Chemotherapeutics of Visceral Leishmaniasis: present and future developments

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SUMMARY

Treatment of Visceral Leishmaniasis (VL), a neglected tropical disease, is very challenging with few treatment options. Long duration of treatment and drug toxicity further limit the target of achieving VL elimination. Chemotherapy remains the treatment of choice. Single dose of liposomal amphotericin B (LAmB) and multidrug therapy (LAmB + miltefosine, LAmB + paromomycin (PM), or miltefosine + PM) are recommended treatment regimen for treatment of VL in Indian sub-continent. Combination therapy of pentavalent antimonials (Sb^v) and PM in East Africa and LAmB in the Mediterranean region/South America remains the treatment of choice. Various drugs having anti-leishmania properties are in preclinical phase and need further development. An effective treatment and secondary prophylaxis of HIV-VL co-infection should be developed to decrease treatment failure and drug resistance.

Keywords

Visceral leishmaniasis; Amphoterecin B; Miltefosine; Paromomycin; Kala-Azar

INTRODUCTION

Visceral leishmaniasis (VL) is one among the various neglected tropical diseases caused by an obligate intracellular protozoan *Leishmania donovani* and transmitted in Indian subcontinent by bite of *Phlebotomus argentipes* (Sand fly) (Singh *et al.*, 2014). Around 0.2 – 0.4 million cases are reported globally. Among these more than 90% of cases are confined to six countries: India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia (Alvar *et al.*, 2012). A joint memorandum was signed in 2005 by governments of India, Nepal and Bangladesh to eliminate VL with the aim to reduce its incidence by 2015 to less than 1 per 10,000 people at sub-district level. However, this target has been recently extended to 2017 (Singh *et al.*, 2016). Another collaborative disease eradication programme, the London

Declaration on Neglected Tropical Diseases was launched on 30 January 2012 in London. It was inspired by the World Health Organization 2020 roadmap to eradicate or prevent transmission for neglected tropical diseases (London Declaration[*]). The emergence of co-infection with HIV in VL is one of the major challenges which makes treatment more complex and increase the chances of drug resistance. Initially, HIV-VL cases were seen from south-western Europe, but now cases are on increase in Ethiopia, South Asia and Brazil. Co-infection has been reported from more than 35 countries (Alvar *et al.*, 2008; Alvar *et al.*, 1997; Desjeux & Alvar, 2003). The prevalence of human immunodeficiency virus (HIV) in Bihar, India (which, till recently, accounted for 40% of world's burden of VL) is considered low (0.2%–0.3%). Around 2.4% of all VL patients of age 14 years were unknowingly found to be co-infected with HIV in an Indian study (Burza *et al.*, 2014a).

VL clinically manifests as prolonged fever, hepatomegaly, splenomegaly, pancytopenia, progressive anemia and weight loss and is fatal without treatment. About 50% of patients in Sudan and 1 – 3% in India after recovery of VL develop a cutaneous manifestation in form indurated nodules or depigmented macules known as post kala-azar dermal leishmaniasis (PKDL). These cases are difficult to treat and also serve as reservoir of *leishmania* (Mukhopadhyay et al., 2014).

With no effective vaccine available, the only option for treatment of VL remains chemotherapy. With limited inventory of drugs and emerging drug resistance the treatment of VL remains challenging.

Chemotherapy of VL

Pentavalent antimonials (Sb^V)—Sodium stibogluconate (SSG) and meglumine antimoniate (MA) are two forms of available Sb^V. It is given in doses of 20 mg/kg subcutaneously for 28 – 30 days. With emerging resistance to this drug in Bihar and adjoining areas of Nepal alternative treatment strategy has been adopted for these areas (Sundar *et al.*, 2000) (Rijal *et al.*, 2003). Its efficacy has been also found to be low in HIV-VL co-infected patients when compared to immunocompetent VL patients (Ritmeijer *et al.*, 2006a). However, in east Africa SSG monotherapy is still effective with 6 month cure rate of 93.9% (Musa *et al.*, 2012). It was recommended by WHO as first line drug for treatment of VL in east Africa along with combination of SSG-Paromomycin (PM) as the first-line treatment of VL patients in Eastern Africa (WHO report, 2010).

Its use is further limited by associated life threatening toxicities like cardiac arrhythmias, prolonged QT interval (QTc), ventricular premature beats, ventricular tachycardia, ventricular fibrillation and torsades de pointes. Other adverse effects includes arthralgia, myalgia, increased pancreatic and liver enzymes (Sundar & Chakravarty, 2015b).

