after as a less toxic alternative to mepacrine. It had already been synthesized and used by Germans in 1934 as 'Resochin'. *Proguanil* was introduced in 1945 by the British as a well tolerated clinical curative.

None of the above drugs were found to be capable of preventing relapses in vivax malaria. *Pamaquine* was the first 8-aminoquinoline to be tested in Germany in the 1920s. However, no attention was paid to it because of its poor schizontocide action. This class of drugs was retested during World War II as radical curative and *Primaquine* emerged as the most desirable drug. *Pyrimethamine* was produced in 1951 under a planned post-war research programme for antimalarial drugs. Subsequently, chloroquine resistance emerged in *P. falciparum* and several drugs were developed to combat it; the important ones are *Mefloquine, Lumefantrine*, *Atovaquone, Pyronaridine,* etc. However, the most significant advance is the Chinese herb derived fast acting *Artemisinin* compounds, the latest one of which is a synthetic derivative *Arterolane* developed in India.

CLASSIFICATION

1.	*4-Aminoquinolines*	Chloroquine (CQ) Amodiaquine (AQ) Piperaquine
2.	*Quinoline-methanol*	Mefloquine
3.	*Cinchona alkaloid*	Quinine, Quinidine
4.	*Biguanide*	Proguanil (Chloroguanide)
5.	*Diaminopyrimidine*	Pyrimethamine
6.	*8-Aminoquinoline*	Primaquine Tafenoquine
7.	*Sulfonamides and sulfone*	Sulfadoxine Sulfamethopyrazine Dapsone

* WHO: World Malaria Report, Dec. 2011

8. *Antibiotics*	Tetracycline Doxycycline Clindamycin
9. *Sesquiterpine lactones*	Artesunate Artemether Arteether Arterolane
10. *Amino alcohols*	Halofantrine Lumefantrine
11. *Naphthyridine*	Pyronaridine
12. *Naphthoquinone*	Atovaquone

OBJECTIVES AND USE OF ANTIMALARIAL DRUGS

The aims of using drugs in relation to malarial infection are:

(i) To prevent clinical attack of malaria (prophylactic).
(ii) To treat clinical attack of malaria (clinical curative).
(iii) To completely eradicate the parasite from the patient's body (radical curative).
(iv) To cutdown human-to-mosquito transmission (gametocidal).

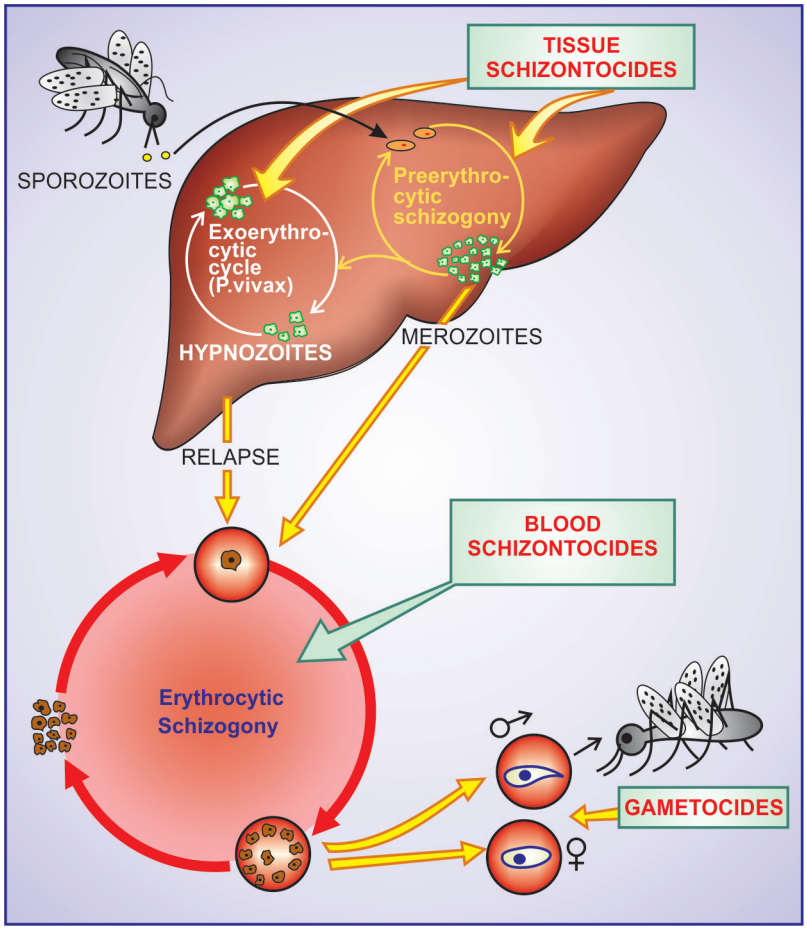


Fig. 59.1: The life cycle of malarial parasite in man. Stages and forms of the parasite at which different types of antimalarial drugs act are indicated.

TABLE 59.1 Comparative properties of antimalarial drugs

DRUG	PRE-ERYTHRO. Fal.	PRE-ERYTHRO. Viv.	ERYTHROCYTIC PHASE Activity	ERYTHROCYTIC PHASE Onset	ERYTHROCYTIC PHASE Duration	HYPNO-ZOITE	GAMETES	RESIS-TANCE	TOXICITY GRADING
1. Chloroquine	–	–	+	Fast	Long	–	–	Slow	+
2. Mefloquine	–	–	+	Int	Long	–	–	Minor	++
3. Quinine	–	–	+	Int	Short	–	–	Minor	+++
4. Proguanil	+	–	+	Int	Short	–	*	Rapid	±
5. Pyrimethamine	–	–	+	Slow	Long	–	–	Rapid	+
6. Primaquine	+	+	–	–	–	+	+	Minor	++
7. Sulfonamides	–	–	±	Slow	Long	–	–	Minor	+±
8. Tetracyclines	–	–	+	Slow	Short	–	–	Nil	+
9. Clindamycin	–	–	+	Slow	Short	–	–	Nil	+
10. Artemisinin	–	–	+	Fastest	Short	–	+	Nil	+
11. Lumefantrine	–	–	+	Int	Long	–	–	Nil	+

*Do not kill gametes but may inhibit their development in mosquito.
Pre-erythro. — Preerythrocytic stage;
Fal. — *P. falciparum*; Viv — *P. vivax*; Int — Intermediate

These are achieved by attacking the parasite at its various stages of life cycle in the human host (*see* Fig. 59.1). Antimalarials that act on erythrocytic schizogony are called *erythrocytic schizontocides,* those that act on preerythrocytic as well as exoerythrocytic (*P. vivax)* stages in liver are called *tissue schizontocides,* while those which kill gametocytes in blood are called *gametocides*. Antimalarial drugs exhibit considerable stage selectivity of action (*see* Table 59-1). Antimalarial therapy is given in the following forms.

1. Causal prophylaxis The preerythrocytic phase (in liver), which is the *cause* of malarial infection and clinical attacks, is the target for this purpose.

- Primaquine is a causal prophylactic for all species of malaria, but has not been used in mass programmes, because of its toxic potential.

  Trials in Kenya and Irian Jaya have successfully used primaquine 0.5 mg/kg daily against both *P. f.* and *P. v.* in subjects with normal G-6-PD levels. The CDC (USA) recommends it for short duration travel to *P.vivax* predominant endemic areas, and for subjects who cannot take any other prophylactic drug.

- Proguanil is a causal prophylactic, primarily for *P.f.*, but is not used in India, because of weak activity against liver stages of *P.v.*, and rapid development of resistance when used alone.

A combined formulation of atovaquone (250 mg) + proguanil (100 mg) is commonly used as a prophylactic by Americans and other western travellers visiting malaria endemic areas. Atovaquone also is active against preerythrocytic stage of *P.f.*, but is not approved in India.

2. Suppressive prophylaxis The schizontocides which suppress the erythrocytic phase and thus attacks of malarial fever can be used as prophylactics. Though the exoerythrocytic phase in case of vivax and other relapsing malarias continues, clinical disease does not appear.

- Chloroquine (CQ) 300 mg (base*) or 5 mg/kg weekly. In travellers, start one week before with a loading dose of 10 mg/kg and continue till one month after return from endemic area. However, it can be used as a prophylactic only in areas with CQ-sensitive *P.f.* (Mexico, Argentina, etc.). Since CQ-resistant *P.f.* is now

* All doses expressed in terms of base, e.g. chloroquine phosphate 250 mg = 150 mg base.

widespread in India, and there are no exclusively *P.v.* areas, CQ is no longer employed as prophylactic in India.

- Mefloquine 250 mg started 1–2 weeks before and taken weekly till 4 weeks after return from endemic area, has been used for areas where CQ-resistant *P.f.* is prevalent. In India, use of mefloquine for prophylaxis is not allowed among residents, but may be used by travellers.

  If tolerated, mefloquine is a prophylactic with proven efficacy, even for long-term travellers and is useful except for mefloquine-resistant *P.f.* areas (Myanmar, Thailand, Cambodia).
- Doxycycline 100 mg daily starting day before travel and taken till 4 weeks after return from endemic area for CQ-resistant *P.f.,* is an alternative regimen for short-term (maximum 6 weeks) visitors and those unable to take mefloquine. It is contraindicated in pregnant women and children < 8 yr.
- Proguanil 200 mg daily with chloroquine 300 mg weekly affords substantial protection against moderately CQ-resistant *P. falciparum,* but less than that afforded by mefloquine. This has been successfully used in Africa, but found ineffective, and not employed in India.

Chemoprophylaxis of malaria should be limited to short-term use in special risk groups, such as — nonimmune travellers, nonimmune persons living in endemic areas for fixed periods (army units, labour forces), infants, children and pregnant women (falciparum malaria has serious consequences in the pregnant).

Intermittent preventive therapy (IPTp) in the form of one dose pyrimethamine (75 mg) + sulfadoxine (1500 mg) each is 2nd and 3rd trimester (gap not < 1 month) is recommended by WHO only in areas with high *P.f.* endemicity (*P.f.* >30%) for pregnant women.

3. Clinical cure The erythrocytic schizontocides are used to terminate an episode of malarial fever. The available drugs can be divided into: (a) *High-efficacy drugs*: Artemisinin, CQ, amodiaquine, quinine, mefloquine, halofantrine, lumefantrine and atovaquone. These drugs can be used singly to treat attacks of malarial fever, but are now generally combined.

(b) *Low-efficacy drugs*: Proguanil, pyrimethamine, sulfonamides, tetracyclines and clindamycin. These drugs are used only in combination for clinical cure.

The faster acting drugs are preferred, particularly in falciparum malaria where delay in treatment may result in death even if the parasites are cleared from blood by the drug. The exoerythrocytic phase (hypnozoites) of *vivax* and *ovale* persists which can cause *relapses* subsequently without reinfection. Thus, the erythrocytic schizontocides are radical curatives for falciparum, but not for vivax or ovale malaria. However, *recrudescences* occur in falciparum infection if the blood is not totally cleared of the parasites by the drug.

The drugs and regimens used for uncomplicated falciparum and vivax malaria are given in the box (p. 820). Only oral drugs are used for uncomplicated malaria.

Relapses of vivax/ovale malaria are treated in the same way as the primary attack because the parasite remains sensitive to the drug. Recrudescence in falciparum malaria indicates resistant infection: should be treated with an alternative drug as per local needs. However, recrudescences and failures with artemisinin-based combination therapy (ACT), used properly, are infrequent.

Falciparum malaria during pregnancy An attack of falciparum malaria occurring during pregnancy has serious implications both for the mother as well as the foetus. It must be treated promptly and aggressively. Drugs recommended are:

1. Quinine 600 mg TDS × 7 days + clindamycin 300 mg TDS/QID (20 mg/kg) for 7 days; can be used during all trimesters, especially the 1st.
2. Artemisinin-based therapy (ACT; *see* box) is a better tolerated 3 day regimen, which may be used during the 2nd and 3rd trimester as an alternative to 7 day quinine + clindamycin therapy.

Treatment of uncomplicated malaria

A. Vivax (also ovale, malariae) malaria

1. Chloroquine 600 mg (10 mg/kg) followed by 300 mg (5 mg/kg) after 8 hours and then for next 2 days (total 25 mg/kg over 3 days) + Primaquine 15 mg (0.25 mg/kg) daily × 14 days

In occasional case of chloroquine resistance

2. Quinine 600 mg (10 mg/kg) 8 hourly × 7 days + Doxycycline 100 mg daily × 7 days or
   + Clindamycin 600 mg 12 hourly × 7 days
   + Primaquine (as above)
   or
   Artemisinin-based combination therapy (see below)
   + Primaquine (as above)

B. Chloroquine-sensitive falciparum malaria£

1. Chloroquine (as above) + Primaquine 45 mg (0.75 mg/kg) single dose (as gametocidal)

C. Chloroquine-resistant falciparum malaria

1.* Artesunate 100 mg BD (4 mg/kg/day) × 3 days +
   Sulfadoxine# 1500 mg (25 mg/kg) + Pyrimethamine 75 mg (1.25 mg/kg) single dose
   or
2. Artesunate 100 mg BD (4 mg/kg/day) × 3 days +
   Mefloquine# 750 mg (15 mg/kg) on 2nd day and 500 mg (10 mg/kg) on 3rd day.
   or
3. Artemether 80 mg + Lumefantrine 480 mg twice daily × 3 days (child 25–35 kg BW ¾ dose; 15–25 kg BW ½ dose; 5–15 kg BW ¼ dose)
   or
4. Arterolane (as maleate) 150 mg + Piperaquine 750 mg once daily × 3 days
   or
5. Quinine 600 mg (10 mg/kg) 8 hourly × 7 days
   + Doxycycline 100 mg daily × 7 days or + Clindamycin 600 12 hourly × 7 days

*First line ACT under NVBDCP

#Sulfadoxine-pyrimethamine (S/P) alone and mefloquine alone are also used, but should preferably be combined with artesunate.

£In India (including under NVBDCP) all *P.f.* cases, irrespective of CQ-resistance status, are treated with artemisinin-based combination therapy (ACT).

Severe and complicated falciparum malaria

This includes *P. falciparum* infection attended by any one or more of—hyperparasitaemia, hyperpyrexia, fluid and electrolyte imbalance, acidosis, hypoglycaemia, prostration, cardiovascular collapse, jaundice, severe anaemia, spontaneous bleeding, pulmonary edema, haemoglobinuria, black water fever, renal failure and cerebral malaria. Parenteral (i.m./i.v.) drugs have to be used; oral drugs may be substituted when the condition improves. Drugs and regimens employed are detailed in the box (p. 821).

4. Radical cure In case of vivax and ovale malaria, drugs which attack the exoerythrocytic stage (hypnozoites) given together with a clinical curative achieve total eradication of the parasite from the patient's body. A radical curative is needed in relapsing malaria, while in falciparum malaria — adequate treatment of clinical attack leaves no parasite in the body (there is no secondary exoerythrocytic tissue phase).

