INTRODUCTION

Visceral Leishmaniasis (VL), also known as “Kala-azar” is typically caused by the *L. donovani* complex, which includes two species: *L. donovani* (Indian subcontinent and East Africa), *L. infantum* (Mediterranean basin) and *L. infantum* syn *chagasi* (Latin America). An estimated 500,000 new cases of VL occur per year, 90% of which occur in the endemic areas of India, Nepal, Bangladesh, Sudan and Brazil. In India, about 100,000 cases of VL are estimated to occur annually. Of these, the state of Bihar accounts for more than 90% of cases.

VL is the systemic and most severe form of leishmaniasis, characterized by prolonged fever, splenomegaly, hepatomegaly, pancytopenia, progressive anemia and weight loss. If untreated, VL is uniformly fatal. Some patients with VL may develop a chronic form of dermal leishmaniasis characterized by indurated nodules or depigmented macules, and is called post kala azar dermal leishmaniasis (PKDL). PKDL is quite common (occurring in > 50% patients with VL) in Sudan, where it may occur concurrently with VL and heals spontaneously in most patients. In the Indian subcontinent it occurs only in a small proportion of patients, 6 months to several years after an episode of VL and treatment is necessary. The HIV/AIDS pandemic has modified the natural history of leishmaniasis. HIV infection increases the risk of developing VL in areas of endemicity, reduces the likelihood of a therapeutic response, and greatly increases the probability of relapse.

HIV/ VL co infection has been reported from more than 35 countries, initially most of these cases were from southwestern Europe but the number of cases are increasing in sub-Saharan Africa, Brazil and south Asia. The spread and overlap of both leishmaniasis and HIV infections in the major foci of leishmaniasis (India, Brazil, and Eastern Africa) make VL-HIV coinfection a serious worldwide concern.

OVERVIEW OF ANTILEISHMANIAL AGENTS

The treatment of VL is far from satisfactory. All antileishmanials with the exception of miltefosine has to be administered parenterally. The duration of treatment is long, the drugs are toxic and hospitalization is required for monitoring. Moreover, there is a regional variation in response to antileishmanial drugs and thus recommendations for treatment of VL vary in different regions.

i) Pentavalent Antimonials have been standard first-line treatment for VL in Africa, South America, Bangladesh, Nepal and India (except North Bihar) at the dose of 20 mg/kg/day parenterally for 28-30 days. However, large scale misuse in Bihar, has contributed to the development of widespread resistance to antimonials (sodium stibogluconate, SbV) in this region. Further, it causes serious cardiotoxicity resulting in ~5% mortality.

ii) Amphotericin B deoxycholate has an excellent cure rate (~100%) in India, at a dose of 0.75-1 mg/kg for 15-20 daily or alternate days intravenous infusions, however, most of the patients experience infusion reactions- e.g. fever, chills, and thrombophlebitis-and occasionally serious toxicity- e.g., hypokalemia, nephrotoxicity, myocarditis, and even death. It was recommended as a first line drug.
by the Indian National Expert Committee for SbV refractory regions. However, the need for infusions, hospitalization for prolonged periods, the high cost of the drug, the requirement for close monitoring and the high incidence of adverse events (occasionally serious), are its important drawbacks, and they have prevented its implementation at the primary health care level in Bihar.

iii) Lipid-associated amphotericin preparations are as effective as conventional amphotericin B, and have an added advantage of negligible adverse reactions. The dose requirement of liposomal amphotericin B varies from region to region; while in the Indian subcontinent a small dose induces high cure rates a higher dose is needed for the Mediterranean region and Brazil 8,9,10.

Until recently its high price precluded its use in the developing countries. However, a preferential pricing agreement with WHO (agreement between Gilead and WHO of 14 March 2007) has recently reduced the price of L-AmB (AmBisome®) for endemic regions to $20 per 50-mg vial 11. Recently in a large study in India, 412 patients were randomly assigned in a 3:1 ratio to receive either liposomal amphotericin B (AmBisome, Gilead Sciences, USA; L-AmB) at a dose of 10 mg per kilogram of body weight as a single dose and discharged after 24 hours or the conventional amphotericin B deoxycholate administered in 15 infusions of 1 mg per kilogram, was given every other day during a 29-day hospitalization. Cure rates at 6 months were similar in the two groups: 95.7% (95% confidence interval [CI], 93.4 to 97.9) in the liposomal-therapy group and 96.3% (95% CI, 92.6 to 99.9) in the conventional-therapy group 12. The preferential pricing, assured compliance, lack of any major side effects, along with a single day of hospitalization, makes single infusion of the liposomal preparation an excellent treatment option for VL in the Indian subcontinent.