Amphotericin B and liposomal Amphotericin B—In the Indian subcontinent for treatment of VL, Amphotericin B deoxycholate is recommended at doses of 0.75 – 1.0 mg/kg given for 15 – 20 intravenous infusions. For PKDL, AmB is recommended at a dose

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[*]**London Declaration** on Neglected Tropical Diseases (http://unitingtocombatntds.org/sites/default/files/resource_file/london_declaration_on_ntds.pdf; accessed 16 March 2015).

of 1 mg/kg/day up to 60 – 80 intravenous infusions for 4 months (Mishra *et al.*, 1992; Thakur, 1997; Thakur *et al.*, 1999). Its toxicity profile includes infusion reactions (in most patients), nephrotoxicity, hypokalemia, myocarditis and occasional death which mandate close monitoring. This along with prolonged hospital stay, escalates the cost of therapy. Lipid formulation of AmB has been developed to minimize side effects and for delivery of drug at large daily doses. Liposomal amphotericin B (AmBisome; Gilead Sciences; LAmB), amphotericin B lipid complex (ABLC; Abelcet, Enzon pharmaceuticals) and amphotericin B colloidal dispersion (ABCD); Amphotec, InterMune Corp.) and several generic formulations are available with LAmB being the only drug which has US FDA approval. Various trials on LAmB has been shown in table 1 Various trials on LAmB has been shown in table 1.

There is considerable geographical variation in the total LAmB dose (Sundar & Chakravarty, 2015b). In the Mediterranean region and South America, 18–21 mg/kg, administered in various regimens, has been recommended (Sundar & Chakravarty, 2015b), (Davidson *et al.*, 1996; Freire *et al.*, 1997; Gradoni *et al.*, 2004; Syriopoulou *et al.*, 2003). Whereas, 10 mg/kg single dose has been shown to cure > 95% VL cases in India (Sundar *et al.*, 2010).. Another study showed that when 20 mg/kg of LAmB was given over 4 – 10 days, relapse rate was 2.4% (Burza *et al.*, 2014b). In Bangladesh, 10 mg/kg single dose of LAmB cured 97% patients (Mondal *et al.*). In another study, LAmB in three doses of 5 mg/kg each (total 15 mg/kg) had cure rate of >95% (Lucero *et al.*, 2015). In Sudan, LAmB is required a much higher dose, when given at 30 mg/kg over 10 days in primary VL cases, showed initial cure rate at 6 months of 92% with treatment failures, deaths and relapses of 1%, 5% and 7% respectively. In relapsed VL cases the initial cure was 94%, treatment failed in 4%, 1% died and 10% relapsed. Six percent were slow responders requiring 50 mg/kg of LAmB (Salih *et al.*, 2014). In Europe, total dose of 18–21 mg/kg is considered adequate (Sundar and Chakravarty, 2013).

However, high cost remains the limiting factor for widespread LAmB use in most of the endemic regions. This was addressed by an agreement for preferential pricing with WHO (agreement between Gilead and WHO for donation of LAmB till 2020) which reduced the price of LAmB to $18 per 50 mg vial for endemic areas of developing countries (Moon *et al.*). Following this, a study was conducted in India in which LAmB was used in a single dose of 10 mg/kg and compared to the conventional AmB administered in 15 infusions of 1 mg/kg, given every other day during a 29 days of treatment. At 6 months, cure rates were comparable in the two groups: 95.7% (95% CI: 93.4–97.9) in the liposomal-therapy group and 96.3% (95% CI: 92.6–99.9) in the conventional-therapy group (Sundar *et al.*, 2010). The decreased treatment cost and hospital stay made liposomal preparation as single infusion an excellent option for treatment of VL in Indian subcontinent. It has been suggested by the WHO Regional Technical Advisory Group (WHO report, 2009) and the WHO Advisory Panel for Leishmaniasis Control (WHO, 2010) to use single dose LAmB as the first line drug for the VL elimination program in the Indian subcontinent. The 10 mg/kg single dose regimen is being used in by the Control Programmes of India, Nepal and Bangladesh.

