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MASTERS' THESIS

Title of Study: **A Systematic Review of Clinical Trials of Visceral Leishmaniasis in the Indian Subcontinent (India, Bangladesh and Nepal)**

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DECLARATION

This thesis « *A Systematic Review of Clinical Trials of Visceral Leishmaniasis in the Indian Subcontinent (India, Bangladesh and Nepal)*" is the result of independent investigation of the existing literature. Where my work is indebted to the work of others, I have made appropriate acknowledgements.

I declare that this study has not already been accepted for any other degree nor is it currently being submitted in candidature for any other degree.

Messiah Mathew Cheeran

16th July 2008

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TABLE OF CONTENTS

A Systematic Review of Clinical Trials of Visceral Leishmaniasis in the Indian Subcontinent (India, Bangladesh and Nepal)

I Abstract

Background. Three countries of the Indian subcontinent (India, Bangladesh and Nepal) share nearly 60% of the global burden of 500,000 cases of Visceral Leishmaniasis (VL, Kala Azar) cases occurring every year. The three countries signed with the World Health Organization (WHO) a common plan to eliminate VL as a public health problem from this region by 2015.

Objectives. The main objective of this thesis was to systematically review the clinical trials of the treatment of VL done in India, Bangladesh and Nepal using Amphotericin B deoxycholate, liposomal AmphotericinB (AmBisome®), Paromomycin, Miltefosine and Sodium Stibogluconate, either alone or in combination. This was done in order to contribute to the evidence base for the treatment options to be used in the course of the VL elimination campaign.

Search strategy. We conducted an internet search, which included databases of PubMed and Clinical trial registries of WHO and NIH (www.clinicaltrials.gov). We also contacted clinical investigators to identify unpublished studies and obtain additional information.

Selection criteria. Comparative, non comparative and dose finding trials involving Amphotericin B, AmBisome®, Paromomycin, Miltefosine and Sodium Stibogluconate were selected. Trials involving Pentamidine, Amphotericin B Colloidal Dispersion (ABCD), Amphotericin B lipid complex, Liposomal Amphotericin B other than AmBisome® were not included in the review.

Data collection and analysis. We extracted data and assessed their methodological quality. 6-month success rates were calculated with 95% confidence intervals (95%CI) out of the enrolled patients (Intent to Treat, ITT) and evaluable patients (Per Protocol, PP) populations. Relative Risks (RR, fixed effect) with 95%CI for failure were calculated using RevMan for comparative studies.

Main results

Twenty-three (23) clinical trials enrolling 5730 patients met the inclusion criteria and were reviewed. AmBisome® is safer than plain Amphotericin B and is very effective. Miltefosine is as effective as Amphotericin B and is the only drug that has been tested in a Phase 4 study; in these conditions, effectiveness was lower than efficacy. Paromomycin is effective both alone and combined with Sodium Stibogluconate and was shown to be not different from Amphotericin B using a non-inferiority trial design. Sodium Stibogluconate is clearly lost to parasite resistance in Bihar but recent data from other areas are not available.

Conclusions

The findings of this systematic review indicate that treatment policies should consider the use of AmBisome®, Miltefosine and Paromomycin.

The body of available evidence was from Bihar, India. Very little evidence exists in Bangladesh and Nepal on Sodium Stibogluconate, none on other drugs.

There is a clear need for more studies in these countries to test the efficacy, safety and effectiveness of the various treatment options and for monitoring of effects while treatments are deployed in the context of the campaign.

The theoretical basis and evidence from both VL and other diseases support testing combination therapies to improve efficacy and adherence, reduce

treatment duration and costs and prolong the drugs' useful lifespan by be protecting them from parasite resistance, particularly in areas of anthroponotic transmission like the Indian Subcontinent where resistant parasites could spread quickly.