Drug of choice for radical cure of vivax and ovale malaria is:

- Primaquine 15 mg daily for 14 days. A shorter course of 5 days used earlier by NAMP in India has been found inadequate, and is no longer recommended. This treatment should be given concurrently with or immediately after chloroquine/other schizontocide only to individuals who test negative for G-6-PD deficiency.

Treatment of severe and complicated falciparum malaria*

1. *Artesunate:* 2.4 mg/kg i.v. or i.m., followed by 2.4 mg/kg after 12 and 24 hours, and then once daily for 7 days. Switchover to 3 day oral ACT inbetween whenever the patient can take and tolerate oral medication.
   or
2. *Artemether:* 3.2 mg/kg i.m. on the 1st day, followed by 1.6 mg/kg daily for 7 days. Switchover to 3 day oral ACT inbetween whenever the patient is able to take oral medication.
   or
3. $*Arteether:* 3.2 mg/kg i.m. on the 1st day, followed by 1.6 mg/kg daily for the next 4 days. Switchover to 3 day oral ACT inbetween whenever the patient is able to take oral medication.
   or
4. *Quinine diHCl:* 20 mg/kg (loading dose) diluted in 10 ml/kg 5% dextrose/dextrose-saline and infused i.v. over 4 hours, followed by 10 mg/kg (maintenance dose) i.v. infusion over 4 hours (in adults) or 2 hours (in children) every 8 hours, untill patient can swallow. Switchover to oral quinine 10 mg/kg 8 hourly to complete the 7 day course.

$Arteether (i.m.) is slower acting than artesunate (i.v.), and appears to be less efficacious. It is used only in India.

1. Volume of fluid for i.v. infusion of quinine should be reduced in patients with volume overload/ pulmonary edema.
2. If possible, oral quinine should be substituted by 3 day oral ACT, or doxycycline 100 mg daily should be combined with it.
3. Chloroquine HCl i.v. to be used only if none of the above is available and only in adults.

* Adopted from Regional guidelines for the management of severe falciparum malaria in large hospitals (2006); WHO, Regional office for South-East Asia, New Delhi.

- Tafenoquine, a new long-acting 8-aminoquinoline exoerythrocytic schizontocide, is being developed as a single dose antirelapse drug for vivax malaria.

There is no point in antirelapse treatment in highly endemic areas, because chances of reinfection would be high; a subsequent attack may be erroneously labelled as failure of radical cure. Antirelapse treatment of vivax malaria should be restricted to:

(a) Areas with low level of transmission (where only sporadic cases occur).

(b) Patients treated during an epidemic and in areas undergoing eradication programme with effective vector control measures to cut down transmission.

5. Gametocidal This refers to elimination of the male and female gametes of *Plasmodia* formed in the patient's blood. Gametocidal action is of no benefit to the patient being treated, but will reduce the transmission to mosquito.

Primaquine is gametocidal to all species of *Plasmodia*, while artemisinins have weak lethal action on early-stage but not mature gametes. Gametes exposesd to proguanil or pyrimethamine may fail to carry on the life cyle normally in the mosquito. Adequate control of clinical attacks will reduce formation of gametes.

- A single 45 mg (0.75 mg/kg) dose of primaquine is employed immediately after clinical cure of falciparum malaria to kill the gametes and cut down transmission to mosquito. This should be given even when an artemisinin is used for clinical cure because artemisinins do not kill all the gametes. Primaquine used for radical cure of vivax malaria eliminates *P.vivax* gametes as well.

Chloroquine

It is a rapidly acting erythrocytic schizontocide against all species of plasmodia; controls most clinical attacks in 1–2 days with disappearance of parasites from peripheral blood in 1–3 days. Therapeutic plasma concentrations are in the range of 15–30 ng/ml. However, it has no effect on primary and secondary hepatic stages of the parasite—does not prevent relapses in vivax and ovale malaria. CQ has no clinically useful gametocidal activity.

The mechanism of action of CQ is not completely known. Plasmodia derive nutrition by digesting haemoglobin in their acidic vacuoles. CQ is actively concentrated by sensitive intraerythrocytic plasmodia; higher concentration is found in infected RBCs than in noninfected ones. By accumulating in the acidic

vecuoles of the parasite and because of its weakly basic nature, it raises the vacuolar pH and thereby interferes with degradation of haemoglobin by parasitic lysosomes. Polymerization of toxic haeme generated from digestion of haemoglobin to nontoxic parasite pigment haemozoin is inhibited by the formation of CQ-haeme complex. Haeme itself or its complex with CQ then damages the plasmodial membranes. Clumping of pigment and changes in parasite membranes follow. Other related antimalarials like quinine, mefloquine, lumefantrine, pyronaridine appear to act in an analogous manner.

Chloroquine-resistance among *P.vivax* has been slow in developing, but *P. falciparum* has acquired significant resistance, and resistant strains have become prevalent in India (especially the east and north east), South East Asia, China, Africa and South America. Some of these have also acquired resistance to sulfapyrimethamine (S/P), proguanil and may be mefloquine, quinine, etc. (multidrug resistant strains). Because *P. falciparum* produces the more severe forms of malaria with considerable mortality, emergence of such strains is the biggest threat to the antimalaria programmes, and is the focus of attention for current research efforts.

Chloroquine-resistance among *P. falciparum* is now widespread in India, and no entirely sensitive areas can be indentified. The largest number of CQ failures are reported from the Northeastern part of India where 24–83% *P. falciparum* cases are resistant to CQ, and some of these (particularly in areas bordering Myanmar) are multidrug resistant. Due to spread of CQ-resistant *P.f.* to most parts of India, with Northeast, Orissa, Karnataka, etc. reporting high rates of resistance, the NVBDCP has switched over to ACT as the first line treatment of *P.f.* cases counrtywide. Resistance in *P. falciparum* is associated with a decreased ability of the parasite to accumulate CQ.

An efflux transporter encoded by the *pfcrt* (P.f. chloroquine-resistance transporter) gene, has been identified in the membranes of the acidic vacuoles of CQ-resistant *P.f.* It serves to pumpout CQ from the vacuoles and thus protects the haeme detoxifying mechanism of the resistant parasite. This appears to be the most important mechanism of CQ-reistance. The *pfmdr* gene encoded P-glycoprotein is an energy-dependent ABC transporter which confers resistance to many antimalarials like quinine, mefloquine, and halofantrine. This transporter is also involved in certain cases of *P.f.* resistance to CQ.

Chloroquine-resistance among *P. vivax* was first reported from Papua New Guinea in 1989. It has now been confirmed from Indonesia, Myanmar, Peru, Columbia, Ethiopia and detected in India, but is focal and sporadic, reported from Chennai, Mathura, tribal areas of Madhya Pradesh, Mumbai and Bihar. It manifests as recrudescence within 1–3 weeks of treating vivax malaria with standard dose of chloroquine. Such cases can be treated by quinine given along with doxycycline/clindamycin or by ACT, followed by primaquine to effect radical cure (*see* box on p. 820). However, CQ given in standard doses remains the first line treatment of vivax malaria as per NVBDCP guidelines.

Other actions Chloroquine is active against *Entamoeba histolytica* and *Giardia lamblia* as well.

It has antiinflammatory, local irritant and local anaesthetic (on injection), weak smooth muscle relaxant, antihistaminic and antiarrhythmic properties.

Pharmacokinetics Oral absorption of CQ is excellent. About 50% gets bound in the plasma. It has high affinity for melanin and nuclear chromatin: gets tightly bound to these tissue constituents and is concentrated in liver, spleen, kidney, lungs (several hundred-fold), skin, leucocytes and some other tissues. Its selective accumulation in retina is responsible for the ocular toxicity seen with prolonged use.

Chloroquine is partly metabolized by liver and slowly excreted in urine. The early plasma t½ varies from 3–10 days. Because of tight tissue binding, small amounts persist in the body with a terminal t½ of 1–2 months.

Adverse effects Toxicity of CQ is low, but side effects like nausea, vomiting, anorexia, uncontrollable itching, epigastric pain, uneasiness,

difficulty in accommodation and headache are frequent and quite unpleasant. Weekly suppressive doses have been safely given for 3 years.

- Prolonged use of high doses (as needed for rheumatoid arthritis, DLE, etc.) may cause loss of vision due to retinal damage. Corneal deposits may also occur and affect vision, but are reversible on discontinuation.
- Loss of hearing, rashes, photoallergy, mental disturbances, myopathy and graying of hair can occur on long-term use.
- Intravenous injection of CQ (rarely given now) can cause hypotension, cardiac depression, arrhythmias and CNS toxicity including seizures (more likely in children).

CQ can be used for treatment of malaria during pregnancy: no abortifacient or teratogenic effects have been reported.

Caution is to be exercised in the presence of liver damage, severe g.i., neurological, retinal and haematological diseases. Attacks of seizures, porphyria and psoriasis may be precipitated.

CQ should not be coadministered with mefloquine, amiodarone and other antiarrhythmics.

Preparations and administration

Chloroquine phosphate: (250 mg = 150 mg base) bitter, tablet should not be chewed. RESOCHIN, CLOQUIN, LARIAGO, NIVAQUIN-P 250 mg tab, 500 mg forte tab, 100 mg (base) per 10 ml oral susp., 40 mg (base)/ml inj in 2 and 5 ml amp, 30 ml vial.

There is hardly any indication now for parenteral (i.v.) chloroquine. It should not be injected i.m. due to its local tissue toxicity.

Uses

1. CQ causes rapid fever clearance and disappearance of parasitaemia in patients of malaria caused by all *P.ovale* and *P.malariae,* most *P.vivax* and some *P.falciparum* that are still sensitive. It is the drug of choice for clinical cure of vivax, ovale and malariae malaria. However, its use for *P.falciparum* is restricted to few areas that still have susceptible *P.f.,* but not in India. It is no longer used as a suppressive prophylactic in India, and such use is made only in vivax predominant countries or in those which have CQ-sensitive *P.f.*
2. Extraintestinal amoebiasis (Ch. 60).
3. Rheumatoid arthritis (Ch. 15).
4. Discoid lupus erythematosus—very effective; less valuable in systemic LE.
5. Lepra reaction (*see* p. 786).
6. Photogenic reactions.
7. Infectious mononucleosis: affords symptomatic relief.

Amodiaquine (AQ) It is almost identical to CQ in properties and is less bitter. Studies over the past 30 years in Africa have found it to be somewhat faster acting than CQ.

In the mid 1980s some fatal cases of toxic hepatitis and agranulocytosis were reported among travellers using AQ for prophylaxis, and WHO in 1990 recommended that it should not be used for prophylaxis of malaria as well as for treatment of CQ failures. The 19th WHO expert committee on malaria (1992) did not accept this recommendation totally, and permitted use of AQ for treatment of clinical attacks. Countries which had continued to use short courses of AQ (25–35 mg/kg over 3 days) for clinical cure did not report any severe reaction, and a subsequent metaanalysis (2003) concluded that such use is as safe as CQ. Thus, it is possible that the suspected hepatotoxicity and agranulocytosis are specific adverse effects of long-term AQ use made for prophylactic purpose.

Experience in Africa over the past 3 decades supports use of AQ in uncomplicated falciparum malaria, but it is not recommended for prophylaxis. There is evidence now that AQ is effective even in areas with CQ-resistant *P. falciparum.* Coformulated with artesunate (AS/AQ) the combined amodiaquine-artesunate tablet has become 1st line treatment of falciparum malaria in many African countries. On the basis of successful clinical trials in India, the combined formulation of this ACT has been recently approved for use in falciparum malaria, irrespective of CQ-resistance status.

Side effects of AQ are similar to that ot CQ; itching may be less common, though still the most common complaint. Neutropenia has been associated with AQ when it is used in children and in HIV patient receiving antiretroviral therapy.

Dose: for treatment of acute attack of malaria: 25–35 mg/kg over 3 days; CAMOQUIN 200 mg (as HCl = 150 mg base) tab; BASOQUIN 150 mg (base) per 5 ml susp.

Piperaquine *(see under ACT, p. 834)*

Mefloquine

This quinoline drug was originally tested during World War II, but introduced for use only in 1963 when it was reinvestigated and found effective against CQ-resistant *P.f.* Mefloquine (MQ) is intrinsically fast acting erythrocytic schizontocide, but slower than CQ or quinine due to prolonged absorption after oral ingestion. It is effective against CQ-sensitive as well as resistant plasmodia. A single dose (15 mg/kg) controls fever and eliminates circulating parasites in infections caused by *P. falciparum* or *P. vivax* in partially immune as well as nonimmune individuals. However, it neither has gametocidal activity, nor kills vivax hypnozoites. Like CQ relapses occur subsequently in vivax malaria. It is also an efficacious suppressive prophylactic for multiresistant *P. falciparum* and other types of malaria. Due to extensive use as monotherapy, MQ-resistance among *P. falciparum* has become common in Thailand, Cambodia and Myanmar, but is sporadic in Africa, South America and Middleeast. Since it has not been widely used in India, MQ-resistance is not a problem, but due to its long t½ chances of selection of resistant strains are high; MQ-resistant *P. falciparum* isolates have been reported from Northeast, Gujarat and Andhra Pradesh. Resistance to MQ confers cross resistance to quinine and halofantrine.

The mechanism of action of MQ is not known, but the morphological changes produced in the intraerythrocytic parasite resemble quinine and CQ induced changes. Like CQ it accumulates in infected RBCs (including those with CQ-resistant *P.f.*), binds to haeme and this complex may be damaging the parasite membranes. However, recent evidence suggests that the site of action of MQ is in the parasitic cytosol rather than in the acidic vacuole. The major mechanism by which *P.f.* develops MQ-resistance is by enhanced translation of *pfmdr1* gene, though *Pfcrt* mutation may also be involved.

Pharmacokinetics Oral absorption of MQ is good but peak concentrations are reached slowly. It is highly plasma protein bound and concentrated in many organs including liver, lung and intestines. Extensive metabolism occurs in liver and it is primarily secreted in bile. Considerable enterohepatic circulation of MQ and its tissue binding accounts for the long t½ which is 2–3 weeks.

Adverse effects MQ is bitter in taste; common reaction is dizziness, nausea, vomiting, diarrhoea, abdominal pain, sinus bradycardia and Q-T prolongation. These are usually mild and largely dose related, but may be severe in some. Major concern has been a variety of neuropsychiatric reactions (disturbed sense of balance, ataxia, errors in operating machinery, strange dreams, anxiety, hallucinations, rarely convulsions) occurring in some recipients. These are dose related and subside over 1–3 weeks on discontinuation. Rare events are haematological, hepatic and cutaneous toxicity. MQ appears to be safe during pregnancy, but should be avoided in 1st trimester unless absolutely essential. MQ is contraindicated in patients with anxiety, depression, psychosis, and in those with cardiac conduction defects.

Interactions Halofantrine or quinidine/quinine or CQ given to patients who have received MQ cause QTc lengthening—cardiac arrests are reported. These drugs should not be administered if MQ has been given < 12 hours earlier.