However, in East Africa low efficacy of LAmB in a randomised controlled trial lead to its midway termination when given as single dose of 7.5, 10 mg/kg body weight, or multiple doses on days 1–5, 14, and 21. Definitive cure at 6 months was 85%, 40% and 58% in

patients treated with multiple doses, and single doses of 7·5 or 10 mg/kg, respectively (Khalil *et al.*, 2014)

An indigenous liposomal amphotericin B (Fungisome, developed by an Indian company Lifecare Innovations, Gurgaon, Haryana, India) was tested in a phase 2 study in two cohorts, cohort 1: 10 mg/kg, cohort 2: 15 mg/kg). Initial cure rate of 100% at day 30 and a definitive cure rate of 93.3% at the 6-month follow-up was achieved in both the cohorts (Sundar *et al.*, 2015).

For HIV-VL co-infection, LAmB is given at a doses of 4 mg/kg for 10 doses (days 1–5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg (WHO report, 2010).. Various trails using LAmB for HIV-VL is shown in table 1.

In a study in Bihar, when intravenous LAmB (20–25 mg/kg) was administered to 159 VL/HIV co-infected patients (both primary infections and relapses) in four or five doses of 5 mg/kg over 4–10 days, the estimated relapse risk at first year, second year and fourth year was 16.1%, 20.4% and 25.9% respectively (Burza *et al.*, 2014a).

In a study in India, excellent initial response was seen with LAmB (a total dose of 20–25 mg/kg in 4–15 days) combined with antiretroviral therapy; however, the probabilities of VL relapse after treatment were 0%, 8.1%, and 26.5% at 6 month, 1 and 2 years respectively (Mahajan *et al.*, 2015). In a retrospective study in Bihar, India, combination of LAmB and miltefosine was tested in 102 HIV-VL co-infected patients. LAmB was given at doses of 30 mg/kg divided in 6 infusions on alternate days, along with oral miltefosine for 14 days. At 6, 12, and 18 months follow-up, the cumulative incidence of all-cause mortality was 11.7%, 14.5%, and 16.6% respectively. Relapse rate were 2.5%, 6.0%, 13.9%, at 6, 12, and 18 month respectively (Mahajan *et al.* 2015). Secondary prophylaxis is also important and found to be effective in HIV-VL co-infected patients as with other opportunistic infections. It has been shown that Amphotericin B lipid complex (3–5 mg/kg per dose once) every 3 weeks for 12 months has 22% relapse rate as comparison to 50% in patients devoid of secondary prophylaxis at one year (Lopez-Velez *et al.*, 2004). LAmB at dose of 5 mg/kg administered every third week has been also studied for use as secondary prophylaxis with relapse free probability of 89.7%, 79.1%, 55.9% and 55.9% at 6, 12 month, 24 and 36 months respectively (Molina *et al.*, 2007). In a retrospective study from eastern India (2005–2015), protective efficacy of monthly amphotericin B (AmB) for secondary prophylaxis in patients with HIV–VL coinfection was done. Secondary prophylaxis was provided in 27 HIV-VL with monthly 1 mg/kg AmB (15 liposomal, 12 deoxycholate). At 6 month, none in secondary prophylaxis group relapsed or died. Secondary prophylaxis remained the sole significant predictor against death in multivariate Cox regression. HIV–VL patients had higher 6-month relapse rate, less relapse-free 12-month survival, and higher mortality than VL mono-infection. (Goswami RP *et al.*).

Miltefosine—Miltefosine, an alkylphospholipid compound, was the first effective oral anti-leishmanial drug in VL. Following a phase III trial, miltefosine was registered in India as first oral antileishmanial drug in 2002. Cure rate of 94% was seen with 50–100 mg/day of miltefosine given for 28 days (Sundar *et al.*, 2002a). Another phase 4 study showed cure rate

of 95% (Bhattacharya *et al.*, 2007). Because of its high efficacy and ease of administration, it was adopted by VL elimination programme in India, Nepal and Bangladesh (Sundar *et al.*, 2008a). Unfortunately, after a decade of its use the efficacy decreased and there was doubling of relapse rate (Burza *et al.*, 2013; Sundar *et al.*, 2012). In Nepal relapse rates of 10.8% and 20% was seen at 6 and 12 months, respectively (Rijal *et al.*, 2013). Cure rate of only 85% and 75.8% was found in studies in Bangladesh and Ethiopia, respectively (Rahman *et al.*, 2011; Ritmeijer *et al.*, 2006b). Similarly for PKDL, miltefosine at doses of 50 mg thrice daily for 60 days or twice daily for 90 days was found to be effective (Ramesh *et al.*, 2011). Another study showed that miltefosine given as 100 mg/day for 12 weeks in PKDL produced high cure rates (Sundar *et al.*, 2013). It is recommended for the treatment of PKDL in the Indian subcontinent at the dose of 50–100 mg for 12 weeks (WHO report, 2010).