II Background

Visceral Leishmaniasis (VL, Kala Azar or "Black fever") is one of the most neglected tropical diseases. While most of the global burden of disease is among the poorest and marginalized populations in the Indian Subcontinent, East Africa and Brazil, the disease is also seen in temperate areas around the Mediterranean basin and Asia. VL is a fatal systemic disease if untreated, caused by various species of the protozoan parasite *Leishmania spp* (essentially *Leishmania donovani donovani* in Asia and Sub Saharan Africa, *L.infantum* around the Mediterranean sea and *L.chagasi* in South America) that multiply in mammalian macrophages. The parasite is transmitted by the bite of female haematophagous sandflies (*Phlebotomus* and *spp.*), which have previously taken a blood meal from an infected reservoir.

In some epidemiological settings where the disease in zoonotic and humans are accidentally infected, a non human mammalian reservoir (domestic and wild animals) act as carriers of the parasite without necessarily being diseased. In other cases transmission is strictly anthroponotic. This is an important distinction as it determines control measures. Where infection is anthroponotic, control this is mainly based on early diagnosis, treatment and prevention by reducing exposure to sandfly bites (normally, with insecticide-impregnated bed nets). The control of zoonotic leishmaniasis is focused on the animal reservoir by reducing the reservoir capacity through a number of approaches (sacrifice of infected animals, treatment, vaccination, etc.), or the contacts with the vector (insecticide spraying, bed nets, repellents, etc.). The problem of drug resistance is also much more in areas of anthroponotic disease, taking into account the fact that Leishmania parasites multiply in a clonal manner. This means that once resistance is acquired by a

parasite, the resistant population will expand within the same individual patient and be transmitted directly between humans and spreads rapidly. Instead, where transmission is zoonotic the drug-resistant parasites will be diluted throughout the mammalian reservoir. It is interesting to note here that while no selection pressure occur in wild animals, domestic animals may be subjected to drug pressure as humans do -as is the case for dogs in Southern European countries.

VL is responsible for approximately 59,000 deaths per annum and approximately 2.4 million disability adjusted life years (DALYs) lost (1,3). VL is a major public health problem in India, Bangladesh, Nepal (Indian Subcontinent), Ethiopia, Kenya, Sudan (East Africa) and Brazil (South America).(2) The estimated world's annual incidence is 500,000 cases, mainly affecting the poorest and marginalized population living in rural areas in India, Bangladesh, Nepal, Sudan and Brazil where over 90% of the total cases of VL occur.(2,5) Of these, ~300,000 (60%) occur in India, Bangladesh and Nepal. (2, 3). India is the most affected country in the world (3); the majority of the cases are in the state of Bihar, which is considered the poorest and least developed state in India (4) and rest of the cases coming from the states of West Bengal, Uttar Pradesh and northern districts of Jharkhand. (It should be noted that Jharkhand was part of Bihar till November 2000, when it became a new state). Approximately 150 million people are at risk of VL in the Indian Subcontinent living in some 94 districts of the neighboring parts of India, Bangladesh and Nepal. (2)

It is rather difficult to obtain exact morbidity and mortality data for VL in most places as the official numbers given from endemic regions usually only include passive case detection from patients who obtain treatment in government facilities. The disease is frequently undetected, undiagnosed and underreported. This is mostly true when access to treatment and medicines are very poor. Most of patients who are non accounted for in official statistics seek treatment in the private sector and are not

followed up for compliance to, efficacy and safety of the prescribed treatment (8). VL occurs mainly in the most disadvantaged populations.(3,7) The actual incidence of VL is considered to be at least 8 to 10 times higher than the reported numbers in India, Nepal and Bangladesh (3,6). The VL endemic regions in India and Bangladesh are given in Figures 10 and 11 (48,49)

In the Indian Subcontinent VL is anthroponotic. While this feature, along with the recent development of new diagnostics and therapeutics creates an opportunity to realistically control and eliminate the disease, it is also conducive to the spread of resistance, as when resistant strains occur, they are re-circulated rapidly (2)