Use Mefloquine is an effective drug for multiresistant *P. falciparum.* Because of its potential toxicity, cost and long t½, its use is restricted. To check the spread of MQ-resistance, current recommendation is to use it only in combination with artesunate as ACT for uncomplicated falciparum malaria, including CQ-resistant and CQ + sulfa-pyrimethamine (S/P) resistant cases. In Southeast Asia artesunate-MQ ACT has been the first line treatment of falciparum malaria. For vivax malaria, it should be used only in the rare case of the parasite being both CQ and quinine + doxycycline resistant. MQ cannot be given parenterally and is not used in complicated/severe malaria.

For prophylaxis of malaria among travellers to areas with multidrug resistance; 5 mg/kg (adults 250 mg) per week is started preferably 1–2 weeks before travel to assess side effects in the individual. It is not recommended for prophylaxis in residents of the endemic area. MEFQUE, CONFAL, FACITAL 250 mg tab; to be taken with plenty of water after meals.

Mepacrine (Quinacrine, Atabrine) It is an acridine derivative erythrocytic schizontocide, more toxic and less effective than chloroquine. It is obsolete as an antimalarial, but is also active against giardia and tapeworms.

Quinine

Quinine is the levo rotatory alkaloid obtained from cinchona bark. Its *d*-isomer quinidine is used as an antiarrhythmic (and for malaria as well in some countries).

Quinine is an erythrocytic schizontocide for all species of plasmodia, but less effective and more toxic than CQ. Resurgence of interest in quinine is due to the fact that most CQ and multidrug-resistant strains of *P. falciparum* still respond to it. However, even quinine-resistance has been described in certain parts of Southeast Asia and in Brazil where quinine + tetracycline has been the standard treatment of complicated malaria. Quinine-resistance has been encountered sporadically in India, particularly along Myanmar border where in a sample study 6% falciparum malaria cases did not respond sequentially to CQ, S/P and quinine. There is partial cross resistance between quinine and MQ, but many MQ-resistant cases respond to quinine. Though effective in terminating an acute attack of falciparum malaria, quinine may not prevent recrudescence—indicating incomplete clearance of the parasites. Doxycycline or clindamycin is mostly added to it for complete parasite clearance.

Quinine has no effect on preerythrocytic stage and on hypnozoites of relapsing malaria, but kills vivax gametes. Like CQ it is a weak base, and acts in an analogous manner to inhibit polymerization of haeme to hemozoin; free haeme or haeme-quinine complex damages parasite membranes and kills it. However, the exact mechanism of action is not known.

Resistance to quinine in *P.f.* appears to involve both enhanced translation as well as mutation of *Pfmdr* gene among different strains.

Quinine has many other actions:

1. *Local irritant and anaesthetic* Quinine is intensely bitter and irritant. Orally it causes nausea, vomiting, epigastric discomfort. Injections can cause pain and local necrosis in the muscle and thrombosis in the vein. Local inflammation may be followed by fibrosis.

2. *Systemic actions* Gastric secretion is increased. Quinine is a weak analgesic and antipyretic; affects hearing and vision at higher doses. Cardiodepressant, antiarrhythmic and hypotensive actions are similar to quinidine (*see* Ch. 38). Rapid i.v. injection can produce marked fall in BP and cardiovascular collapse.

Quinine directly decreases contractile power of skeletal muscle fibre (*see* Ch. 25). It stimulates the myometrium and can cause abortion in early pregnancy. However, it is not a dependable abortifacient. Blood sugar is slightly lowered due to release of insulin from the pancreas. Rapid i.v. injection of quinine has caused hypoglycaemia.

Pharmacokinetics Quinine is rapidly and completely absorbed orally. It is 70% bound to plasma proteins, especially α_1 acid glycoprotein, which increases during acute malarial infection. CSF concentrations are low. A large fraction of the dose is metabolized in the liver by CYP3A4 and excreted in urine with a t½ of 10–12 hours. Quinine is noncumulative.

Adverse effects Toxicity of quinine is high and dose related; 8–10 g taken in a single dose may be fatal.

Cinchonism A large single dose or higher therapeutic doses taken for a few days produce a syndrome called ‘cinchonism’. It consists of ringing in ears, nausea, vomiting (due to both gastric irritation and CTZ stimulation), headache, mental confusion, vertigo, difficulty in hearing and visual defects (due to direct neurotoxicity as well as constriction of retinal and auditory vessels). Diarrhoea, flushing and marked perspiration may also appear. The syndrome subsides completely if the drug is stopped.

Poisoning with still higher doses results in the above symptoms in an exaggerated form. In addition, delirium, fever,

tachypnoea followed by respiratory depression, pulmonary edema, hypoglycaemia, marked weakness and prostration can occur. Hypotension, cardiac arrhythmias develop only on rapid i.v. injection — the patient may die. Watch Q-T prolongation during i.v. infusion of quinine; stop if it exceeds 25%.

Few individuals are idiosyncratic/hypersensitive to quinine; cinchonism may appear after a single therapeutic dose. Purpura, rashes, itching, angioedema of face and bronchoconstriction may develop.

Quinine occasionally causes haemolysis, especially in pregnant women and in patients of falciparum malaria, resulting in haemoglobinuria (black water fever) and kidney damage.

During pregnancy it should be used only for life-threatening infection, with special care to prevent hypoglycaemia.

Uses

1. *Malaria* Quinine is used orally for uncomplicated CQ-resistant malaria, and i.v. for complicated/cerebral malaria.

(a) *Uncomplicated resistant falciparum malaria:* Quinine may be used orally as an alternative to S/P-ACT in uncomplicated CQ-resistant falciparum malaria. It acts more rapidly than S/P alone. The 7 day quinine + doxycycline/clindamycin regimen (*see* box on p. 820) is the 2nd line treatment of CQ-resistant malaria (both falciparum and vivax) under NVBDCP. Certain CQ-resistant strains are also resistant to S/P, but respond to quinine.

(b) *Complicated and severe malaria including cerebral malaria:* Quinine (i.v.) has been the drug of choice for cerebral malaria (falciparum malaria with impaired consciousness) and other forms of complicated malaria. However, recent studies indicate that parenteral artemisinins are faster acting, more effective, better tolerated and more conveniently administered. Therefore, artesunate (i.v./i.m.) or artemether (i.m.) or arteether (i.m.) are now preferred over quinine for severe malaria. The dosage and schedule for i.v. infusion of quinine for severe malaria is given in the box on p. 821. Hypoglycaemia due to hyperinsulinemia is the most important side effect which can be prevented by infusing quinine in 5% dextrose.

Supportive treatment needed in cerebral malaria is cooling for fever, i.v. diazepam for convulsions, correction of fluid and electrolyte balance and acidosis. Corticosteroids are useless, may be harmful—avoid them.

2. Nocturnal muscle cramps: a single tablet of quinine (300 mg) at bed time may benefit some, but not all cases, and risks may not justify use. Quinine is also effective in myotonia congenita.

REZOQUIN, QUININE, QUINARSOL 300, 600 mg tab, 600 mg/2 ml inj.

Proguanil (Chloroguanide)

It is a relatively slow-acting erythrocytic schizontocide for both *P.f.* and *P.v.* In addition, it inhibits the preerythrocytic stage of *P.f.* Gametocytes exposed to proguanil are not killed but may fail to develop properly in the mosquito. Proguanil is cyclized in the body to a triazine derivative (cycloguanil) which inhibits plasmodial DHFRase-thymidylate synthase in preference to the mammalian DHFRase. Resistance to proguanil develops rapidly due to mutational changes in the plasmodial DHFRase-thymidylate synthase enzyme. There is partial cross-resistance between proguanil and pyrimethamine, which is a directly acting plasmodial DHFRase inhibitor.

Absorption of oral proguanil is slow, but almost complete. It is partly metabolized and excreted in urine; t½ is 16–20 hr; noncumulative. It is very well tolerated; side effects are less compared to CQ. Mild abdominal symptoms, vomiting, occasional stomatitis, haematuria, rashes and transient loss of hair are reported.

In the late 1940s and early 1950s it was extensively used as a clinical curative for vivax malaria, especially in endemic areas with partially immune population. However, proguanil alone cannot be depended upon in nonimmune patients, particularly those with falciparum malaria, due to slow response and chances of rapid resistance. Currently in India, proguanil has little role either in prophylaxis or in clinical cure of malaria. However, its combination with atovaquone (*see* p. 831) is commonly used in Thailand, USA and some other countries as a fast-acting erythrocytic schizontocide for treatment of multidrug resistant falciparum malaria. Proguanil (without conversion to cycloguanil) by a DHFRase unrelated action potentiates the schizontocidal action of atovaquone. Moreover, *P.f.* does not easily develop resistance to this combination.

Atovaquone-proguanil is also used by western travellers as a causal prophylactic while visiting CQ-resistant/multidrug-resistant *P.f.* endemic areas. In Africa proguanil combined with CQ has been used as a suppressive prophylactic in moderately CQ-resistant *P.f.* areas.

PROGUMAL 100 mg tab.

Pyrimethamine

It is a directly acting inhibitor of plasmoidal DHFRase (does not require conversion to a cyclic

triazine, as is the case with proguanil). Selective antimalarial action depends on high affinity for plasmodial enzyme (~2000 times greater than for the mammalian enzyme). In contrast to trimethoprim, it has very poor action on bacterial DHFRase. Under the influence of pyrimethamine, schizogony of malarial parasite in blood gradually stops. At high doses, it inhibits *Toxoplasma gondii*.

Pyrimethamine is more potent than proguanil, and a slowly acting erythrocytic schizontocide, but does not eliminate the preerythrocytic phase of *P. falciparum* or the exoerythrocytic phase of *P.vivax*. If used alone, resistance develops rather rapidly by mutation in the DHFRase enzyme of the parasite wiith reduced affinity. These organisms exhibit cross resistance to proguanil.

Pharmacokinetics Absorption of pyrimethamine from g.i.t. is good but slow. Certain organs like liver, spleen, kidney and lungs concentrate pyrimethamine. It is metabolized and excreted in urine with a t½ of 4 days. Prophylactic concentrations remain in blood for 2 weeks.

Adverse effects Pyrimethamine is relatively safe. The only side effects are occasional nausea and rashes. Folate deficiency is rare; megaloblastic anaemia and granulocytopenia may occur with higher doses, especially in those with marginal folate stores. This can be treated by folinic acid.

Use Pyrimethamine is used only in combination with a sulfonamide (S/P) or dapsone (*see* below) for treatment of falciparum malaria.

Sulfonamide-pyrimethamine (S/P)

Sulfonamides/dapsone are not particularly effective antimalarial drugs in their own right; have some inhibitory influence on the erythrocytic phase, especially of *P. falciparum*. However, they form supra-additive synergistic combination with pyrimethamine due to sequential block (as in case of cotrimoxazole: p. 706). Though, both components are slow acting, the combination acts faster, so that it can be employed as a clinical curative, particularly for *P. falciparum*. Efficacy against *P. vivax* is rather low. By the addition of sulfonamide, development of resistance to pyrimethamine is retarded. There is no cross-resistance with other groups of antimalarial drugs.

The popular combinations are:

Sulfadoxine 500 mg + pyrimethamine 25 mg tab: RIMODAR, FANCIDAR, LARIDOX, MALOCIDE; REZIZ 500 mg + 25 mg tab and per 10 ml susp; REZIZ FORTE 750 mg + 37.5 mg tab.

Sulfamethopyrazine 500 mg + pyrimethamine 25 mg tab: METAFIN, MALADEX.

Dapsone 100 mg + pyrimethamine 25 mg tab; MALOPRIM.

*As clinical curative: S*ulfadoxine 1500 mg + pyrimethamine 75 mg (3 tab) single dose (children 9–14 yr 2 tab, 5–8 yr 1½ tab, 1–4 yr 1 tab).

Sulfadoxine and sulfamethopyrazine are ultra-long acting sulfonamides — attain low blood concentrations, but are able to synergise with pyrimethamine which also has long t½. The combination has the potential to cause serious adverse effects (exfoliative dermatitis, Stevens-Johnson syndrome, etc.) due to the sulfonamide. Therefore, use is restricted to single dose treatment of uncomplicated CQ-resistant falciparum malaria. Prophylactic use, needing multiple unsupervised doses is not approved. It is contraindicated in infants and in individuals allergic to sulfonamide. There is no evidence that single dose of the combination used for treating malaria harms the foetus during pregnancy, but should be avoided if possible.

The major importance of this combination is due to its efficacy against CQ-resistant *P. falciparum*. Compliance is good due to single dose therapy and few acute side effects. Resistance to S/P among *P. falciparum* was first noted in 1980, and has spread globally now. It is high in South East Asia, South America and Southern Africa, so much that it is no longer employed in these countries. In India, S/P resistance appears to be sporadic, except in the North east. A sample study from Assam found 9% CQ-resistant *P. falciparum* cases to be

nonresponsive to S/P as well, while in the area bordering Myanmar 35–44% S/P failures were recorded. To contain further spread of S/P resistance in India, the National drug policy on malaria mandates compulsory use of artesunate along with S/P for treatment of all falciparum malaria cases.

It is not an effective drug for vivax malaria. S/P is the first choice treatment for toxoplasmosis, which mainly occurs in immunocompromised patients.

Primaquine

Unlike other antimalarial drugs, primaquine is a poor erythrocytic schizontocide: has weak action on *P. vivax*, but blood forms of *P. falciparum* are totally insensitive. On the other hand, it is more active against the preerythrocytic stage of *P. falciparum* than that of *P. vivax*. Primaquine differs from all other available antimalarials in having a marked effect on primary as well as secondary hepatic phases of the malarial parasite. It is highly active against gametocytes and hypnozoites.

The mechanism of action of primaquine is not known. However, it is different from that of CQ. Though, resistance among *P. vivax* against primaquine can be induced, it is not a clinical problem.

Pharmacokinetics Primaquine is readily absorbed after oral ingestion. It is oxidized in liver with a plasma t½ of 6–8 hrs and excreted in urine within 24 hours. It is not a cumulative drug.

Adverse effects The usual doses of primaquine produce only abdominal pain, g.i. upset, weakness or uneasiness in chest as side effect. These can be minimized by taking the drug with meals. CNS and cardiovascular symptoms are infrequent. Leucopenia occurs rarely with larger doses.

The most important toxic potential is dose related haemolysis, methaemoglobinaemia, tachypnoea and cyanosis. These are due to the oxidant property of primaquine. Its metabolites are more potent in this regard. However, in normal individuals doses < 60 mg (base) produce little haemolysis. Those with G-6-PD deficiency are highly sensitive and haemolytic anaemia can occur with 15–30 mg/day. There are several variants of G-6-PD deficiency, and the defect is graded. Massive haemolysis is associated only with the Mediterranean and few other variants. The incidence of G-6-PD deficiency is low among Indians, except in some tribal people of Jharkhand, Andhra Pradesh, Madhya Pradesh and Assam. It is high among black races and Mediterranean people. Spot tests are available for detecting G-6-PD deficiency. Passage of dark urine is an indication of haemolysis; primaquine should be promptly stopped if it occurs. The risk of haemolysis and leucopenia is increased in patients of rheumatoid arthritis, SLE and in those acutely ill.