Miltefosine is associated with gastrointestinal adverse events chiefly vomiting and diarrhea.. Occasionally hepatotoxicity and nephrotoxicity might occur. It has a long half life (~ one week) which renders it vulnerable for development of its resistance in the parasites. It also has teratogenic potential, so women of child-bearing age are advised contraception for the duration of treatment and for three additional months after the end of therapy. (Sundar & Chakravarty, 2015b).

Paromomycin (aminosidine)—Paromomycin (PM) is an aminoglycoside antibiotic which act by interference with protein synthesis in the ribosome of the target organism and inhibit the respiration (Chawla *et al.*, 2011). In a phase II study of VL patients, PM at dose of 16 mg/kg/day for 21 days led to cure in 93% (Jha *et al.*, 1998). A Phase III trial of PM at a dose of 15 mg/kg (11 mg base) for 21 days showed 95% cure rate (Sundar *et al.*, 2007). PM was approved by the Indian government for VL treatment in Indian subcontinent in August 2006. However, PM was found to be ineffective in curing PKDL with efficacy of only 37.5% (Sundar *et al.*, 2014).

In Bangladesh, in an open label Phase IIIb multicentre study where PM showed cure rate of 94.2% at 6 months when administered at 11 mg/kg (base) intramuscularly once daily for 21 consecutive days (Jamil *et al.*, 2015). In a phase II study in Sudan, Ethiopia and Kenya, its efficacy was low compared to SSG alone and combination of SSG and PM (Hailu *et al.*, 2010). In East Africa, PM efficacy was significantly lower than SSG (84.3% vs 94.1%) in a multi-center randomized-controlled trial (Musa *et al.*, 2012). In Sudan, in a dose-finding phase II study, PM showed efficacy of 80% (95% CI: 56.3 – 94.3%) and 81% (95% CI: 58.1 – 94.6%) when used for a longer duration (15 mg/kg/day for 28 days) or at a higher dose of 20 mg/kg/day for 21 days, respectively (Musa *et al.*, 2010). Pain at the injection site, reversible ototoxicity, and hepatic transaminitis are common adverse effects. Although low cost of PM is an advantage, its parenteral route of administration limits its use in a control program. Monotherapy also pose a danger for development of resistance.

Pentamidine—Pentamidine was used as an alternative treatment for refractory VL in India. However, side effects such as insulin-dependent diabetes mellitus and declining efficacy precludes its further usage (Jha *et al.*, 1991). Injection site pain, indurations and abscess, nausea, vomiting, myalgia, headache, dizziness, hypotension, syncope, transient

hyperglycemia and hypoglycaemia are other adverse effects of this drug (Sundar & Chakravarty, 2015b). It is currently recommended for secondary prophylaxis in HIV-VL co-infection as in a study from Ethiopia revealed relapse-free survival probability of 79% and 71% at 6 months and at 12 months respectively (Diro *et al.*, 2015)

Multidrug therapy—Multidrug therapy advocated for other diseases like malaria, tuberculosis, leprosy, etc. has also been explored for VL treatment. The rationale behind it is to use drugs with synergistic or additive activity making the duration of therapy short with decrease in drug doses which lowers the occurrence of adverse effect and treatment cost (Sundar & Chakravarty, 2015b). Further with monotherapy, there is always a higher chance of development of drug resistance.

In Sudan a study showed initial cure rate of 97% with combination therapy of PM at a dose of 15 mg/kg (equivalent to 11 mg/kg of PM base) plus Sb^v at a dose of 20 mg/kg for 17 days compared to cure rate of 92.4% with Sb^v monotherapy given for 30 days (Melaku *et al.*, 2007). It became the preferred regime in the region following another large multicenter trial which showed comparable efficacy of combination therapy for 17 days with SSG monotherapy (Musa *et al.*, 2012). A prospective pharmacovigilance study sponsored by the Ministries of Health, Médecins Sans Frontières (MSF) and Drugs for Neglected Diseases initiative (DNDi) was recently conducted at 12 centres in cohort from Sudan, Kenya, Uganda and Ethiopia for PM plus Sb^v combination therapy in VL. The initial cure rate was 95.1% with no geographical variation. Thirty four percent (34%) and 1.96% of patients had at least one adverse event (AE) and serious adverse event (SAE) during treatment respectively. Mortality occurred in 1.0% of patients. HIV/VL co-infected patients had initial cure rates of 56 % which was significantly lower than that in VL patients without HIV. (Kimutai *et al.*, 2017)