The theoretical basis for VL elimination from the Indian Subcontinent is: (i) human beings are the only reservoir; (ii) there is only one vector species, which can be controlled; and (iii) the geographical distribution is limited and quite well defined. The three endemic countries have manpower and existing infrastructure to implement the elimination program. In India, funds have been allocated for VL elimination. Miltefosine, the only oral drug for VL is available and so is rK39 - rapid diagnostic test for VL. These are also supplemented by the high level of political commitment at the top echelons of India, Nepal and Bangladesh. The Ministers of Health of Bangladesh, India and Nepal signed a Memorandum of Understanding (MOU) in Geneva in 2005 for joint efforts to eliminate VL from Indian Subcontinent by the year 2015. (2, 9) The target is to reduce the annual incidence of VL in the endemic regions to less than one per 10,000 population, at the district level or sub district level by 2015 (9)

The VL elimination prospects will also result in reducing poverty and promoting equity leading to the socio economic development of the targeted region (2). Thus, VL elimination also has relevance to the Millennium Development Goals. Prioritized intensification of control of neglected tropical diseases will contribute directly to the reduction of the communicable disease burden (Goal 6 Target 8) and indirectly to

efforts to reduce poverty and hunger (Goal 1). (10) Current treatment modalities include Amphotericin B, AmBisome and other lipid formulations, Miltefosine, Paromomycin, and Sodium Stibogluconate. Parasites have become resistant to Antimonials in Bihar in India and probably neighboring parts of Nepal, but they appear to be still sensitive in other parts of India, Bangladesh and Nepal. (5, 11-13)

III Objectives

We aimed at properly documenting, analyzing and reviewing the safety and efficacy profiles of drugs of relevance for treatment and control of VL in the Indian Subcontinent, i.e. Amphotericin B deoxycholate, liposomal Amphotericin B (AmBisome®), Miltefosine, Paromomycin, and Sodium Stibogluconate. A systematic review of clinical trials of treatments of VL in India covered the period 1980-2004.(5)

This review aimed at updating and completing the previous review by including information of the clinical trials done in Bangladesh and Nepal in order to produce reliable summaries of safe and effective regimens in support of policy or research decisions specifically in the context of the elimination campaign.

IV Materials & Methods

1 Criteria for considering studies for this review

a Types of studies

Comparative, Non Comparative and Dose finding trials of Amphotericin AmBisome, Paromomycin, Miltefosine and Sodium Stibogluconate.

b Types of participants

Male and female patients proven positive for VL by either splenic or bone marrow aspirate. Patients with TB, pneumonia, HIV+, diabetes, jaundice, renal, hepatic, cardiac diseases, pregnant or lactating were excluded from the trials.

c Types of interventions

Amphotericin B, AmBisome®, Paromomycin, Miltefosine, Sodium Stibogluconate and Paromomycin + Sodium Stibogluconate. Doses varied from trial to trial and arm to arm (where applicable) and are given in table. 5

d Types of outcome measures

- Safety evaluation. Efficacy was evaluated based on final cure at 6 months of follow up, including primary failures and relapses, for all studies but two (Mishra AmphB vs. SB 1994 and Thakur AmBi 3 regimens 1996) (15,36) which followed patients for 12 months.
- Safety evaluation. Safety evaluation was based on the Serious Adverse Effects or Adverse effects occurred and their CTC grades

where applicable or available. The safety outcomes for all the trials in the review are included in table.6

2 Search methods for identifying studies

We conducted an internet search, which included databases of PubMed and Clinical trial registries of WHO and NIH (www.clinicaltrials.gov). The key words used were “clinical trials”, “visceral leishmaniasis”, “Kala azar”, “India”, “Bangladesh”, “Nepal”. In addition the targeted study drugs included were “AmBisome”, “Amphotericin B deoxycholate”, “Miltefosine”, “Paromomycin”, “and Sodium Stibogluconate”. The search was restricted to the Clinical trials conducted in India, Nepal and Bangladesh and published between 1990 to 2008. The only study from Bangladesh (29) was done in 1988-1990 but published in 1993. The last online search was done on May 21st 2008. We also contacted investigators for additional trials which might have been missed or be yet unpublished. Investigators in Bangladesh, Nepal and India also provided full articles when only abstracts were available online.