iv) Miltefosine, an alkyl phospholipid is the first oral agent approved for the treatment of leishmaniasis. At the recommended doses (100mg daily for patients weighing ≥25 kg and 50 mg daily for those weighing <25 kg for 4 weeks) cure rates were 94% for VL 13. Its limitation are high cost, need for monitoring for gastrointestinal side effects, occasional hepatic and nephrotoxicity. As it is teratogenic, women of child bearing potential have to observe contraception for the duration of treatment and an additional three months because of its half life of nearly one week. Thus, subtherapeutic levels may remain for some weeks after a standard course of treatment which may lead to the emergence of resistance.

Free availability, gastrointestinal adverse events, and quick recovery (within 10 days most patients feel better), 4 week long regimen may drive patients to prematurely discontinue treatment and suboptimal compliance will ultimately lead to the development of parasite resistance 14. In a recent Phase IV trial of the drug in India, the final cure rate was only 82% by intention to treat and 95% by per protocol analysis15. Thus, to prevent the development of resistance, miltefosine needs to be given strictly as a directly observed therapy.

v) Paromomycin, an aminoglycoside-aminocyclitol antibiotic, has been used for the treatment of VL in a parenteral formulation and CL in both topical and parenteral formulations. In the phase III trial in the Indian subcontinent, a dose of 15 mg/kg paromomycin sulfate (11 mg base) for 21 days gave a cure rate of 95% and was noninferior to amphotericin B. It was approved by the Indian government in August 2006 for the treatment of patients with visceral leishmaniasis 16. The advantages of this agent is its cost, approximately US$ 10-15 per patient 17. The disadvantages are need for administering intramuscular injection, and monitoring of serum transaminases.

COMBINATION THERAPY

The growing resistance of the parasite to antileishmanial drugs suggests that the currently used monotherapy needs to be reviewed. Multidrug combination therapy has been used successfully in tuberculosis, leprosy and malaria. The rationale behind combination therapy are increased activity through use of compounds with synergistic or additive activity, preventing the emergence of drug resistance, lower dose requirement thereby reducing chances of toxic side effects and cost, and increased spectrum of activity. The other advantages are shorter duration of hospitalisation and decongestion of the overcrowded treatment centres.

Paromomycin has been used extensively in Sudan in combination with sodium stibogluconate for the treatment of VL. The combination of sodium stibogluconate at 20 mg/kg SbV plus paromomycin given at 15 mg/kg (11 mg base) for 17 days showed an efficacy of 93% 18. The combination is synergistic, decreases the duration of treatment and also gives better survival rates. As paromomycin has antimicrobicidal properties, it also decreases the incidence of infections in these patients. Experimental studies using including recently approved
drugs have shown encouraging results with combination of multiple drugs. In vivo studies in mice and in vitro macrophage sensitivity assays demonstrated encouraging results. Different interactions were found in vivo, where the highest potentiation of miltefosine activity was achieved with amphotericin B (activity enhancement index [AEI] of up to 11.3). No significant interaction was observed when miltefosine was combined with sodium stibogluconate (AEI of up to 2.38). The potentiation of miltefosine in vivo was also achieved with the combination of miltefosine and paromomycin (AEI of up to 7.22)\(^\text{19}\).

Recently, a randomized, noncomparative, group-sequential, triangular design study assigned 181 subjects to treatment with 5 mg/kg of L-AmB alone (Group A; 45 subjects), 5 mg/kg of L-AmB followed by miltefosine for 10 days (Group B; 46 subjects) or 14 days (Group C; 45 subjects), or 3.75 mg/kg of L-AmB followed by miltefosine for 14 days (Group D; 45 subjects). When it became apparent that all regimens were effective, 45 additional, nonrandomized patients were assigned to receive 5 mg/kg of L-AmB followed by miltefosine for seven days (group E). All 226 subjects showed initial apparent cure responses. Nine months after treatment, final cure rates were similar: group A, 91% (95% confidence interval [CI], 78%-97%); group B, 98% (95% CI, 87%-100%); group C, 96% (95% CI, 84%-99%); group D, 96% (95% CI, 84%-99%); and group E, 98% (95% CI, 87%-100%). These results suggest that single infusion of L-AmB (in most instances, administered in an outpatient setting) followed by a brief self-administered course of miltefosine could be an excellent option against Indian kala-azar\(^\text{20}\). The preferential pricing opens the prospect of combining lower total doses of Liposomal Amphotericin B in other combination regimens.