Combination of miltefosine and LAmB was recently evaluated in Sudan and Kenya where a phase II open-label, non-comparative randomized trial was conducted. Three regimens [10 mg/kg single dose LAmB plus 10 days of SSG (20 mg/kg/day), 10 mg/kg single dose LAmB plus 10 days of miltefosine (2.5 mg/kg/day) and miltefosine alone (2.5 mg/kg/day for 28 days)] were evaluated for efficacy and safety. Although safe, the definitive cure was < 90% in all treatment arms so none regimen was evaluated for phase 3 trials (Wasunna M *et al.*, 2016).

In a multidrug randomized, non-comparative, group-sequential, triangular design study 181 patients were randomly assigned to 5 mg/kg of LAmB alone, 5 mg/kg of LAmB followed by MIL for 10 days or 14 days or 3.75 mg/kg of LAmB followed by miltefosine for 14 days. When efficacy of all regimens was apparant, 5 mg/kg of LAmB followed by miltefosine for 7 days were given 45 additional patients. All groups had similar cure rates (> 95%) (Sundar *et al.*, 2008b).

In a Phase III study in the India, three multidrug regimens were tested (Single injection of 5 mg/kg L AmB and 7-day oral miltefosine or 10-day 11 mg/kg intramuscular PM; or 10 days each of miltefosine and PM). Cure rate of > 97% was found in all the three drug regimens

used (Sundar *et al.*, 2011a). Cure rate of 91.9 % with single dose of LAmB 5 mg/kg with miltefosine 2.5 mg/kg/day for 14 days was shown in another study (Sundar *et al.*, 2011b).

Combination therapy is also attractive option for the treatment of PKDL. (Ramesh V, *et al.*, 2014). Combination therapy is excellent and effective alternative strategy to decrease the cost of therapy by decreasing duration of treatment, side effect associated with drugs and hospital stay. Moreover combination therapy delays drug resistance, thus prolongs use of the drugs.

Newer drugs, Immunotherapy and Vaccine development—The various new compounds at various stages of development have been included in Drugs for Neglected Disease Initiative (DNDi) portfolio as shown in table 2. Each of them is in preclinical stages.

Alternative approach is to use immunotherapy and/or immunochemotherapy against VL. IFN-γ, a cytokine capable has been found to kill intracellular *Leishmania* by activating macrophages (Murray & Cartelli, 1983). Accelerated clearance of parasite is seen on addition of IFN-γ. Treatment of VL with IFN-γ plus Sb^V showed a cure rate of >80% cure rate (Badaro, 1988; Badaro *et al.*, 1990; Sundar *et al.*, 1994). and enhanced the clinical efficacy of conventional Sb^V therapy (Sundar & Murray, 1995). Similarly results were seen in a study in Kenya where Sb^V or Sb^V plus IFN-γ for 30 days was given in two groups for VL treatment with combination therapy showing quick parasite clearance (Squires *et al.*, 1993). In India in a large study, however, low cure rates of 36%, 49% and 42% were obtained at 6 months on treatment with 30 days of Sb^V alone, or 30 days of Sb^V plus IFN-γ at dose of 10^7 U/mg/day, or 15 days of Sb^V plus IFN-γ respectively with maximum efficacy in immunotherapy group (Sundar *et al.*, 1997). Low cure rates in this study led to stoppage of the development of IFN-γ as adjunct to anti-leishmania drugs.

No vaccine is recommended for treatment of VL till now. To be an effective vaccine apart from eliciting prolong immunity it should be protective broadly against VL and CL. Infectious Disease Research Institute (IDRI) has developed vaccines such as Leish-F1, F2 and F3 based on selected *Leishmania* antigen epitopes, and has found to be immunogenic and safe in clinical trials with Leish-F2 completed phase 2 study. The Sabin Vaccine Institute are investigating on the immunogenicity by combination of sand fly salivary gland antigen with the recombinant Leishmania antigens (Chakravarty *et al.*, 2011) (IDRI Vaccine[**]). Recently, a first-in-human dose escalation Phase I trial to assess the safety, tolerability and immunogenicity of a prime-only adenoviral vaccine (ChAd63-KH) was conducted in 20 healthy volunteers for human VL and PKDL. ChAd63-KH was found to be safe and immunogenic and need further development to emerge as a novel third generation vaccine for VL and PKDL (Osman *et al.*, 2017). Various recombinant antigens have been studied to have protective role against *Leishmania* infection however limited to experimental level with minimal experience in preclinical human studies.(Carrillo *et al.*, 2008; Chakravarty *et al.*, 2011; Connell *et al.*, 1993; Gurunathan *et al.*, 1997; Kumar *et al.*, 2010; Noazin *et al.*, 2009; Rafati *et al.*, 2006; Singh *et al.*, 2012; Stober *et al.*, 2005; Sundar & Chakravarty, 2015a)