3 Methods of the review

a Trial selection

Potentially relevant clinical trials identified through the search were reviewed and examined. Trials for Visceral Leishmaniasis drugs like Pentamidine, Sitamaquine, Amphotericin B Colloidal Dispersion (ABCD), AmphotericinB Lipid Complex (ABLC), and liposomal AmphotericinB other than AmBisome were excluded from this review. Comparative, non comparative and dose finding for Amphotericin B, AmBisome®, Sodium Stibogluconate, Miltefosine, Paromomycin either alone or in combination were included in this review.

b Assessment of methodological quality

The method used to generate the sequence of allocation was assessed and considered to be adequate if it was described and the resulting sequences were unpredictable, and unclear if it was stated that the trial was randomized without specifying the method. The method used to conceal allocation was deemed to be adequate if the participants and the investigators enrolling them could not foresee the assignment; unclear if the trial was randomized but method not described, and inadequate if both participants and investigators could foresee the assignment. The blinding in the trials were classified as double (neither the investigator/care provider nor patient knew the nature of treatment given); single (either the investigator/care provider or patient knew the nature of the treatment given or open (the investigator/care provider and patients knew the nature of the treatment given). We assessed the loss from the initial cohort and those who were available for final evaluation.

c Data extraction

Data extracted were cross checked for accuracy and entered into Excel spreadsheets and in the RevMan software of the Cochrane collaboration for comparative studies.

d Data analysis

Statistical methods. Data extracted were keyed in Excel® spreadsheets. 6-month success rates were calculated with 95% confidence intervals out of the enrolled patients (Intent to Treat, ITT) and evaluable patients (Per Protocol, PP) populations. Results are presented in both tabular and graphical form.

For comparative studies, data were entered in RevMan and Relative Risks (fixed effect) with 95%CI for failure were calculated and presented in both tabular and graphical (funnel plots) form. Heterogeneity (Chi-square, I-square) and overall effect (Z test) were tested.

Comparisons are also presented using L'Abbé plots for success rates with bubble proportional to the sample size (enrolled patients).

V Results

1 Description of studies

a Studies contributing to the analysis.

We identified a total of 104 publications through internet search, and one additional clinical trial was provided by investigators in Bangladesh. There were also other four clinical trials for which the full articles were mailed by the investigators upon request as only abstracts were available online. Two other clinical study articles were obtained from the library of WHO and two others from the library of WHO/TDR.

We finally had a total of 105 publications of which 104 were published online and the remaining one obtained through contacting the investigator. We excluded 82 publications from reviewing. These included 27 publications which were not clinical trials, 18 were clinical trials of drugs not included (Sitamaquine, Pentamidine, AmphotericinB lipid complex, AmphotericinB colloidal dispersion, atovaquone, ketoconazole, fluconazole, roxithromycin, verapamil, INH, rifampicin, ethambutol, etc), 7 clinical trials were either ongoing or just completed and not published, and another 30 publications were excluded for other reasons (they were diagnostic and interventional trials, review publications etc.)

Thus a total of 23 clinical trials were included for data extraction. Among this 11 are comparative, 4 non comparative and 8 were dose finding studies. These details are shown in (Figure 1)

Approximately one fourth of the patients enrolled non-comparative trials (largely from a Phase IV trial on Miltefosine (Bhattacharya Phase 4 Milt

2007)); (26) the remaining patients were in studies comparing different drugs (36%, mostly Paromomycin and Amphotericin B) or dosages of the same drug (37%, largely Amphotericin B). (Table 1 and 2, Figure 1 and 2.)

b Type of interventions.

