INTRODUCTION
Leishmaniasis, a vector-borne neglected tropical disease, caused by an obligate intracellular protozoan. The only proven vector of human disease is sandfly. Visceral leishmaniasis (VL; also known as kala-azar), the severest form of leishmaniasis is caused by the Leishmania donovani complex: L. donovani, is the causative organism of VL in the Indian subcontinent and Africa; L. infantum (L. chagasi) which causes VL in the Mediterranean basin, Central and South America.

EPIDEMIOLOGY
More than 90% of global VL cases occur in just six countries: India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia. It is endemic in 54 districts of Bihar, Jharkhand, Uttar Pradesh and West Bengal. The state of Bihar accounts for most of the cases. With the implementation of The Kala-azar elimination program in India, there has been a dramatic reduction in new cases and deaths due to VL. In India as per report of 2014, more than 70% of endemic blocks have achieved elimination i.e. the incidence rate was below 1/10,000 population. As compared to 2011 the number of cases have reduced by 72% and the number of deaths by 86%. There was a decreasing trend also in the number of PKDL (post kala-azar deenal leishmaniasis) cases.

CLINICAL FEATURES
The incubation period is approximately to be 2–3 months but may be up to 1 year or more, and the onset of the disease is usually gradual. The common symptoms are fever with chills and rigor, malaise, weight loss, anorexia and discomfort in the left hypochondrium. The common clinical signs are splenomegaly which is usually palpable by 2 weeks and may become huge as the illness progresses, moderate hepatomegaly, and there is wasting and pallor of mucous membranes. Blackish discoloration of the skin of the face, hands, feet and abdomen (the vernacular name, kala-azar, means black fever or deadly fever). Anemia can be severe and may lead to congestive heart failure. Thrombocytopenia can lead to epistaxis, retinal hemorrhages, and gastrointestinal bleeding. Intercurrent infections are common. VL is usually fatal if left untreated.

In the Indian subcontinent 5–15% patients (highest in Bangladesh) with VL develop a chronic form of dermal leishmaniasis characterized by hypopigmented macules, papules and/or indurated nodules which is called PKDL. PKDL occur 6 months to 3 years after the cure of VL and spontaneous resolution is rare in India. Approximately 5–6% of cases of PKDL cases occur without the preceding history of Kalaazar.

Initially, HIV-VL coinfection was reported from the Mediterranean countries, but the number of cases is increasing in sub-Saharan Africa especially in Ethiopia, Brazil and Indian subcontinent. HIV infection increases the risk of developing VL by 100–2,320 times in areas of endemicity, reduces the likelihood of a therapeutic response, and greatly increases the probability of relapse. VL promotes the clinical progression of HIV.

DIAGNOSIS
Parasite Detection
The visualization of the amastigote form of the parasite by microscopic examination of aspirates from bone marrow or spleen is the gold standard for the diagnosis of VL. Although the specificity is high, the sensitivity of microscopy varies, being higher for spleen (93–99%) than for bone marrow (53–86%). However, splenic aspiration can be complicated by life threatening haemorrhage and bone marrow aspiration is painful and both procedures requires technical expertise. The national vector borne disease control program of India recommends parasite detection only in those with a past history of kala-azar or if antibody based rapid diagnostic tests are negative.

MOLECULAR DIAGNOSIS
The detection of parasite DNA by PCR in blood or bone marrow aspirates is substantially more sensitive than microscopic examination, although its use is currently restricted to referral hospitals and research centres.

Serological Tests
Serological tests is the preferred mode of diagnosis. The direct agglutination test (DAT) and the rK39-based immunochromatographic test (ICT) are two serological tests that have been specifically developed for field use. DAT needs multiple pipetting, has a long incubation time, cost of antigen is high and there is limited production facility of quality controlled antigen. Therefore immunochromatographic strip tests (ICTs) based on rK39 is preferred in the national program are it is easy to perform in the periphery, rapid, cheap and yields reproducible results. rK39 is a 39-amino acid repeat that is part of a kinesin-related protein in Leishmania chagasi and is conserved within the L. donovani complex. A meta-analysis that included 13 validation studies of the rK39 ICT showed sensitivity and specificity estimates of 93.9% (95% CI, 87.7–97.1) and 95.3% (95% CI, 88.8–98.1), respectively.
The major drawbacks of antibody based tests are: serum antibody levels remain detectable up to several years after cure, therefore, VL relapse cannot be diagnosed by antibody detection. Secondly, up to 32% healthy individuals living in endemic areas with no history of VL are positive for anti-leishmanial antibodies owing to asymptomatic infections. Thus antibody-based tests must always be used in combination with a standardized clinical case definition for visceral leishmaniasis.