Primaquine should not be given during pregnancy, because foetus is G-6-PD deficient.

Use

Vivax malaria: The primary indication of primaquine is for radical cure of relapsing (vivax) malaria.The dose used in most countries is 30 mg/day, but in India 15 mg/day (children 0.25 mg/kg/day) for 2 weeks is given along with full curative dose of CQ or another blood schizontocide to eliminate the erythrocytic phase. Relapse rate with 5 day primaquine treatment, employed earlier by NAMP (India), has been found similar to no treatment; therefore not recommended now. The G-6-PD status of the patient should be tested before giving 14 day primaquine course. It is to be taken with food to reduce g.i. side effects.

Falciparum malaria: A single 45 mg dose of primaquine is given with the curative dose of CQ or ACT to kill the gametes and cut down transmission to mosquito. This use is restricted to low transmission areas or where effective vector control is implimented.

MALIRID, EVAQUIN (as phosphate 26 mg = 15 mg base) 2.5, 7.5, 15, 45 mg tab.

Primaquine 15 mg/day given with clindamycin 600 mg TDS is an alternative drug for *Pneumocystis jiroveci* pneumonia in AIDS patients.

Tafenoquine

This new 8-aminoquinoline is being developed as a single dose antirelapse drug for vivax malaria. The need for 14 daily doses of primaquine for effective relapse prevention is the biggest hurdle in implementing antirelapse therapy. Tafenoquine has a long plasma t½ of 16–19 days (t½ of primaquine is 6–8 hours). Thus, it continues to act for weeks. In phase 3 clinical trials 1–3 day treatment (along with CQ) has achieved upto 100% relapse prevention.

Tafenoquine is highly active against vivax hypnozoites. It has also shown some activity against asexual erythrocytic stages of *P.v.* and *P.f.* (including CQ-resistant strains), but clearance of fever and parasitaemia were slow. Therefore, it must be accompanied by CQ or another rapidly acting erythrocytic schizontocide for vivax malaria. Tafenoquine shares with primaquine the potential to cause haemolysis in G-6-PD deficient individuals. Incidents of anaemia, haemolysis and methaemoglobinemia are reported, but overall tolerability appears to be good.

Tafenoquine is undergoing phase-3 dose titration trial in India (along with standard 3 day CQ) for relapse prevention in vivax malaria, and is likely to emerge as a single dose radical curative.

Tetracycline and Doxycycline

These antibiotics have slowly acting and weak erythrocytic schizontocidal action against all plasmodial species including CQ, MQ and S/P resistant *P. falciparum*. However, no clinically useful action is exerted on the preerythrocytic stage. Gametocytes and vivax hypnozoites are also not killed. Tetracyclines are never used alone to treat malaria, but only in combination with quinine for the treatment of CQ-resistant falciparum as well as vivax malaria. Tetracycline 250 mg QID or doxycycline 100 mg OD are equally efficacious. Doxycycline 200 mg/day has also been combined with artesunate to treat mefloquine/chloroquine/S/P-resistant falciparum malaria in Thailand.

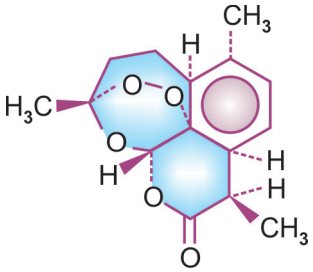
Doxycycline 100 mg/day is used as a 2nd line prophylactic for short-term travellers to CQ-resistant *P. falciparum* areas. Tetracyclines are not to be given to children and pregnant women.

Clindamycin (*see* p. 756)

This is another bacteriostatic antibiotic that has slow acting erythrocytic schizontocidal property against all species of plasmodia including multidrug resistant strains of *P. falciparum*. Liver stages and gametocytes are not affected. It markedly potentiates the antimalarial activity of quinine and artemisinin, and is always used in combination with one of these. Clindamycin is a second choice drug to doxycycline for adding to quinine or to artesunate for the treatment of multidrug resistant falciparum malaria, or CQ-resistant vivax malaria. In contrast to doxycycline, it can be used in children and pregnant women. However, clindamycin is not used for prophylaxis of malaria, because of thrice daily dosing and risk of adverse effects.

ARTEMISININ DERIVATIVES

Artemisinin is the active principle of the plant *Artemisia annua* used in Chinese traditional medicine as 'Quinghaosu'. It is a sesquiterpine lactone endoperoxide active against *P. falciparum* resistant to all other antimalarial drugs as well as sensitive strains and other malarial species. Potent and rapid blood schizontocide action is exerted eliciting quicker defervescence and parasitaemia clearance (<48 hr) than CQ or any other drug. In the erythrocytic schizogony cycle, artemisinins exert action on a wide range of stages—from ring forms to early schizonts; thus have the broadest time window of antimalarial action.



ARTEMISININ

Artemisinin is poorly soluble in water as well as in oil. Several derivatives have been produced for clinical use. *Artemether* is soluble in oil, while *Artesunate* (sod.) is water soluble. Both can be given orally as well as i.m., but artesunate sod. can also be given i.v. Their active metabolite generated in the body *Dihydroartemisinin* (DHA) is also used orally. An injectable compound *Arteether* (i.m. in oil) was produced in India in the 1990s, and recently a totally synthetic oral compound *Arterolane* has been

developed here. All these drugs are collectively referred to as '*Artemisinins*'.

In addition to their potent schizontocidal action, these drugs are lethal to early stage malarial gametes but not mature ones. By decreasing the population of gametes, they reduce but do not totally interrupt disease transmission. Artemisinins do not kill primary liver forms or vivax hypnozoites.

The duration of action is short and recrudescence rate is high when they are used alone in short courses. Recrudescence depends upon the dose and duration of therapy as well as on severity of disease. Resistance among *P.f.* to artemisinins is not a clinical problem yet, but in some areas (Cambodia, Thailand, Myanmar) delayed parasitaemia clearance has been noted, that is indicative of decreased responsiveness. This reemphasizes the need to use artemisinins only in combination (as ACT) with a drug which acts by a different mechanism. No cross resistance with any other class of antimalarial drugs occurs.

Because artemisinins are short acting drugs, monotherapy needs to be extended beyond the disappearance of the parasites to prevent recrudescence. After 5 days treatment recrudescence rate is ~10%, while with a 3 day course it is ~50%. Recrudescence can be totally prevented by combining 3 day artemisinin with a long-acting drug (*see* ACT later).

Mechanism of action of artemisinin is not definitely known. The endoperoxide bridge in its molecule appears to interact with haeme in the parasite. Ferrous iron-mediated cleavage of the bridge releases a highly reactive free radical species that binds to membrane proteins, causes lipid peroxidation, damages endoplasmic reticulum, and ultimately results in lysis of the parasite. Another line of evidence has shown that the artemisinin free radicals specifically inhibit a plasmodial sarcoplasmic-endoplasmic calcium ATPase labelled 'Pf ATP6'.

Pharmacokinetics Data on pharmacokinetics of artemisinin derivatives is limited and incomplete. Both artesunate and artemether are prodrugs.

Artesunate Its sodium salt is water-soluble and is administered by oral, i.m. or i.v. routes. In addition, rectal route has been tried. After oral ingestion, absorption is incomplete but fast, reaching peak in <60 min. It is rapidly converted to the active metabolite DHA with a t½ of 30–60 min. The t½ of DHA is 1–2 hours. After repeated dosing, artesunate causes autoinduction of its own metabolism by CYP2B6 and CYP3A4.

FALCIGO, FALCYNATE, ARTINATE 50 mg tab, 60 mg/vial inj; LARINATE, ARNATE 50 mg tab.

Artemether It is lipid-soluble and is administered orally or i.m., but not i.v. Absorption after oral as well as i.m. dosing is slower taking 2–6 hours. It undergoes substantial first pass metabolism and is converted to DHA. Extensive metabolism by CYP3A4 yields a variable t½ of 3–10 hours.

PALUTHER, LARITHER, MALITHER 80 mg inj (in 1 ml arachis oil).

α/β Arteether This compound developed in India is available for i.m. administration only to adults for complicated malaria. Because of its longer elimination t½ (23 hours), it is recommended in a 3 day schedule, but is considered less dependable in severe/complicated malaria. The WHO recommends a 5 day course (*see* box p. 821).

Dose: 150 mg i.m. daily for 3 days in adults.

E-MAL, FALCY, RAPITHER-AB 150 mg/2 ml amp (box of 3 amp).

Dihydroartemisinin and *Arterolane* These are available for oral use only in combination, and are considered with ACT (*see* p. 833, 834).

Adverse effects Data from >10000 monitored patients shows that artesunate/artemether produce few adverse effects; most are mild: nausea, vomiting, abdominal pain, itching and drug fever. Headache, tinnitus, dizziness, bleeding, dark urine, S-T segment changes, Q-T prolongation, first degree A-V block, transient reticulopenia and leucopenia are rare and subside when the patient improves or drug is stopped. Millions of patients

have been treated so far without any serious neurological or other toxicity, but close monitoring of the patient is advocated. Intravenous artesunate is much safer than i.v. quinine.

Interactions Concurrent administration of artemisinins with drugs prolonging Q-T, like astemizole, antiarrhythmics, tricyclic antidepressants and phenothiazines may increase the risk of cardiac conduction defects. However, no interference with the ACT partner drugs has been noted.

Use

Uncomplicated falciparum malaria Oral artemisinins are indicated for the treatment of all cases of uncomplicated falciparum malaria (CQ-resistant as well as sensitive) as ACT. Even when used alone, they are almost 100% effective, but because of short duration of action recrudescence rates are high. In order to preserve their powerful antimalarial activity and to reduce recrudescence rates, they must be used in combination with a long-acting schizontocide which acts by a different mechanism. The Drugs Controller General of India has prohibited use of oral artemisinins as single drugs. Fixed-dose drug combination formulations of ACT are being encouraged.

For *vivax* malaria, artemisinins (as ACT) are indicated only in case of CQ-resistant infection and when quinine + doxycycline/clindamycin also cannot be used. Use of artemisinins for prophylaxis of malaria is not allowed. They have short duration of action and higher potential toxicity. Moreover, wide spread prophylactic use will foster resistance. Their cidal action on early stage gametes reduces transmission of resistant *P.f.* infection, but does not totally interrupt it. Single dose primaquine is recommended after ACT to kill all circulating gametes.

Severe and complicated falciparum malaria Parenteral artemisinins are higly effective and are the drugs of choice irrespective of CQ-reistance status. Quinine infused i.v. had been the drug of choice for severe and complicated malaria, including cerebral malaria, but now i.v./i.m. artemisinins are preferred, while quinine is used only as an alternative when artemisinins cannot be used. Quinine (i.v.) continues to be the drug used for severe falciparum malaria during 1st trimester of pregnancy, because safety of artemisinins is not yet proven. Artesunate (i.v.) offers several advantages:

- It causes faster parasite clearance than i.v. quinine.
- It is safer and better tolerated than i.v. quinine.
- Its dosing schedule is simpler.
- Recent evidence indicates higher efficacy and lower mortality.*

Because i.v. injection achieves more rapid peak concentration, and only artesunate sod. can be given i.v., the NVBDCP has decided to use only i.v. artesunate for severe malaria.

Halofantrine It is a phenanthrene methanol blood schizontocide having activity comparable to mefloquine with which it exhibits cross resistance. It is effective against *P. falciparum* resistant to CQ and S/P, as well as against *P. vivax*. It is not active against gametocytes or hepatic stages of the malarial parasite.

Oral absorption of halofantrine is low and erratic, and side effects are relatively common. Prolongation of QTc interval is seen even at therapeutic doses and few cases of serious ventricular arrhythmia (some fatal) are on record.

It is not approved in India, but in other countries it has been used for multiresistant falciparum malaria when no other effective alternative is available.

Lumefantrine *(see below under ACT)*

Pyronaridine (*see* below under ACT)

Atovaquone This synthetic naphthaquinone is a rapidly acting erythrocytic schizontocide as well as active against preerythrocytic stage of *P. falciparum* and other plasmodia. *Pneumocystis jiroveci* and *Toxoplasma gondii* are also susceptible to atovaquone. It collapses plasmodial mitochondrial membranes and interferes with ATP production. Proguanil potentiates its antimalarial action and prevents emergence of resistance. A fixed dose oral combination of the two drugs is used for 3 day treatment of uncomplicated CQ-resistant *P. falciparum* as well as *P. vivax* malaria in the USA and some other countries, but not in India.Taken once daily with food, this combination is also used as a prophylactic by nonimmune travellers visiting endemic areas.

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* Artesunate versus quinine for treatment of severe falciparum malaria: a randomized trial. *Lancet,* **2005;** *366*: 717-25. (Trial conducted in India, Bangladesh, Myanmar and Indonesia).

Atovaquone is also employed as a second line drug for opportunistic infections with *P. jiroveci* and *T. gondii* in AIDS patients. It produces few side effects—diarrhoea, vomiting, headache, rashes, fever, and is contraindicated during pregnancy.

ARTEMISININ-BASED COMBINATION THERAPY (ACT)

Noting that use of antimalarial drugs singly has failed to curtail the prevalence of malaria globally, particularly due to emergence of CQ-resistant, followed by multidrug-resistant *P. falciparum,* the WHO has recommended that all cases of acute uncomplicated falciparum malaria should be treated only by combining one of the artemisinin compounds with another effective erythrocytic schizontocide. In choosing the companion drug, the most important consideration is its elimination t½ (governing stay in the body), because effective concentrations in blood must be maintained for at least 3–4 asexual cycles of the parasite, i.e. 6–8 days, to exhaust the parasite burden. Therefore, short t½ drugs have to be given for 7 days, while longer acting drugs can be given for 1–3 days. However, long t½ drugs allow subinhibitory concentrations to persist in the blood facilitating selection of resistant mutants. Combining a short t½ drug with a long t½ drug in the conventional 3 day regimen runs the risk of *de facto* monotherapy after the short t½ drug is eliminated. This risk is minimized by choosing a short t½ drug that reduces the parasite load rapidly and drastically. Artemisinin compounds fillin this requirement, as they rapidly kill > 95% plasmodia. They leave only a small biomass of the parasites to be eliminated by the long t½ drug, reducing the chances of selecting resistant mutants. Advantages of ACT over other antimalarials are:

- Rapid clinical and parasitological cure.
- High cure rates (>95%) and low recrudescence rate.
- Absence of parasite resistance (the components prevent development of resistance to each other).
- Good tolerability profile.

The ACT regimens for oral treatment of uncomplicated falciparum malaria that are already in use in India, or are WHO approved, or have completed clinical trial are given in the box on p. 833. Oral ACTs are not to be used in severe or complicated malaria, for which parenteral drugs are needed.