Of the total 5730 patients enrolled, Amphotericin B and Miltefosine contributed most patients (36% and 33% respectively) followed by Paromomycin and sodium stibogluconate (~12% each, plus ~2% combined) and AmBisome (8%). (Table 1, Figure 2.)

c Methodological quality

Methods of allocation as such were not applicable to four non comparative trials included in this review. (Bhattacharya Milt 2004, Bhattacharya Phase 4 Milt 2007, Rijal SB 2003 and Sundar AmBi non comp 2003). (25-28)

For one dose finding study (Chowdhury SB 1993), (29) there was only mention of the study being randomized but the method of randomization was not specified. The study was open labeled and there was no concealment of treatment allocation. For two other dose finding studies (Jha Milt 1999 and Sundar Milt 2003) (30,35) patient allocation were made in sequential groups. The dose finding study Karki SB 1998 (31) was open label with no concealment of allocation. Two studies (Sundar AmphB, 15d vs alt day 2007 and Thakur AmBi, 3 regimens 1996) (34, 36) were open label, having computer generated randomization and no concealment of treatment. One study (Sundar AmBi single vs daily 2001) (32) was open label, had computer generated randomization with treatment concealment. Another study (Sundar

AmBi, 3 regimens 2002) (33) was double blinded, had computer generated randomization with treatment concealment.

For three randomized, open labeled comparative studies (Sundar AmphB vs Par2007, Mishra AmphB vs SB 1994 and Thakur AmphB vs SB 1993), (17, 15, 21) the method of randomization was not specified. For two randomized open labeled studies (Thakur AmphB vs SB 2004 and Thakur AmBi vs AmphB 2001) (22,19) the allocation was not specified, but they reported having matched patients by the age and sex. Two randomized open label studies (Jha PM vs SB 1998 and Thakur PM+SB vs SB 2000) (14, 24) had computer generated non concealed allocation. Another two randomized open label studies (Thakur PM vs SB 2000 and Sundar AmphB, Conv vs lipid 2004) (24, 18) had computer generated concealed allocation. One open label comparative study (Sundar AmphB vs Milt 2002) (20) having non concealed allocation was randomized using blocks in the ratio 3:1.Another open label comparative study (Singh AmphB vs Milt 2006) (16) having non concealed allocation was randomized using slips.

d **Efficacy population.**

5730 patients enrolled these trials (the denominator for ITT analysis) and ~6% were lost to follow-up leaving 5380 patients for the PP analysis. ≥2% were lost for AmBisome, Amphotericin B and Paromomycin alone or combined; the larger losses were for Miltefosine (10%, essentially from the non-comparative Phase IV trial) and sodium stibogluconate (~19%). (Table 2).

2 Crude efficacy (6-month success rates in comparative and non-comparative trials).

a Sodium stibogluconate

We identified 9 clinical trials (13 study arms) of which 2 were dose finding, 6 comparative and 1 non comparative trial. Sodium stibogluconate is the only drug for which trials have been done in Bangladesh and Nepal. We identified 2 studies from Nepal (1 non comparative and 1 dose finding study) (27, 31) and 1 from Bangladesh (dose finding study with 4 arms viz Chowdhury SB 1993) (29) A total of 686 (12% of database) patients received Sodium Stibogluconate. 558 patients (10.4% of database) were evaluable and hence 81.3% of patients on Sodium Stibogluconate were evaluable based on ITT. Of this 285 (5%) were in comparative trials, 281 (4.9%) in dose finding trials and 120 (2.1%) were in non comparative trials. Table 1 and 2,,Figure 2 and 6

Chowdhury SB 1993, (29) the only study from Bangladesh had 4 arms; the randomization method was unspecified; the 6-month cure rates were 28.8% and 68% (sample size 59); 39.6 and 72.4% (53 patients); 36.4% and 83.3% (55 patients); 38.3% and 85.2% (60 patients) by ITT and PP respectively.

Karki SB 1998(31) (dose finding, 2 arms) and Rijal SB 2003 (non comparative) (27) were the studies from Nepal. For Karki SB 1998 (31)the cure rates were 77.8% and 77.8% (27 patients); 92.6% and 92.6% (27 patients) by ITT and PP respectively. For Rijal SB 2003 (27) the cure rates were 82.5% and 85.3% (120 patients) by ITT and PP respectively.