A ‘suspect’ case: history of fever of more than 2 weeks and enlarged spleen and liver not responding to anti malaria in a patient from an endemic area. Pancytopenia and hypergammaglobulinemia resulting in reversal of albumin globulin ratio is common.

All patients with above symptoms should be screened with rK39 based Rapid Diagnostic Test (RDT) and if found positive should be treated with an effective drug.

In cases with past history of Kala-azar or in those with high suspicion of Kala-azar but with negative RDT test result, confirmation of Kala-azar can be done by examination of bone marrow/spleen aspirate for LD bodies.

In the national program a probable case of PKDL is a patient from a KA-endemic area with multiple hypopigmented macules, papules, plaques or nodules, who are RDT positive.

While a confirmed case of PKDL is a patient from a KA-endemic area with multiple hypopigmented macules, papules, plaques or nodules, who is parasite positive in slit-skin smear (SSS) or biopsy.

### ANTILEISHMANIAL DRUGS

#### Pentavalent Antimonials (SB’)
Sodium stibogluconate (100mg of SbV/ml) and meglumine antimoniate at the dose of 20 mg/kg body weight for 28-30 days has been the standard treatment for VL in most parts of the world. However, it is no longer used in India due to its ineffectiveness in Bihar and adjoining Nepal where the cure rate is <50% due to growing resistance. Another drawback of this drug is its toxicity which is more in patients with HIV.

#### Amphotericin B (AMB)
AmB is a polynene antibiotic was recommended for the treatment of antimony resistant VL in Bihar, India. It has excellent cure rates (~100%) at doses of 0.75-1.0 mg/kg for 15 days but therapy is prolonged and needs close monitoring due to its adverse effects. Infusion reactions are the commonest but, nephrotoxicity, hypokalemia, hypersensitivity reaction, bone marrow toxicity and myocarditis are some of its serious side effects.

Lipid formulations of AmB are rapidly concentrated into reticuloendothelial tissues, decreasing the amount of free drugs available and leading to less toxicity. Thus a large dose of the drug can be given over a short period. Liposomal amphotericin B (AmBisome; Gilead Sciences; L-AmB), is the only US Food and Drug Administration approved lipid formulation.

The cost of L-AmB was prohibitive however, a preferential pricing agreement with WHO (agreement between Gilead and WHO of 14 March 2007) reduced the price of L-AmB for endemic regions of developing countries to $18 per 50 mg vial. Encouraged by this preferential pricing and the low dose of L-AmB required to cure VL in India, a study to compare a single dose of 10 mg/kg of body weight L-AmB to the conventional amphotericin B deoxycholate administered in 15 infusions of 1 mg/kg, given every other day during a 29-day hospitalization was conducted. Cure rate at 6 months were excellent in both the groups. The preferential pricing, along with a single day of hospitalization, makes a single infusion of the liposomal preparation an excellent option and has been recommended as the preferred treatment for this region.

#### MILTEFOSINE
Miltefosine is an alkyl phospholipid (hexadecylphosphocholine) and the first oral antileishmanial agent. It is registered for use in India since 2002 for the treatment of VL. The recommended dose in children between 2-11 years is 2.5mg/kg for 28 days, for children 12 years and above 50mg for those <25kg and 50 mg twice daily for those >25 kg for 28 days. Cure rate is 94% in India. Although it had an oral advantage there are many drawback: long duration of therapy, adverse events like vomiting, diarrhea, elevation of liver enzymes and nephrotoxicity and teratogenicity due to which women of child-bearing potential have to observe contraception for the duration of treatment and for an additional three months. Its long half life also makes it vulnerable to the rapid development of drug resistance which is evident from a study done after a decade of its use in India which observed a decline in its efficacy and doubling of relapse rate.