1. Artesunate-sulfadoxine + pyrimethamine (AS-S/P) This ACT has been adopted as the first line drug for uncomplicated falciparum malaria under the 'National antimalaria drug policy' of India, and has replaced CQ throughout the country. This does not imply that it is the most effective/best ACT, because it is not effective against multidrug-resistant strains which are nonresponsive to S/P. However, treatment failures with AS-S/P ACT are mostly restricted to Northeast areas bordering Myanmar; while in rest of India so far this ACT appears to be working satisfactorily with >96% success rate. As such, NVBDCP continues to use AS-S/P ACT as the firstline therapy, including that during 2nd and 3rd trimester of pregnancy. This ACT appears to produce fewer side effects than artesunate/mefloquine. Private clinics, however, are using other ACTs. Most other malaria endemic countries have found AS-S/P ACT to be inferior.

2. Artesunate-mefloquine (AS/MQ) This is the standard and most extensively used ACT in Thailand, Myanmar and other Southeast Asian countries as well as South-America and Africa. It was found highly effective and well tolerated in uncomplicated falciparum malaria. However, many areas in far East already have MQ-resistant *P. f.,* but by combining with AS, further spread of MQ resistance was checked. Nevertheless, some of them have switched over to alternative ACTs. In India AS/MQ has been used to a limited extent, but small studies have shown ~ 100% efficacy. A kit with separate As and MQ tablets is available and a FDC formulation has been approved. Side effects of MQ need to be watched for.

3. Artemether-lumefantrine Lumefantrine is an orally active, high efficacy, long-acting

ACT regimens for uncomplicated falciparum malaria*

1. *Artesunate-mefloquine (AS/MQ)*£
   Artesunate 100 mg BD (4 mg/kg/day) × 3 days + mefloquine 750 mg (15 mg/kg) on 2nd day and 500 mg (10 mg/kg) on 3rd day (total 25 mg/kg).
   FALCIGO PLUS kit (Artesunate 50 mg tab + Mefloquine 250 mg tab kit), (a FDC tablet has been approved in India).
2. *Artemether-lumefantrine (1:6)*£
   Artemether (80 mg BD) + lumefantrine (480 mg BD) × 3 days
   COARTEM, COMBITHER, LUMETHER (artemether 20 mg + lumefantrine 120 mg tab.) to be taken with fatty meal.
   Adult and child >35 kg 4 tab BD; child 25–35 kg 3 tab BD; 15–25 kg 2 tab BD; 5–15 kg 1 tab BD, all for 3 days.
   FALCIMAX PLUS, ARTE PLUS (artemether 80 mg + lumefantrine 480 mg tab) 1 tab BD × 3 days for adults.
3. *Artesunate-sulfadoxine + pyrimethamine (AS/S/P)*£
   Artesunate 100 mg BD (4 mg/kg/day) × 3 days + sulfadoxine 1500 mg (25 mg/kg) and pyrimethamine 75 mg (1.25 mg/kg) single dose.
   ZESUNATE kit, MASUNATE kit, FALCIART kit (Artesunate 100 mg × 6 tab + sulfadoxine 500 mg/pyrimethamine 25 mg × 3 tab kit)
4. *Arterolane-piperaquine*
   Arterolane (as maleate) 150 mg + piperaquine 750 mg daily × 3 days
   SYNRIAM (arterolane 150 mg + piperaquine 750 mg) cap, 1 cap OD × 3 days
5. *Dihydroartemisinin-piperaquine (DHA/PPQ 1:8)*£ (ARTEKIN)
   DHA 120 mg (2 mg/kg) + piperaquine 960 mg (16 mg/kg) daily × 3 days
6. *Artesunate-amodiaquine (AS/AQ)*£
   Artesunate 200 mg (4 mg/kg) + amodiaquine 600 mg (10 mg/kg) per day × 3 days
   Artesunate 25 mg/50 mg/100 mg +Amodiaquine 67.5 mg/135 mg/270 mg fixed dose combination tablets have been approved in India.
7. *Artesunate-pyronaridine (1:3)*
   Artesunate 100–200 mg (2–4 mg/kg) + pyronaridine 300–600 mg (6–12 mg/kg) per day × 3 days

* All drugs are administered orally
£ WHO approved ACTs

erythrocytic schizontocide, related chemically and in mechanism of action to halofantrine and MQ. Additionally, nucleic acid and protein synthesis of the parasite is affected. Like the others, vivax hypnozoites are not affected. Lumefantrine is highly lipophilic; absorption starts after 2 hours of ingestion and peaks at 6–8 hours. Antimalarial action is slower than CQ. Plasma protein binding is 99%, and it is metabolized predominantly by CYP3A4. Terminal t½ is 2–3 days, which is prolonged to 4–6 days in malaria patients.

Lumefantrine is used only in combination with artemether, as FDC tablets. The two components protect each other from plasmodial resistance. As such, no clinically relevant resistance has developed so far. Clinical efficacy is high achieving 95–99% cure rate, which is comparable to AS/MQ. Artemether-lumefantrine is active even in multidrug resistant *P.f.* areas including MQ-resistant. It has been extensively employed in Southeast Asia and Africa. In India it is frequently used by private doctors. While artemether quickly reduces parasite biomass and resolves symptoms, lumefantrine prevents recrudescence. Gametocyte population is reduced, checking transmission.

Artemether-lumefantrine must be administered with fatty food or milk, which markedly enhances lumefantrine (and to some extent artemether) absorption, and ensures adequate blood levels. Failure to take it with fat rich food

limits absorption and may result in recrudescence. This ACT is generally well tolerated; side effects are—headache, dizziness, sleep disturbances, abdominal pain, arthralgia, myalgia, pruritus and rash. Some studies indicate that it is better tolerated than AS/MQ. Artemether-lumefantrine should not be given with drugs metabolized by CYP2D6 (metoprolol, neuroleptics, tricyclic antidepressants, etc), because lumefantrine inhibits the isoenzyme CYP2D6. Lumefantrine shares with halofantrine the potential to prolong QTc, but the risk is much less. Since artemether can also prolong Q-Tc to some extent, artemether-lumefantrine ACT should not be given to patients receiving Q-Tc prolonging drugs. It is contraindicated in first trimester of pregnancy and during breast-feeding.

4. Dihydroartemisinin (DHA)-piperaquine

Piperaquine is a bisquinoline congener of CQ developed in China as a high efficacy long-acting (t½ 3–4 weeks) erythrocytic schizontocide with a slower onset of action because of larger volume of distribution. The mechanism of action is similar to CQ, and it is equally active against CQ-sensitive, but more active against CQ-resistant *P. falciparum*. In 1978, piperaquine replaced CQ in China, where it has been extensively used for mass prophylaxis as well as treatment of malaria.

Piperaquine has been coformulated with DHA in a dose ratio of 8:1 (ARTEKIN) and extensively evaluated in multidrug resistant *P.f.* areas of Cambodia, Thailand, Vietnam, etc. with high success rate. In clinical trials, efficacy of DHA-piperaquine fixed dose combination has been found comparable to artemether-lumefantrine or AS/MQ. Safety profile of DHA-piperaquine is good and it is well tolerated even by children. However, dizziness, vomiting and other g.i. symptoms are common; rashes are rare. DHA-piperaquine FDC has completed clinical trials in India producing > 98% response rate in uncomplicated falciparum malaria, and is likely to be approved soon.

5. Artesunate-amodiaquine (AS/AQ)

Amodiaquine (AQ; *see* p. 823) has long been used parallel to CQ. While AQ itself has a short t½ due to rapid metabolism, its metabolite, an equally potent antimalarial has long t½ of 10–18 days. Because of close structural resemblance of AQ to CQ, it was apprehended that AQ may not be an effective antimalarial in areas with CQ-resistant *P.f.* However, trials in Africa showed that AQ produced satisfactory response in such areas. Addition of artesunate further improved the cure rate. Trials were conducted in Africa with AS/AQ coformulated as FDC tablets, which produced high cure rates, and now this ACT has become the first-line therapy of uncomplicated falciparum malaria in many African countries. Recent trial in India also yielded ~ 97% cure of falciparum malaria. This ACT has been approved in India as FDC tablets in 3 strengths for different age groups (*see* box on p. 833), to be taken twice daily for 3 day treatment of uncomplicated falciparum malaria.

6. Arterolane-piperaquine

Arterolane is a novel orally active synthetic trioxolane congener of artemisinin that has been developed in India and recently marketed in combination with piperaquine. Arterolane acts rapidly at all stages of asexual schizogony of malarial parasite including multidrug resistant *P.f.*, but has no effect on the hepatic stages. It accumulates in the food vacuole of the parasite, and thus differs from artemisinins which do not accumulate at this site. It also has moderate gametocidal activity similar to that of artemether-lumefantrine.

Both arterolane and piperaquine are well absorbed orally, and absorption is unaffected by food. Peak plasma arterolane concentration is reached in 3–5 hours and it has a large volume of distribution. The major metabolic pathway is oxidation, mainly by CYP3A4, which is also the primary isoenzyme responsible for piperaquine metabolism. Arterolane is short acting and its plasma t½ varies between 1–3 hours.

Arterolane-piperaquine FDC has undergone multicentric clinical trials in India, Bangladesh

and Thailand. In uncomplicated falciparum malaria this ACT has produced ≥ 95% cure rate with a fever and parasitaemia clearance time of 24–48 hours. In a comparative trial its efficacy and tolerability has been found equivalent to artemether-lumefantrine. Side effects are generally mild headache, postural dizziness, vomiting, abdominal pain and diarrhoea. Thus, arterolane-piperaquine appears to be an effective and well tolerated alternative ACT.

7. Artesunate-pyronaridine Pyronaridine is a water-soluble naphthyridine Mannich base erythrocytic schizontocide with high efficacy and mechanism of action similar to CQ, that has been used in China for ~ 40 years. It is active against both CQ-sensitive and CQ-resistant *P. falciparum* and other malarial species. The onset of action is slower and duration long. It is concentrated in RBCs and metabolized with a terminal t½ of 7 days. Weak analgesic-antipyretic action is produced at higher doses.

Clinical efficacy of artesunate-pyronaridine FDC (dose ratio 1:3) has been tested in falciparum malaria in China, Thailand and Africa with >95% success and no recrudescence in 28 days. Multidrug-resistant *P. falciparum* and *P. vivax* also respond. Clinical trials have been completed in India with > 95% cure rate. Artesunate-pyronaridine is well tolerated. Side effects noted are abdominal pain, vomiting, headache, dizziness, loss of appetite, palpitation and transient ECG changes, but no serious reactions have occurred. However, this ACT has not yet been approved for use in India.

☞ PROBLEM DIRECTED STUDY

59.1 A 20-year-old girl reported to the district hospital OPD with irregular episodes of high fever for the past 3 days. The fever is preceded by chills and shivering and attended by headache, body ache, pain in abdomen, nausea and weakness. The fever lasts 4–6 hours and subsides after sweating. On enquiry she informed that she belongs to a village in the tribal area of Madhya Pradesh. About a month back she had returned from her home after a 3 weeks vacation and she works as a house maid in the city. Blood smear examination showed presence of intraerythrocytic *P. vivax* parasites. She was treated with the standard 1.5 g chloroquine (base) course over 3 days, and was given primaquine 15 mg tab to be taken once daily for 14 days, after she tested negative for G-6PD deficiency. She was afebrile on the 4th day, but returned back 7 days later with similar episode of chills and fever. Finger prick blood smear was positive for *P. vivax*. She confirmed continuing to take daily primaquine medication.

(a) What is the most likely cause of recurrence of fever and parasitaemia?

(b) How should the 2nd episode of fever be treated?

(c) Should primaquine medication be continued or stopped?

(*see* Appendix-1 for solution)

Chapter 60 Antiamoebic and Other Antiprotozoal Drugs

ANTIAMOEBIC DRUGS

These are drugs useful in infection caused by the anaerobic protozoa *Entamoeba histolytica*. Other Entamoeba species are generally non-pathogenic.

Amoebiasis has a worldwide distribution (over 50 million people are infected), but it is endemic in most parts of India and other developing countries. Poor environmental sanitation and low socio-economic status are important factors in the spread of the disease, which occurs by faecal contamination of food and water. Amoebic cysts reaching the intestine transform into trophozoites which either live on the surface of colonic mucosa as commensals—form cysts that pass into the stools (luminal cycle) and serve to propagate the disease, or invade the mucosa—form amoebic ulcers (Fig. 60.1) and cause acute dysentery (with blood and mucus in stools) or chronic intestinal amoebiasis (with vague abdominal symptoms, amoeboma).

Occasionally the trophozoites pass into the bloodstream, reach the liver *via* portal vein and cause amoebic liver abscess. Other organs like lung, spleen, kidney and brain are rarely involved in extraintestinal amoebiasis. In the tissues, only trophozoites are present; cyst formation does not occur. Tissue phase is always secondary to intestinal amoebiasis, which may be asymptomatic. In fact, most chronic cyst passers are asymptomatic. In the colonic lumen, the *Entamoebae* live in symbiotic relationship with bacteria, and a reduction in colonic bacteria reduces the amoebic population.

The 'Brazil root' or *Cephaelis ipecacuanha* was used for the treatment of dysentery in the 17th century. The pure alkaloid emetine obtained from it was found to be a potent antiamoebic in 1912. Emetine remained the most efficacious and commonly used drug for amoebiasis till 1960. Many 8-hydroxyquinolines (quiniodochlor, etc.) became very popular drugs for diarrhoea and amoebic dysentery, but have come under a cloud since they were held responsible for causing epidemics of 'Subacute myelo-optic neuropathy' (SMON) in Japan in 1970s.

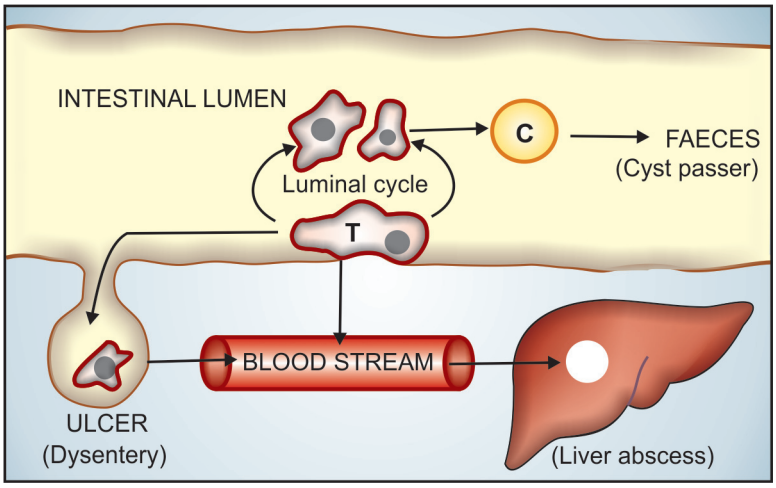

Fig. 60.1: The luminal cycle and invasive forms of amoebiasis.
T—trophozoite; C—cyst

Soon after its triumph as an antimalarial in 1948, chloroquine was found to be an effective and safe drug for hepatic amoebiasis. Diloxanide furoate was a useful addition in 1960, covering mainly chronic intestinal forms of the disease. However, the most remarkable development was the demonstration of antiamoebic property of metronidazole in the early 1960s. This drug had been introduced a few years back as a well tolerated, orally effective agent for trichomonas vaginitis. Of the many congeners of metronidazole that were tested, tinidazole has emerged in the 1970s as a good alternative, and others have been added subsequently.