Five comparative trials were from India. Cure rates for were: Mishra AmphB vs SB 1994 (15) = 62.5% and 62.5 % (40 patients) by ITT and PP respectively; Thakur AmphB vs. SB 1993, (21) = 76.0% (75 patients) by both

ITT and PP; Thakur AmphB vs. SB 2004 (22) = 46.7% (60 patients) by both ITT and PP; Jha PM vs. SB 1998, (14)= 63.3% and 63.3% (30 patients) by ITT and PP respectively; Thakur PM vs. SB 2000 (23) = 66.7% and 69% (30 patients) by ITT and PP respectively; Thakur PM+SB vs. SB 2000 (24) = 52% and 53.1% by ITT and PP respectively. (Table 3 and Figure 5)

b Paromomycin

We identified 3 trials with 7 arms (all trials were comparative) enrolling a total of 681 patients (11.9% of database) in Paromomycin arms of whom 676 (12.6% of database) were evaluable. Thus 99.3% of patients on Paromomycin were evaluable based on PP The arms 12mg/kg for 21 days, 16mg/kg for 21 days and 20mg/kg for 21 days (all 3 of Jha PM vs SB 1998) had 6 months ITT cure rates of 76.7%, 80% and 83.3% respectively. In the case of the 3 arms of 12mg/kg for 21 days, 16mg/kg for 21 days and 20mg/kg for 21 days (of Thakur PM vs SB 2000) the 6 month ITT cure rates were 90% 93.3% and 96.7% respectively. The 6 month ITT cure rate for 11mg/kg for 21 days (Sundar AmphB vs Par2007) was 94.6%. Table 3,and Figure 6.

c Paromomycin + Sodium stibogluconate

We identified one trial (comparative) where 2 arms were Paromomycin-Sodium Stibogluconate combinations (Thakur PM+SB vs SB 2000). There were 100 patients enrolled (1.7% of the database). All of them were evaluable (100% by ITT) and it constituted 1.9% of the total 5380 evaluable patients. The arms PM12mg/kg + SB20 mg/kg daily for 21 days and PM18mg/kg + SB20 mg/kg daily for 21 days had 6 months ITT cure rates of 92.3% and 93.8% respectively.(PP Cure rates 92.3% and 93.8% respectively) Table 3 and Figure 6.

d Miltefosine

Six trials were identified for Miltefosine with 11 treatment arms (2 comparative, 2 dose finding and 2 non comparative trials.) enrolling 1734 patients (30.3% of the data base), of whom 1560 were available for evaluation by PP (29% of the database). Miltefosine trials comprised the second largest drug group with respect to number of patients after Amphotericin B (35.8%).

The two comparative trials were Singh AmphB vs Milt 2006 (2 arms) and Sundar AmphB vs Milt 2002 (1 arm) with 363 patients (6.3% of database). The cure rates for Singh AmphB vs Milt 2006 were 93.2% and 97.6% respectively by ITT and PP for the arm with a sample size of 44 patients. For the second arm with 20 patients the cure rates were 95% and 100% by ITT and PP respectively. The second comparative trial Sundar AmphB vs Milt 2002 had a cure rate of 94.3% and 96.9% by ITT and PP respectively (Sample size 299).

There were 159 patients enrolled in the 2 dose finding studies (2.8% of the database.) Jha Milt 1999 had a total of 120 patients, with 30 patients each in 4 four arms. The cure rates of the first two arms were 93.3% by ITT and PP and the last 2 arms had a cure rate of 96.7% by ITT and PP. The second dose finding study Sundar Milt 2003 had 2 arms of 18 and 21 patients. The first arm had a cure rate of 83.3% and 88.2% by ITT and PP respectively. The second arm had a cure rate of 90.5% by ITT and PP.