#### PAROMOMYCIN (PM, AMINOSIDINE)
It is an aminoglycoside-aminocyclitol antibiotic approved by the Indian government in 2006 for the treatment of VL. It has excellent cure rate of 95% in the Indian subcontinent at the dose of 11 mg base/kg intramuscular injection daily for 21 days. The dose in other endemic region has not been established.

Pain at the injection site is the commonest adverse event (55%), reversible ototoxicity occurs in 2% of patients, 6% patients developed reversible rise in hepatic transaminases. Renal toxicity is rare. There is no data regarding its use in pregnancy. The main advantage of the drug is its low cost.

#### MULTIDRUG THERAPY
With the growing resistance to antileishmanials, multidrug therapy was thought to have certain advantage: i) increased activity through use of drugs with synergistic or additive activity acting at different sites ii) shorter duration of therapy iii) lower dose requirement of individual drugs thereby decreasing toxicity and cost, and iv) preventing the emergence of drug resistance.

In a phase III study combination of single injection of
5 mg/kg L AmB and 7-day 50 mg oral miltefosine or single injection of 5 mg/kg L AmB plus 10-day 11 mg/kg intramuscular paromomycin; or 10 days each of miltefosine and paromomycin showed excellent cure rates (>97% in all arms) in India. The combination of miltefosine and paromomycin has been adopted by the national program.

TREATMENT GUIDELINES

Within the Indian National Programme, assuming availability of drugs, appropriate training of health personnel, infrastructure and indication, the following drugs are used in order of preference at all levels:

- Single Dose 10mg/kgbw Liposomal Amphotericin B (LAMB)
- Combination regimens (e.g. Miltefosine & Paromomycin)
- Amphotericin B emulsion
- Miltefosine
- Amphotericin B deoxycholate in multiple doses

For PKDL, miltefosine for 12 weeks or liposomal amphotericin B: 5mg/kg per day by infusion two times per week for 3 weeks for a total dose of 30mg/kg or Amphotericin B 60 -- 80 doses over 4 months or are the recommended regimens.

Liposomal AmB is the drug of choice for HIV-VL co-infection. A dose of 3 -- 5 mg/kg/day or intermittently for 10 doses (days 1 -- 5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg is recommended but relapse is common. Antiretroviral therapy should be initiated and secondary prophylaxis should be given till the CD4 counts are >200/µL to prevent relapse.

VL ELIMINATION PROGRAMME

The National Health Policy (2002) set the goal of Kala-azar elimination in India by the year 2010 and later revised in 12th Five Year Plan document to 2015. The Kala-azar elimination programme has the objective of reducing the annual incidence of Kala-azar to less than 1 case per 10,000 population at block PHC level. In 2014, the Penta-lateral MoU signed between Bangladesh, Nepal, Bhutan, and Thailand which also included India as a signatory, the target date for elimination was revised to 2017 or earlier by WHO South East Asia Region at Dhaka.

The rationale for VL elimination in the Indian subcontinent are as follows: the disease in this area is anthroponotic, with humans being the only reservoir and Phlebotomous argentipes sandflies the only known vector; new and more effective drugs and a rapid diagnostic test, the rk39 immunochromatographic test, are available that can be used in the field; there is strong political commitment and inter-country collaboration; and the disease is endemic in only a limited number of districts.

The national strategy for elimination of Kala-azar is a multipronged approach which is in line with WHO Regional Strategic Framework for elimination of Kala-azar from the South-East Asia Region (2011-2015) and includes:

I. Early diagnosis & complete case management
II. Integrated Vector Management and Vector Surveillance
III. Supervision, monitoring, surveillance and evaluation
IV. Strengthening capacity of human resource in health
V. Advocacy, communication and social mobilization for behavioral impact and inter-sectoral convergence
VI. Programme management.

REFERENCES