CLASSIFICATION

1. *Tissue amoebicides*
   (a) For both intestinal and extraintestinal amoebiasis:
   Nitroimidazoles: Metronidazole, Tinidazole, Secnidazole, Ornidazole, Satranidazole
   Alkaloids: Emetine, Dehydroemetine
   (b) For extraintestinal amoebiasis only: Chloroquine
2. *Luminal amoebicides*
   (a) *Amide* : Diloxanide furoate, Nitazoxanide
   (b) *8-Hydroxyquinolines:* Quiniodochlor (Iodochlorohydroxyquin, Clioquinol), Diiodohydroxyquin (Iodoquinol)
   (c) *Antibiotics*: Tetracyclines, Paromomycin

NITROIMIDAZOLES

Metronidazole

It is the prototype nitroimidazole introduced in 1959 for trichomoniasis and later found to be a highly active amoebicide. It has broad-spectrum cidal activity against anaerobic protozoa, including *Giardia lamblia* in addition to the above two. Many anaerobic and microaerophilic bacteria, such as *Bact. fragilis, Fusobacterium, Clostridium perfringens, Cl. difficile, Helicobacter pylori, Campylobacter,* peptococci, spirochetes and anaerobic *Streptococci* are sensitive. Though, it does not directly inhibit the helminth *Dracunculus medinensis,* extraction of the worm from under the skin is facilitated. Metronidazole does not affect aerobic bacteria. Clinically significant resistance has not developed among *E. histolytica,* but decreased responsiveness of *T. vaginalis* has been observed in some areas. Anaerobic bacteria and *G. lamblia* also can develop metronidazole resistance, but this is a clinical problem only in the case of *H. pylori*.

Metronidazole is selectively toxic to anaerobic and microaerophilic microorganisms. After entering the cell by diffusion, its nitro group is reduced by certain redox proteins operative only in anaerobic microbes to a highly reactive nitro radical which exerts cytotoxicity. The nitro radical of metronidazole acts as an electron sink which competes with the biological electron acceptors of the anaerobic organism for the electrons generated by the pyruvate : ferredoxin oxidoreductase (PFOR) enzyme pathway of pyruvate oxidation. The energy metabolism of anaerobes that have no mitochondria is thus, disrupted. Aerobic environment attenuates cytotoxicity of metronidazole by inhibiting its reductive activation. Moreover, O_2 competes with the nitro radical of metronidazole for the free electrons generated during energy metabolism of anaerobes. Anaerobes which develop metronidazole resistance become deficient in the mechanism that generates the reactive nitro radical from it or have lower levels of PFOR.

Metronidazole, in addition, has been found to inhibit cell mediated immunity, to induce mutagenesis and to cause radiosensitization.

Pharmacokinetics Metronidazole is almost completely absorbed from the small intestines; little unabsorbed drug reaches the colon. It is widely distributed in the body, attaining therapeutic concentration in vaginal secretion, semen, saliva and CSF. Metabolism occurs in liver primarily by oxidation and glucuronide conjugation followed by renal excretion. Plasma t½ is 8 hrs.

Adverse effects Side effects of metronidazole are relatively frequent and unpleasant, but mostly nonserious.

- Anorexia, nausea, metallic taste and abdominal cramps are the most common. Looseness of stool is occasional.

- Less frequent side effects are—headache, glossitis, dryness of mouth and dizziness.
- Urticaria, flushing, heat, itching, rashes and fixed drug eruption occur in allergic subjects, warrant discontinuation of the drug and preclude future use of nitroimidazoles.
- Prolonged administration may cause peripheral neuropathy and CNS effects. Seizures have followed very high doses. Leucopenia is likely with repeated courses.
- Thrombophlebitis of the injected vein occurs if the solution is not well diluted.

Contraindications Metronidazole is contraindicated in neurological disease, blood dyscrasias, first trimester of pregnancy (though no teratogenic effect has yet been demonstrated, its mutagenic potential warrants caution). Cautious use in chronic alcoholics.

Interactions A disulfiram-like intolerance to alcohol occurs in some patients taking metronidazole.

Alcohol-metronidazole interaction occurs only in some individuals, while majority of those taking it can consume alcohol without any reaction. There is no convincing evidence of disulfiram-like action of metronidazole, but manufactures advise caution in drinking during metronidazole therapy.

Enzyme inducers (phenobarbitone, rifampin) may reduce its therapeutic effect.

Cimetidine can reduce metronidazole metabolism: its dose may need to be decreased.

Metronidazole enhances warfarin action by inhibiting its metabolism. It can decrease renal elimination of lithium and precipitate toxicity.

Preparations

FLAGYL, METROGYL, METRON, ARISTOGYL ALDEZOLE 200, 400 mg tab, 200 mg/5 ml susp. (as benzoyl metronidazole: tasteless); 500 mg/100 ml i.v. infusion; UNIMEZOL 200, 400 mg tabs, 200 mg/5 ml susp. METROGYL GEL, LUPIGYL GEL: 1% gel for vaginal/topical use.

Uses

1. *Amoebiasis*: Metronidazole is a first line drug for all forms of amoebic infection. Many dosage regimens have been tried; the current recommendations are:

For invasive dysentery and liver abscess—800 mg TDS (children 30–50 mg/kg/day) for 7–10 days.

In severe cases of amoebic dysentery or liver abscess 500 mg may be infused i.v. slowly every 6–8 hours for 7–10 days or till oral therapy can be instituted.

For mild intestinal disease—400 mg TDS for 5–7 days. Metronidazole is less effective than many luminal amoebicides in eradicating amoebic cysts from the colon, because it is nearly completely absorbed from the upper bowel.

2. *Giardiasis* It is highly effective in a dose of 400 mg TDS for 7 days. A shorter course of 3 days with 2 g/day is equally effective.

3. *Trichomonas vaginitis* It is the drug of choice; 2.0 g single dose is preferred. Alternatively 400 mg BD–TDS may be used for 7 days. Additional intravaginal treatment is needed only in refractory cases. Repeated courses may be necessary in some patients, but should be given with gaps of 4–6 weeks. The male partner should be treated concurrently in cases of recurrent infections.

Nonspecific bacterial vaginosis also responds.

4. *Anaerobic bacterial infections* They occur mostly after colorectal or pelvic surgery, appendicectomy, etc. Brain abscesses and endocarditis may be caused by anaerobic organisms.

Metronidazole is an effective drug for these and is generally used in combination with gentamicin or cephalosporins (many are mixed infections). For serious cases i.v. administration is recommended: 15 mg/kg infused over 1 hr followed by 7.5 mg/kg every 6 hrs till oral therapy can be instituted with 400–800 mg TDS. *Prophylactic use* in high risk situations (colorectal/biliary surgery) is recommended.

Other drugs effective in anaerobic infections are clindamycin and chloramphenicol.

5. *Pseudomembranous enterocolitis* due to *Cl. difficile* is generally associated with use of

antibiotics. Oral metronidazole 400–800 mg BD–TDS for 10–14 days is more effective, more convenient, less toxic, and therefore preferred over vancomycin which may be used in non-responsive cases, or when the infection recurs.

6. *Acute necrotizing ulcerative gingivitis (ANUG)* Metronidazole/tinidazole are the drugs of choice for ANUG (also called 'trench mouth') which is caused by anaerobes like fusobacteria, spirochetes and bacteroides. Metronidazole 200–400 mg TDS (15–30 mg/kg/day) is often combined with amoxicillin, tetracycline or erythromycin. The response is rapid with disappearance of the spirochete-fusobacterium complex from the lesions and resolution of pain, bleeding, ulceration and bad breath within 2–3 days; but treatment must be continued for at least 5 days.

7. *Helicobacter pylori gastritis/peptic ulcer* (*see* p. 657) Metronidazole or tinidazole alone are ineffective in eradicating *H. pylori*; resistance develops. Metronidazole 400 mg TDS or tinidazole 500 mg BD are combined with amoxicillin/clarithromycin and a proton pump inhibitor in triple drug 2 week regimens.

8. *Guinea worm infestation* Niridazole is considered to be the drug of choice, but because it is not available in India, metronidazole is used. A 7 day course with 200– 400 mg TDS produces symptomatic relief. The local reaction to the worm may be suppressed by its antiinflammatory action, and extraction is facilitated. (This infestation is now rare in India).

Tinidazole It is an equally efficacious congener of metronidazole, similar to it in every way except:

- Metabolism is slower; t½ is ~12 hr; duration of action is longer; dosage schedules are simpler. Thus, it is more suited for single dose or once daily therapy.
- Some comparative trials in amoebiasis have reported higher cure rates.
- It appears to be better tolerated; the incidence of side effects is lower: metallic taste (2%), nausea (1%), rash (0.2%).

TINIBA 300, 500, 1000 mg tabs; 800 mg/400 ml i.v. infusion; TRIDAZOLE 300, 500 mg tab; FASIGYN 0.5 g and 1 g tab., TINI 0.3 g, 0.5 g, 1.0 g tabs, 75 mg/5 ml and 150 mg/5 ml oral susp.

Recommended schedules are—

Intestinal amoebiasis: 2 g OD for 3 days (children 30–50 mg/kg/day) or 0.6 g BD for 5–10 days.

Amoebic liver abscess: The 2 g daily dose may be continued for 3–6 days.

Trichomoniasis and giardiasis: 2 g single dose or 0.6 g OD for 7 days.

Anaerobic infections:
prophylactic—2 g single dose before colorectal/biliary surgery;
therapeutic—2 g followed by 0.5 g BD for 5 days.

H. pylori: 500 mg BD for 2 weeks in triple combination.

Secnidazole A congener of metronidazole with the same spectrum of activity and potency. Absorption after oral administration is rapid and complete, but metabolism is slower resulting in a plasma t½ of 17–29 hours. After 48 hr of a single 2 g dose, plasma secnidazole concentration may still remain within the range of MIC values against sensitive organisms. In intestinal amoebiasis a single 2 g dose has been found to yield high cure rates. Side effect profile is similar to metronidazole and reported incidence is 2–10%.

Dose: 2 g single dose (children 30 mg/kg) for mild intestinal amoebiasis, giardiasis, trichomonas vaginitis and nonspecific bacterial vaginosis. For acute amoebic dysentery 0.5 g TDS for 5 days is recommended.

SECNIL, SECZOL 0.5, 1.0 g tabs; NOAMEBA-DS 1.0 g tab.

Ornidazole It has activity similar to metronidazole, but it is slowly metabolized—has longer t½ (12–14 hr). Dose and duration of regimens for amoebiasis, giardiasis, trichomoniasis, anaerobic infections and bacterial vaginosis resemble those for tinidazole. In chronic intestinal amoebiasis and asymptomatic cyst passers 0.5 twice daily for 5 to 7 days has also been used. Side effect profile is also similar to tinidazole.

DAZOLIC 500 mg tab, 500 mg/100 ml vial for i.v. infusion. ORNIDA 500 mg tab, 125 mg/5 ml susp.

Satranidazole Another nitroimidazole having longer t½ (14 hr). Advantages claimed are: better

tolerability—no nausea, vomiting or metallic taste, absence of neurological and disulfiram-like reactions and that it does not produce the acetamide metabolite which is a weak carcinogen.

Dose: Amoebiasis 300 mg BD for 3–5 days, giardiasis and trichomoniasis 600 mg single dose.

SATROGYL 300 mg tab.

ALKALOID

Emetine

It is an alkaloid from *Cephaelis ipecacuanha*. Emetine is a potent and directly acting amoebicide—kills trophozoites but has no effect on cysts. It acts by inhibiting protein synthesis in amoebae by arresting intraribosomal translocation of tRNA-amino acid complex.

In acute dysentery the stool is rapidly cleared of the trophozoites and symptomatic relief occurs in 1–3 days (even faster than metronidazole), but it is not curative in the sense that the patient continues to pass cysts in the stool. It is highly efficacious in amoebic liver abscess also.

Emetine cannot be given orally because it will be vomited out. It is administered by s.c. or i.m. injection: 60 mg OD. It is a local irrirant and has high systemic toxicity, *viz*, nausea, vomiting (due to CTZ stimulation and gastric irritation), abdominal cramps, diarrhoea, weakness, stiffness of muscles, myositis, hypotension, ECG changes and myocarditis.

Use Emetine is now rarely used for acute amoebic dysentery or for amoebic liver abscess, only in patients not tolerating metronidazole. A luminal amoebicide must always follow emetine to eradicate the cyst forming trophozoites.

It is also effective in liver fluke infestation.

EMETINE HCl: 60 mg /2 ml inj; for not more than 10 days to avoid cumulative toxicity.

Dehydroemetine It is equally effective but less cumulative and less toxic to the heart. Thus, it is usually preferred over emetine.

Dose: 60–100 mg s.c./i.m.OD for not more than 10 days.

DEHYDROEMETINE HCl: 30 mg/ml inj, 1 and 2 ml amps.

Chloroquine

The pharmacology of chloroquine is described in Ch. 59. It kills trophozoites of *E. histolytica* and is highly concentrated in liver. Therefore, it is used in hepatic amoebiasis only. Because it is completely absorbed from the upper intestine and not so highly concentrated in the intestinal wall—it is neither effective in invasive dysentery nor in controlling the luminal cycle (cyst passers).

Efficacy of chloroquine in amoebic liver abscess approaches that of emetine, but duration of treatment is longer and relapses are relatively more frequent, but amoebae do not develop resistance to chloroquine. A luminal amoebicide must always be given with or after chloroquine to abolish the luminal cycle.

Dose for amoebic liver abscess: 600 mg (base) for two days followed by 300 mg daily for 2–3 weeks. Though chloroquine is relatively safe, side effects are frequent. The 2–3 week course is poorly tolerated. It is employed only when metronidazole fails to clear the infection or is not tolerated.

AMIDES

Diloxanide furoate

It is a highly effective luminal amoebicide which directly kills trophozoites responsible for production of cysts. The furoate ester is hydrolysed in intestine and the released diloxanide is largely absorbed. Diloxanide is a weaker amoebicide than its furoate ester. No systemic antiamoebic activity is evident despite its absorption. It is primarily metabolized by glucuronidation and is excreted in urine.

Diloxanide furoate exerts no antibacterial action. It is less effective in invasive amoebic dysentery, because of poor tissue amoebicidal action. However, a single course produces high (80–90%) cure rate in mild intestinal amoebiasis and in asymptomatic cyst passers.