Non comparative trials accounted for the majority of patients for Miltefosine trials (1212 patients, 21.2% of the total database). Of these, 1132 patients were from the Phase 4 trial, Bhattacharya Phase 4 Milt 2007. The cure rates

for this study were 81.9% and 95.5% by ITT and PP respectively. The second trial Bhattacharya Milt 2004 with 80 patients had cure rates of 93.8% and 94.9% by ITT and PP respectively. Figure 7 depicts the ITT cure rates vs the PP cure rates of Miltefosine. (Table 3.)

e Amphotericin B deoxycholate

Amphotericin B trials contributed the largest share of patients.(2053 patients, 35.8% of the database).(Figure 2,Tables 1 and 2.) Of these 25.9% (1485) were from a dose finding study Sundar AmphB, 15d vs alt day 2007 with 4 arms. We identified 8 comparative trials with 9 arms and 568 patients (9.9% of the total database). Of the 2053 patients on Amphotericin B (35.8%), 2012 patients were evaluable (37.4% of evaluable patients, the largest study). No non comparative studies were identified for Amphotericin B.

The cure rates by ITT and PP for the dose finding study (Sundar AmphB, 15d vs alt day 2007) were 95.5% and 97.1% (group A 245 patients-dose of 1 mg/kg,15 infusions, alternate days), 92.2% and 96.2% (group B, 244 patients dose of 0.75 mg/kg,15 infusions, alternate days), 96.6% and 98.4% (group C 500 patients dose of 1 mg/kg,15 infusions, daily), 96% and 97.7% (group D, 496 patients-dose of 0.75 mg/kg ,15 infusions, daily)

The comparative trial Singh AmphB vs Milt 2006 had a cure rate of 91.3% and 100% by ITT and PP respectively (38 patients) for group 1(AmB for previously treated with SAG-1 mg/kg ,cumulative dose 15mg/kg). Group 2(AmB for previously untreated with SAG-1 mg/kg ,cumulative dose 15mg/kg cure rates were 92.1% and 100% (23 patients).The study Sundar AmphB vs Milt 2002 had 99 patients on Amphotericin B (1mg/kg,15 infusions, alternate days)and the cure rates were 97% and 100% by ITT and PP respectively.

The Amphotercin B arm of the study “Sundar AmphB vs Par2007” had 165 patients(1 mg/kg ,alternate days for 30 days) and cure rates were 98.8% and 99.4% by ITT and PP respectively. Cure rates for “Sundar AmphB,Conv vs lipid 2004” were 96.1% by both ITT and PP(51 patients)(1 mg/kg ,alternate days for 30 days). The trial “Thakur AmBi vs AmphB 2001” had cure rates of 100% by both ITT and PP (17 patients).(1 mg/kg daily for 20 days)

The cure rates for “Mishra AmphB vs SB 1994” were 100% by both ITT and PP (40 patients).(0•5 mg/kg infused in 5% dextrose,14 doses, alternate days) Cure rates for “Thakur AmphB vs SB 1993” were 100% by both ITT and PP (75 patients)(1 mg/kg, starting with 0.5mg/kg,alternate days, till 20mg/kg is given). The trial “Thakur AmphB vs SB 2004” had cure rates of 100% by both ITT and PP (60 patients).(1 mg AMB/kg daily for 20 days)The cure rates for 8 trials and the 9 arms of Amphotericin B comparative trials are given in Figure 8.The cure rates of Amphotericin B when compared to other drugs is depicted in Figure 9 and Figure 4 shows the Funnel plots of of 6-month ITT failure rates in trials comparing Amphotericin B to other drugs with Relative Risk and 95% Confidence Intervals.

f Liposomal Amphotericin B (AmBisome®)

We identified 6 trials and 11 treatment arms for AmBisome®. There were 2 comparative (2 arms), 3 dose finding (8 arms) and 1 non comparative trials. A total of 476 patients were enrolled (8.3% of the database) and 474 patients were evaluable (8.8% of evaluable patients). (Tables 1 and 2, Figures 2 and 3.)