A study to identify the efficacy of combination therapy with drugs like lipid formulations of amphotericin B, miltefosine and paromomycin with 8-11 days duration of therapy have been completed. If successful, this would be a groundbreaking find providing affordable treatment with much improved compliance and prevent the emergence of resistance.

**MANAGEMENT OF HIV/VL CO-INFECTION**

Few clinical studies have been conducted of the efficacy of treatment for HIV- visceral leishmaniasis co-infection outside the Mediterranean area. HIV/VL coinfected patients have high parasite burden, a weak immune response, respond poorly to treatment and have a high relapse rate. Therefore they are the ideal candidates to harbor drug resistant parasites. All antileishmanial therapies are less effective in HIV-positive patients. There is a high mortality rate due to concurrent illness, complications, and drug toxicity. Pentavalent antimonials and amphotericin B are more toxic to HIV patients, who require close monitoring for pancreatitis, cardiotoxicity, and nephrotoxicity\(^\text{7}\). The best option for these patients are Liposomal Amphotericin B. Lipid formulations infused at a dose of 3-5 mg/kg daily or intermittently for 10 doses (days 1–5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg are recommended. Secondary prophylaxis to prevent relapses has been reported in several publications, but more evidence from clinical trials is needed to establish a beneficial effect\(^\text{7}\). Initiation of HAART dramatically decreases the incidence of VL coinfection. Therefore; HAART in combination with antileishmanials should be advocated strictly in these patients.

**PRESENT TREATMENT GUIDELINES**

Recent WHO recommendations on the control of leishmaniasis in Bangladesh, Bhutan, India and Nepal are as follows, ranked by preference and qualified by grade of evidence\(^\text{21}\):

1. **Liposomal amphotericin B**: 3-5 mg/kg over 3-5 days up to a total dose of 15 mg/kg by infusion (A) or 10 mg/kg as a single dose by infusion (A)

2. **Combinations (co-administered) (A)**
   - liposomal amphotericin B (5 mg/kg by infusion, single dose) plus miltefosine (7 days, as below)
   - liposomal amphotericin B (5 mg/kg by infusion, single dose) plus paromomycin (10 days, as below)
   - miltefosine plus paromomycin, both for 10 days, as below
   - amphotericin B deoxycholate: 0.75-1.0 mg/kg per day by infusion, daily or on alternate days for 15-20 doses (A)

3. **Miltefosine**: for children aged 2-11 years, 2.5 mg/kg per day; for people aged 12 years and < 25 kg body weight, 50 mg/day; 25-50 kg body weight, 100 mg/day; > 50 kg body weight, 150 mg/day; orally for 28 days(A) or

   **Paromomycin**: 15 mg (11 mg base) per kg body weight per day intramuscularly for 21 days (A)

4. **Pentavalent antimonials**: 20 mg Sb\(^\text{IV}\)/kg per day intramuscularly or intravenously for 30 days in areas where they remain effective: Bangladesh, Nepal and the Indian states of Jharkhand, West Bengal and Uttar Pradesh (A). Rescue treatment in case of non-response: conventional
amphotericin B deoxycholate infusions or liposomal amphotericin B at higher doses.

The recommendation for PKDL in Bangladesh, India, Nepal qualified by grade of evidence are

1. Amphotericin B deoxycholate: 1 mg/kg per day by infusion, up to 60-80 doses over 4 months (C)
2. Miltefosine orally for 12 weeks at dosage as above (A).

CONCLUSION
Inventory of antileishmanial drugs is very small, and emergence of drug resistance is further complicating the control of leishmaniasis. Short course chemotherapy or combination chemotherapy is rapidly emerging as the norm for treating VL. Directly observed therapy given free, in treatment centres manned by trained personnel, will go a long way in controlling the disease. Either single dose L-Amb treatment or multidrug regimens should be used for the treatment of VL in Indian subcontinent.

REFERENCES