Dose: 500 mg TDS for 5–10 days; children 20 mg/kg/day.

FURAMIDE, AMICLINE 0.5 g tab; in TINIBA-DF 250 mg + 150 mg tinidazole and TINIBA-DF FORTE 500 mg + 300 mg tabs; in ENTAMIZOLE 250 mg + 200 mg metronidazole and ENTAMIZOLE FORTE 500 mg + 400 mg tabs.

Diloxanide furoate is very well tolerated; the only side effects are flatulence, occasional nausea, itching and rarely urticaria. It is a preferred drug for mild intestinal/asymptomatic amoebiasis, and is given after or along with any tissue amoebicide to eradicate cysts. Combined use with metronidazole/tinidazole is quite popular. Some chronic cases require repeat courses for eradication.

Nitazoxanide This salicylamide congener of the anthelmintic niclosamide, introduced for the treatment of giardiasis and cryptosporidiosis is also active against many other protozoa and helminths including *E. histolytica, T. vaginalis, Ascaris, H. nana,* etc. It is a prodrug which on absorption is converted to the active form *tizoxanide,* an inhibitor of PFOR enzyme that is an essential pathway of electron transport

energy metabolism in anaerobic organisms. Activity against metronidazole-resistant *Giardia* has also been demonstrated. Tizoxanide generated from nitazoxanide is glucuronide conjugated and excreted in urine and bile.

Nitazoxanide is the most effective drug for *Cryptosporidium parvum* infection (upto 88% cure), which causes diarrhoea, especially in children and AIDS patients. It is also indicated in giardiasis, and in amoebic dysentery as luminal amoebicide. Abdominal pain, vomiting and headache are mild and infrequent side effects.

Dose: 500 mg (children 7.5 mg/kg) BD × 3 days

NITACURE, NITCOL, NITARID 200 mg, 500 mg tabs, 100 mg/5 ml dry syrup.

8-HYDROXYQUINOLINES

Several 8-hydroxyquinolines including *Quiniodochlor* and *Iodoquinol* were widely employed in the past: have similar properties; are active against *Entamoeba, Giardia, Trichomonas,* some fungi (dermatophytes, *Candida*) and some bacteria. They kill the cyst forming amoebic trophozoites in the intestine, but do not have tissue amoebicidal action. Like diloxanide furoate, they are not very effective in acute amoebic dysentery but afford relief in chronic intestinal amoebiasis. Their efficacy to eradicate cysts from asymptomatic carriers is rated lower than that of diloxanide furoate. They are totally valueless in extraintestinal amoebiasis.

Absorption of 8-hydroxyquinolines from the intestine is variable. The absorbed fraction is conjugated in liver with glucuronic acid and sulfate and excreted in urine; t½ ~12 hours. Therapeutic concentrations are not attained in the intestinal wall or in liver. The unabsorbed part reaches lower bowel and acts on luminal cycle of amoebae.

Being inexpensive, these drugs have been widely and injudiciously used for the prophylaxis and treatment of nonspecific diarrhoeas, traveller's diarrhoea, dietary indiscretion, etc., but are infrequently prescribed now, except in some poor localities.

8-Hydroxyquinolines produce few side effects—nausea, transient loose and green stools, pruritus, etc. but carry toxic potential if improperly used.

Iodism (furunculosis, inflammation of mucous membranes) may occur due to chronic iodine overload. Goiter may develop. Individuals sensitive to iodine may experience acute reaction with chills, fever, angioedema and cutaneous haemorrhages.

Prolonged/repeated use of relatively high doses of quiniodochlor caused a neuropathic syndrome called 'subacute myelo-optic neuropathy' (SMON) in Japan in an epidemic form, affecting several thousand people in 1970. Other 8-hydroxyquinolines have also produced neuropathy and visual impairment. However, despite widespread use in the past, only sporadic and unconfirmed cases have been reported from India. These drugs have been banned in Japan and few other countries, but in India they are prohibited only for pediatric patients, because their use for chronic diarrhoeas in children has caused blindness. Their fixed dose combinations, except for external application, are banned in India, and a cautionary note is inserted that use of high doses for more than 14 days can cause neuritis and optic damage.

8-Hydroxyquinolines are cheap and have good patient acceptability. They may be employed in intestinal amoebiasis as alternative to diloxanide furoate.

Other uses are—giardiasis; local treatment of monilial and trichomonas vaginitis, fungal and bacterial skin infections.

Quniodochlor (Iodochlorohydroxyquin, Clioquinol): 250–500 mg TDS; (not to exceed 1.5 g/day for 14 days).

ENTEROQUINOL, QUINOFORM, DEQUINOL 250 mg tab.

Diiodohydroxyquin (Iodoquinol): 650 mg TDS;, (not to exceed 2.0 g/day for 14 days).

DIODOQUIN 650 mg tab, 210 mg/5 ml susp.

ANTIBIOTICS

Tetracyclines

Tetracyclines have modest direct inhibitory action on Entamoeba. In addition the older tetracyclines are incompletely absorbed in the small intestine, reach the colon in large amounts and inhibit the bacterial flora with which *Entamoebae* live symbiotically. Thus, they indirectly reduce proliferation of entamoebae in the colon and are especially valuable in chronic, difficult to treat cases who have only the luminal

cycle with little mucosal invasion. Tetracyclines have an adjuvant role in the management of such cases, in conjunction with a more efficacious luminal amoebicide. They have also been added as the third drug along with a nitroimidazole + a luminal amoebicide in the treatment of amoebic dysentery, but have no role in hepatic amoebiasis.

Paromomycin

It is an aminoglycoside antibiotic which closely resembles neomycin. Distinctively, paromomycin is active against many protozoa like *Emtamoeba, Giardia, Cryptosporidium, Trichomonas, Leishmania* and some tape worms, in addition to having antibacterial spectrum like neomycin. In the 1960s an oral formulation of paromomycin was introduced as a luminal amoebicide and was briefly marketed in India as well. However, it was soon overshadowed by metronidazole, became commercially unviable and was discontinued. It has gained popularity again and is being frequently used in USA and some other countries. In India and Africa, parenteral (i.m.) paromomycin is being used in resistant Kalaazar (*see* p. 847).

The mechanism of antiprotozoal action of paromomycin appears to be the same as its antibacterial action; *viz.* binding to 30S ribosome and interference with protein synthesis. Orally administered paromomycin acts only in the gut lumen. It is neither absorbed nor degraded in the intestines, and is eliminated unchanged in the faeces. Thus, it is free from systemic toxicity. Its effect on gut flora resembles that of neomycin. Paromomycin can substitute for neomycin in hepatic coma and for preoperative preparation of bowel.

Paromomycin is an efficacious luminal amoebicide, achieving similar or even better clearing of cysts from stools compared to diloxanide furoate in asymptomatic cyst passers. Good symptomatic relief and cyst clearance is obtained in chronic amoebic colitis. It can be given along with metronidazole in acute amoebic dysentery as well as in hepatic amoebiasis to eradicate the luminal cycle.

Paromomycin is an alternative drug for giardiasis, especially during 1st trimester of pregnancy when metronidazole and other drugs are contraindicated. It has been used in cryptosporidiosis, but efficacy is uncertain. Topically, it may used in trichomonas vaginitis and dermal leishmaniasis.
Dose: Oral: 500 mg (children 10 mg/kg) TDS, for 7 days for amoebiasis/giardiasis/cryptosporidiosis.
Side effects are limited to the g.i.t.; nausea, vomiting, abdominal cramps, diarrhoea; rarely rashes.

NOTES ON THE TREATMENT OF AMOEBIASIS

1. Acute amoebic dysentery Most cases of amoebic dysentery respond to a single adequate course of treatment. Metronidazole/tinidazole are the drugs of choice. Secnidazole, ornidazole, are the alternatives. Adjuvant measures for diarrhoea and abdominal pain may be needed. Dehydroemetine is rarely used in the most severe cases or when metronidazole produces severe allergic reaction or neurotoxicity. It should be discontinued as soon as acute symptoms are controlled (2–3 days) and metronidazole started.

The above treatment should be followed by a course of luminal amoebicide to eradicate *E. histolytica* from the colon and to prevent carrier (cyst passing) state. A tetracycline, added as the third drug, may have adjuvant value.

2. Mild intestinal amoebiasis/asymptomatic cyst passers
Nitroimidazoles afford rapid symptomatic relief in mildly symptomatic intestinal amoebiasis as well, and are the first line drugs. However, they mostly fail to clear cysts, and the standard practice is to give diloxanide furoate or another luminal amoebicide, either concurrently or immediately after. Luminal amoebicides alone are generally slower in action, but avoid side effects of metronidazole. Asymptomatic cyst passers are mostly treated wtih only luminal amoebicide. Chronic cases may require 2–3 repeated courses in which drugs may be alternated. A tetracycline may be given concurrently with the luminal amoebicide in cases which fail to clear completely.

3. Amoebic liver abscess It is a serious disease; complete eradication of trophozoites from the liver is essential to avoid relapses. Metronidazole/tinidazole are the first choice drugs effective in > 95% cases. Critically ill patients may be treated with i.v. metronidazole for the entire course, or at least initially, followed by oral dosing. Dehydroemetine is to be used only if metronidazole cannot be given for one reason or the other, and in patients not cured by metronidazole. Large abscesses usually take months to resolve, even if all trophozoites are killed. If a big abscess has formed, it may be aspirated.

Treatment of different forms of amoebic infection

Drugs of Choice	Alternative Drugs
Acute Amoebic Dysentery	
• Metronidazole 800 mg oral TDS × 7–10 days (in severe cases 500 mg slow i.v. 6 hourly till oral therapy can be instituted) or • Tinidazole 2.0 g oral daily × 3 days + *Luminal amoebicide* • Diloxanide furoate 500 mg TDS × 5–10 days	• Ornidazole 2.0 g oral daily × 3 days or • Secnidazole 0.5 g oral TDS × 5 days *Alternative luminal amoebicides* • Quiniodochlor 250–500 mg oral TDS × 7–14 days or • Iodoquinol 650 mg oral TDS × 7–14 days or • Paromomycin 500 mg oral TDS × 7–10 days ± • Tetracycline 250 mg TDS × 7–10 days (adjuvant)
Mild intestinal amoebiasis/Asymptomatic cyst passers*	
• Metronidazole 400 mg oral TDS × 5–7 days or • Tinidazole 2.0 g oral OD × 2–3 days + *Luminal amoebicide* (as above)	• Ornidazole 0.5 g oral BD × 5–7 days or • Secnidazole 2.0 g oral single dose *Alternative luminal amoebicides* (as above) ± Tetracycline 250 mg TDS × 7–10 days (adjuvant)
Amoebic liver abscess	
• Metronidazole 800 mg oral TDS × 10 days (in serious cases 500 mg slow i.v. 6 hourly × 10 days) or • Tinidazole 2.0 g oral daily × 3–6 days + *Luminal amoebicide* (as above)	• Emetine/Dehydroemetine 60 mg i.m./s.c. × 8–10 days Followed by/alternatively • Chloroquine 600 mg (base) oral daily × 2 days, followed by 300 mg daily for 2–3 weeks. *Alternative luminal amoebicides* (as above, but no role of tetracycline)
* In asymptomatic cases, a luminal amoebicide alone may be used (the nitroimidazole may be omitted). Repeat courses after a gap of 2–3 weeks may be needed with the same or alternative drugs to eradicate the chronic luminal cycle.	

A luminal amoebicide must be given later to finish the intestinal reservoir of infection. A course of chloroquine may be administered after that of metronidazole/dehydroemetine in those with incomplete response or to ensure that no motile forms survive in the liver.

DRUGS FOR GIARDIASIS

Giardia lamblia is a flagellate protozoon which infects children and adults by oro-faecal contamination and mostly lives as a commensal in the intestine. It sometimes invades the mucosa and causes acute watery short duration diarrhoea with foul smellling stools, gas and abdominal cramps. If untreated, it may pass on to chronic diarrhoea with greasy or frothy stools but no blood or mucus. Many drugs useful in amoebiasis are also effective in giardiasis.

1. *Metronidazole* 400 mg TDS (children 15 mg/kg/day) for 5–7 days or 2 g daily for 3 days

Or

tinidazole 0.6 g daily for 7 days or 2 g single dose

Or

secnidazole 2 g single dose

These may be considered as the drugs of choice, but ~ 10% patients may not be cured, and a second course or alternative drug may be needed.

2. *Nitazoxanide* (*see p. 840*) This prodrug of the PFOR enzyme inhibitor tizoxanide has become available for the treatment of diarrhoea and dysentery caused by *Cryptosporidium parvum, Giardia lamblia, E. histolytica.* The dosage schedule is convenient—500 mg (children 7.5 mg/kg) twice daily for 3 days, efficacy (~80%) approaches that of metronidazole and tolerability is good.

3. *Quiniodochlor* 250 mg TDS for 7 days is a somewhat less effective alternative.

4. *Paromomycin* In a dose of 500 mg TDS for 5–7 days, it is somewhat less effective than metronidazole, but is free of systemic side effects and can be used during pregnancy. However, oral formulation is not available in India.

5. *Furazolidone* It is a nitrofuran compound active against many gram-negative bacilli including *Salmonella* and *Shigella*, also *Giardia* and *Trichomonas*. For giardiasis 100 mg TDS for 5–7 days has been used, but is inferior to metronidazole or tinidazole. It has also been used in bacterial enteritis, food poisoning diarrhoeas and bacillary dysentery, but is not a first line treatment for any of these.

Furazolidone is partly absorbed from intestines and excreted in urine which turns orange—patients should be told about it. Side effects are mild and infrequent—nausea, headache, dizziness.
FUROXONE 100 mg tab, 25 mg/5 ml susp.

DRUGS FOR TRICHOMONIASIS

Trichomonas vaginalis is another microaerophilic flagellate protozoon which causes vulvovaginitis. It is a common sexually transmitted disease affecting ~ 10% sexually active women. Several drugs are partly effective by vaginal application, but may not entirely clear the infection; recurrences are frequent; repeat courses are required.

1. Drugs used orally

Metronidazole 400 mg TDS for 7 days or 2 g single dose, or *Tinidazole* 600 mg daily for 7 days or 2 g single dose or *Secnidazole* 2 g single dose, are the drugs of choice. They produce upto 90% cure. However, vaginitis due to nitroimidazole resistant *T. vaginalis* is being reported. Some resistant cases respond to higher doses, particularly of tinidazole. Additional intravaginal treatment is required only in refractory cases. A hard core of recurrent cases may remain. A repeat course can be given after 6 weeks. Additional treatment for nonspecific vaginosis often helps. In some cases recurrences are due to reinfection from the male partner who harbours the parasite in the seminal vesicles but remains asymptomatic. In such cases, both partners should be treated concurrently to prevent cross infection of each other.