[**]LEISH-F3 + GLA-SE and the LEISH-F3 + MPL-SE Vaccine. https://clinicaltrials.gov/ct2/show/NCT01751048.

CONCLUSION

With meagre treatment options in chemotherapy and emerging risk of resistance to available drugs, discovery of new drugs with anti-leishmania activity is the need of the hour. Combination therapy of Sb^v with PM and LAmB are recommended in Africa and Mediterranean region respectively. Newer approaches with other drug combination need to be investigated in these different geographical areas. PKDL patients serve as reservoir of infection. Shorter and effective treatment is warranted for success of VL Elimination programme. Drugs for Neglected Diseases Initiative (DNDi) has taken the initiative of finding new novel agents with anti-leishmania agents. Also, feasibility of use of LAmB at district and public health centre in South Asia has also been explored by DNDi. The burden of HIV VL co-infection in increasing and LAmB found effective in Mediterranean region has limited efficacy in Ethiopia having high HIV-VL co-infection burden. Thus newer treatment regimes for this region need to be explored.

Acknowledgments

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Table 1

L-AmB trials in VL and HIV-VL co-infection

Serial no.	Type of study	Author	Dose used	Overall cure rate percentage	Disease
1	Randomized open study	Thakur *et al.*, 1996	2 mg/kg/day on day 1, 2, 3, 4, 5, 6 and 10 vs. days 1, 2, 3, 4 and 10	100%	VL
2	Randomised	Thakur, 2001	15 mg/kg single dose (i.v)	100%	VL
3	Open label, dose finding	Sundar *et al.*, 2001	5 mg/kg (single dose) vs. 1 mg/kg for 5 days (iv)	91% vs 93%	VL
4	Randomized, dose ranging, multicentre	Sundar *et al.*, 2002b	0.75 mg/kg/days for 5 days (i.v) vs 1.5 mg/kg/days for 5 days (i.v) vs 3 mg/kg/days for 5 days (i.v)	89% vs 93% vs 96%	VL
5	Open label non comparative study	Sundar *et al.*, 2003	5.0 mg/kg/days for 5 days (i.v)	90%	VL
6	Observational cohort	Sinha *et al.*, 2010	5.0 mg/kg/day (i.v) on 0, 1, 4, and 9	98.8%	VL
7	Retrospective, multicentre	Di Masi *et al.*, 2014	Variable (40.8 ± 6.7 mg/kg for 12.0 ± 3.4 days)	72%	HIV-VL
8	Retrospective, non-comparative, multicentre	Sinha *et al.*, 2011	20 – 25 mg/kg on day 1, 2, 5, 10, 15 (5th dose for relapsed cases)	78.2%	HIV-VL
9	Retrospective, non-comparative, multicentre	Ritmeijer *et al.*, 2011	30 mg/kg in 6 doses of 5 mg/kg alternate day	66.1%	HIV-VL
10	Prospective non-comparative, multicentre	Russo *et al.*, 1996	4 mg/kg for 10 doses (days 1 – 5, 10, 17, 24, 31 and 39)	80%	HIV-VL
11	Prospective, non-comparative, single centre	Molina *et al.*, 2007	4 mg/kg/day for 5 days followed by one per week for 5 weeks	50%	HIV-VL

Table 2

Newer compounds in pipeline for Visceral leishmaniasis in various stages of development:

Serial no.	Drugs/compound	Stage of Development	Reference
1	Nitroimidazooxazine (DNDi-0690)	Translation phase	DNDi (2017) leishmaniasis portfolio
2	Oxaboroles (DNDi-5421 and DNDi-5610)	Lead optimisation	
3	Oxaboroles (DNDi-6148)	Translation phase	
4	CGH VL Series 1	Lead optimisation	
5.	Aminopyrazoles	Lead optimisation	