2. Drugs used intravaginally

1. *Diiodohydroxyquin* 200 mg inserted intravaginally at bed time for 1–2 weeks;
   FLORAQUIN 100 mg vaginal pessaries.
2. *Quiniodochlor* 200 mg inserted in the vagina every night for 1–3 weeks;
   GYNOSAN 200 mg vaginal tab.
3. *Povidone-iodine* 400 mg inserted in the vagina daily at night for 2 weeks;
   BETADINE VAGINAL 200 mg pessaries.

DRUGS FOR LEISHMANIASIS

Visceral leishmaniasis (VL; kala-azar) caused by *Leishmania donovani* (and other Leishmania species) occurs in several tropical and subtropical regions of the world. According to WHO the global burden of VL is ~0.5 million new cases and ~50,000 deaths annually. About 90% of the cases occur in India, Bangladesh, Nepal, Sudan and Brazil, but the disease is also present in other countries of East Africa, South America, Mediterranean basin and central Asia. In india, leishmaniasis is prevalent in Bihar, West Bengal, Jharkhand and eastern UP; the worst affected being Bihar which contributes 50% cases that occur world over. The geographical location is important, because the species of *Leishmania* causing VL and its responsiveness to different drugs differs between different regions. The disease is highly concentrated in North Bihar and the parasite is resistant to sodium stibogluconate (SSG), the first line drug in many other countries.

Leishmaniasis is transmitted by the bite of the female sandfly phlebotomus. In the fly the parasite exists in the flagellate extracellular (*promastigote*) form, while in man it is found only intracellularly within macrophages in the

nonflagellate (*amastigote*) form. Mucocutaneous and dermal leishmaniasis are caused respectively by *L. braziliensis* and *L. tropica* (also other species). Visceral leishmaniasis (VL) is fatal unless treated.

The currently used drugs for treatment of VL are:

1. Sodium stibogluconate (SSG)
   (or Meglumine antimonate—in French speaking countries)
2. Amphotericin B (AMB)
3. Miltefosine
4. Paromomycin

Pentamidine was used in resistant kala-azar till 10 years back but not now. *Ketoconazole* and *Allopurinol* have weak anti-leishmania action, but are not used now.

Kala-azar is primarily a disease of the economically poor class, and the areas affected are underdeveloped. India launched a kala-azar control programme in 1990, which was upgraded in the year 2000 to aim at elimination of the disease. The programme is implemented under the NVBDCP, which has laid down its own treatment guidelines, and provides free treatment. Under the programme 33,043 cases of VL were treated in 2011 with 80 deaths. However, the actual number of cases is much greater. Only confirmed cases (by 'rapid diagnostic test' or splenic aspirate examination) are to be treated with antileishmania drugs.

The choice of drugs, doses and regimens as currently recommended by WHO and NVBDCP are summarized in the box.

Cure is indicated by clinical improvement and absence of relapse within 6 months. This can be confirmed by absence of leishmania in splenic aspirate smear examination.

1. Sodium stibogluconate (SSG) It has been the standard first line drug for VL in most parts of the world achieving > 90% cure rate, and is still used in East Africa, Central Asia, Mediterranean basin and South America, but is no longer effective in India and Nepal because of extensive resistance. Over 60% cases in Bihar are unresponsive. SSG is a water soluble pentavalent antimonial, the supplied solution

*** Recommended treatment regimens for visceral leishmaniasis (Kala-azar) caused by *L. donovani* in the Indian subcontinent**

£1. Amphotericin B deoxycholate (AMB-DOC): 0.75–1.0 mg/kg i.v. infusion over 4 hours daily or on alternate days till 15 mg/kg total dose.

¥2. Liposomal amphotericin B (L-AMB): 3–5 mg/kg i.v. infusion daily for 3–5 days (total dose 15 mg/kg)
or
L-AMB 10 mg/kg single dose i.v. infusion

$3. Miltefosine (all doses given orally with meals for 28 days)
Adults (>12 years) weighing > 25 kg: 100 mg/day (50 mg cap twice daily)€
Adults (>12 years) weighing < 25 kg: 50 mg/day (50 mg cap once daily)
Children (2–11 years): 2.5 mg/kg/day (as 10 mg caps)

4. Paromomycin sulfate: 15 mg (11 mg base) per kg/day i.m. for 21 days

5. Sodium stibogluconate (SSG): 20 mg (Sb^{5+})/kg i.m. or slow i.v. daily for 30 days (only in areas where the *Leishmania* is still sensitive to SSG).

COMBINATIONS (co-administered drugs)

1. L-AMB (5 mg/kg i.v. infusion single dose) + Miltefosine (as above) for 7 days.
2. L-AMB (5 mg/kg i.v. infusion single dose) + Paromomycin (as above) for 10 days.
3. Miltefosine (as above) daily for 10 days + Paromomycin (as above) daily for 10 days.

RESCUE TREATMENT (of failure/non-responsive cases)

1. AMB-DOC or L-AMB at higher doses.

* Adopted from Report of meeting of the WHO Expert Committee on control of leishmaniasis, March 22–26, 2010; WHO Technical Report Series No. 949 (2010)

$ Used as 1st line treatment under NVBDCP

£ Used as 2nd line treatment by NVBDCP.

¥ 1st preference regimen recommended by WHO.

€ The WHO in additon recommends miltefosine dose to be 150 mg/day for adults weighing > 50 kg, while NVBDCP treats all adults above 25 kg with 100 mg/day

contains 10% (100 mg/ml) antimony, and doses are expressed in terms of elemental Sb. The mechanism of action and the basis of selective toxicity to the leishmania amastigotes is unclear. It was believed that -SH dependent enzymes are inhibited by antimony and bioenergetics of the parasite is interfered with. This occurs due to blocking of glycolytic and fatty acid oxidation pathways. However, recent evidence indicates that a specific reductase enzyme, present in leishmania amastigots, reduces pentavalent-Sb of SSG to the toxic trivalent form, which then promotes efflux of glutathione and other reduced thiols from the parasite residing within macrophages, exposing them to oxidative damage. Resistance to SSG may involve reduced capacity of the parasite to convert it to the trivalent form, and/or alteration in thiol metabolism of the parasite.

Sod. stibogluconate is rapidly absorbed from the site of i.m. injection and excreted unchanged in urine within 6–12 hrs. A small fraction enters tissues and remains stored for long periods. Repeated doses are cumulative. Accumulation of SSG within macrophages accounts for its prolonged inhibitory effect on leishmania residing there. SSG is administered by deep i.m. injection (into buttocks) or by slow i.v. injection daily or on alternate days.

Adverse effects Though, antimonials are toxic drugs, but the pentavalent compounds (particularly SSG) are better tolerated. Nausea, vomiting, metallic taste, cough, pain abdomen, pain and stiffness of injected muscle, sterile abscesses, and mental symptoms often occur. Pancreatitis, liver and kidney damage, myelosuppression are possible, but are seldom severe. Q-T prolongation may herald arrhythmias. Few cases of shock and death are on record.

Sod. stibogluconate, nevertheless, is less toxic than amphotericin B. Used alone or in combination with paromomycin, SSG is still a 1st line drug in East Africa, Central Asia and South America. However, response is relatively poor in older and malnourished patients as well as in those coinfected with TB, HIV and other immunodeficient states.

2. Amphotericin B (AMB) (*see* Ch. 57) This antifungal antibiotic is available in two types of preparations. The older and less expensive one is formulated with deoxycholate (AMB-DOC), while in the newer one it is incorporated in liposomes (L-AMB), and is very expensive. Like fungi, leishmania has high percentage of ergosterol and is susceptible to this antibiotic which has high affinity for ergosterol and acts by binding to it. Presently, AMB is the drug with highest cure rate in kala-azar: up to 99% clinical and parasitological cure has been reported from India in SSG resistant cases, and it is treated as the 'reference drug' while comparing the efficacy of other drugs. However, high toxicity and need for prolonged hospitalization, monitoring and repeated slow i.v. infusions limit its application. Therefore, it is the 2nd line treatment of VL under NVBDCP, though the WHO recommendations accord it higher preference over miltefosine. Because miltefosine is teratogenic, AMB is the drug of choice in pregnant women and breast feeding mothers.

Liposomal AMB is particularly suited for kala-azar because it delivers the drug inside the reticuloendothelial cells in spleen and liver where the amastigotes live, but high cost is prohibitive. As such, use of L-AMB in India is largely limited to clinical trial setting. Using L-AMB, the total dose of 15 mg/kg can be administered over 3–5 days with ~ 98% cure, and WHO has accorded it the highest preference. Even a single dose treatment has been tried, reporting 90% cure at 5 mg/kg, and 98% cure at 10 mg/kg.

AMB is also useful in mucocutaneous leishmaniasis.

3. Miltefosine It is a derivative of alkyl phosphocholine with potent antileishmania activity that has been tested in India since the 1980s, but was approved only in 2002 as the first orally active drug for kala-azar. Due to spread of SSG resistance in Bihar and neighbouring areas, NVBDCP is now using miltefosine as the 1st line treatment of VL in India. A 4 week course of miltefosine has achieved >95% cure rate in India and 90% in Ethiopia. Curaneous leishmaniasis can also be cured by 4 week therpy. Miltefosine is available in India only through NVBDCP. It is also available in few other countries of the Indian region and in South America.

The mechanism of antileishmania action of miltefosine is not known. However, studies suggest that it may be interfering with lipid metabolism of the parasite or prevent synthesis of some critical cell surface anchor molecules, or alter signal transduction. Leishmania can develop resistance to miltefosine and this may be due to mutation limiting transport of the drug into the parasite cell. To prevent development of resistance to this useful drug, combination therapy with paromomycin or AMB is being promoted.

Miltefosine is rapidly absorbed after oral medication, and widely distributed in the body. It is a long acting drug with biphasic elimination. In the early phase, t½ is ~7 days while the terminal t½ is ~ 4 weeks. Anorexia, vomiting and diarrhoea are the commonest side effects occurring in over 50% patients. However, these are generally brief and resolve with continued use. Skin allergy and rise in hepatic transaminases occurs in some recipients indicating hepatic derangement, but this is usually mild and reverses on stopping the drug. Reversible kidney dysfunction with rise in serum creatinine has also been noted. Miltefosine is teratogenic. It is contraindicated in pregnant women. When miltefosine is given, it should be ensured that female patients do not get pregnant during and till 3 months after miltefosine course.

4. Paromomycin This aminoglycoside antibiotic is described with antiamoebic drugs on p.842. In intestinal protozoal infections, it is used by the oral route and remains confined to the gut. It has been later (in 2006) approved in India for use in VL by the i.m. route. Over the past decade paromomycin has been widely tried in India and Africa for kala-azar and found to be effective in SSG-resistant cases. The WHO recommends 21 day paromomycin treatment as an alternative to miltefosine.

In a recent phase III trial on 667 kala-azar patients in Bihar,* paromomycin 11 mg/kg/day × 21 days has yielded 95% cure rate, which was not inferior to 99% cure rate obtained with AMB 1 mg/kg × 15 injections over 30 days. Mortality was <1% with both the drugs. Several other trials have confirmed the efficacy of paromomycin in VL. In Sudan, a 17 day course of SSG + paromomycin has become the 1st choice treatment of kala-azar, because it yielded higher initial cure rate and better survival than monotherapy with 30 day course of SSG. However, in India, combination of SSG + paromomycin has not been encouraging.

Though paromomycin produces ototoxicity (in 2% recipients), reversible elevation of serum transaminase and injection site pain, but renal toxicity is rare. It has proven to be an effective, less expensive and easier to use alternative to AMB in kala-azar.

Topical paromomycin is effective in dermal leishmaniasis.

Combination therapy

Like in the case of TB, leprosy, HIV and malaria, combination therapy with 2 effective drugs has several advantages in the treatment of VL. These are:

- Limiting risk of development of drug resistance, thereby prolonging the effective life-time of available medicines.
- Attaining higher efficacy and cure rate.
- Shortening of duration of therapeutic regimen; better compliance and convenience.
- Reduction of overall dose; lower toxicity and cost.

Clinical studies in India have testified to the high efficacy of drug combinations, and have shown that duration of treatment can be reduced by half or more. The 3 combinations tested were:

a. L-AMB (5 mg/kg i.v. single dose) + Miltefosine (oral) daily × 7 days
b. L-AMB (5 mg/kg i.v. single dose) + Paromomycin (i.m.) daily × 10 days
c. Miltefosine (oral) daily × 10 days + Paromomycin (i.m.) daily × 10 days.

Each of these combinations yielded 98–99% cure rate. As such, these combinations are recommended with high preference by WHO. However, cost of L-AMB (even single dose) is high.

HIV and Leishmania coinfection

HIV and leishmania infections worsen each other. In endemic areas, HIV positive subjects are more likely to develop VL, harbour higher and disseminated leishmania load, and have poorer prognosis. Similarly, occurrence of VL in a HIV positive subject is regarded to be a sign of AIDS and warrants initiation of antiretroviral treatment irrespective of CD4+ count. Coinfected patients have a poorer response to antileishmania as well as anti-HIV drugs. Therapy of such patients is difficult and mortality is high.

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* Sundar S *et al:* Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med.* **2007**;*356:* 2571-2581.

Drugs used locally for dermal leishmaniasis (oriental sore)

Dermal leishmaniasis is not a life-threatening condition; many cases are treated by local application of drugs.

1. *Sodium stibogluconate*: Infiltrate 2 ml of the solution (100 mg antimony/ml) round the sore.
2. *Paromomycin* (15%) *ointment:* applied topically on the sore, twice daily for 20 days.

Small and mild lesion may heal by itself in a few months. Multiple sores and severe cases should be treated by systemic drugs as for kala-azar.

Antibiotics may be needed for secondary infection of the sore.

☞ PROBLEM DIRECTED STUDY

60.1 A 50-year-old gardner weighing 58 kg was admitted to the hospital with fever for 4 days, severe pain in right upper part of abdomen, loss of appetite, vomiting and marked weakness. He was not well for the past 2–3 weeks and had lost weight. There was no history of chronic diarrhoea. Palpation of abdomen revealed soft tender enlargement of liver 2 cm below costal margin. Marked tenderness was noted in the lower right intercostal region. Ultrasound showed a solitary 2.5 cm diameter abscess with sharp margins in the right lobe of liver. Stool examination was negative for any kind of ova and cysts. A clinical diagnosis of amoebic liver abscess was made and he was treated with:

Injection Metronidazole 500 mg i.v. over 1 hour every 8 hours for 5 days along with infusion of glucose-saline and vitamins. The fever and vomiting subsided and he started eating food. The injections were substituted by oral metronidazole 800 mg 3 times a day for another 5 days, and the patient became well, except weakness and mild tenderness in the right lower chest. Repeat ultrasound showed abscess cavity size to decrease to 1.5 cm. The patient was discharged with advise for vitamins and food.

(a) Was the choice of medication and route correct, or a better drug/route of administration is available?

(b) Should metronidazole therapy be extended or a repeat course given?

(c) Should the patient be given any other antiamoebic medication in addition to or following metronidazole?

(*see* Appendix-1 for solution)