The dose finding trial “Sundar AmBi single vs daily 2001” had cure rates of 91.3% % by both ITT and PP (46 patients) for group 1(5 mg/kg as single

infusion). For group 2 (1 mg/kg for 5 days) the cure rates are 93.3% by both ITT and PP (45 patients). For “Sundar AmBi, 3 regimens 2002” the cure rates are 89.3%, 92.9% and 96.4% by both ITT and PP for group A (0.75 mg/kg per day for 5 days (cumulative dose, 3.75 mg/kg) group B (1.5 mg/kg per day for 5 days (cumulative dose, 7.5 mg/kg)and group C (3.0 mg/kg per day for 5 days(cumulative dose, 15.0 mg/kg) respectively. (all 3 groups had 28 patient each).In case of “Thakur AmBi,3 regimens 1996” group 1(2mg/kg on days 1,2,3,4,5,6, and 10 (total dose 14 mg/kg) and 3 (2mg/kg on days 1, 5 and 10 (total dose 6 mg/kg) (10 patients each) had cure rates of 100% by both ITT and PP. Group 2 (2mg/kg on days 1,2,3,4and 10 (total dose 10 mg/kg) had a cure rate of 90% and 100% by ITT and PP respectively. For “Sundar AmphB,Conv vs lipid 2004” (51 patients) (2 mg/kg/ day for 5 days),the cure rates were 96.1% and 98% by ITT and PP respectively. Cure rates were 100% by both ITT and PP for “Thakur AmBi vs AmphB 2001” (17 patients) (15 mg/kg, single dose). The trial “Sundar AmBi non comp 2003”(7.5mg/kg single infusion) had cure rates of 90.1% by both ITT and PP. (203 patients). (Table 3.)

3 Comparative trials

Amphotericin B deoxycholate was compared to other treatment in 8 trials (9 comparisons: miltefosine=3; paromomycin=1; AmBisome=2; Sodium Stibogluconate=3) involving a total of 1675 patients (Figure 9) There was no significant difference with Miltefosine on either aggregate data or individual comparisons and with AmBisome. Amphotericin B was better than Paromomycin (only one study, RR(95%CI)=0.22(0.05-0.94)), however the study was designed as a non-inferiority trial and Paromomycin was within the pre-defined delta to declare it not inferior to Amphotericin B. Amphotericin B

was consistently more effective than sodium stibogluconate (aggregate RR(95%CI) 0.02(0.00-0.11). There was no significant heterogeneity. (Table 4.) All comparisons display around the line of equality in the L'Abbé plot except the three studies against sodium stibogluconate. (Figure 9.)

4 Safety outcomes

a Sodium stibogluconate

Myocarditis and cardiotoxicity were reported in 5 trials. Thakur AmphB vs SB 2004 had 9 cases of cardiotoxicity (15%) of which there were 2 deaths (3.3%). Rijal SB 2003 reported 4 cases of cardiotoxicity (3.3%), two of these lethal (1.65%) and the other two required shifting to Amphotericin B. Myocarditis not needing treatment discontinuation was reported in 2 patients each by. Jha PM vs SB 1998 and Thakur PM vs SB 2000 (6.7% in both studies) and one (2%) by Thakur PM+SB vs SB 2000. Thus, a total of 18 patients (2.6%) had Myocarditis or cardiotoxicity of 686 patients who had Sodium stibogluconate and 4 deaths (0.6%)

Other adverse events included bleeding (24 cases, which is 3.4% of total patients on Sodium Stibogluconate, and included 2 deaths from severe bleeding, all from Chowdhury SB 1993), splenic infraction (1 death,0.15%, from Chowdhury SB 1993) one death(0.15%) due to unexplained shock, one sudden death(0.15%) on the last day on injection, arthralgia (15 cases from 2 studies, 2.2%), anorexia (32 cases from 4 studies, 4.7%) icterus (2 cases,0.3%), rash (8 cases,1.2%), vomiting (1 case,0.15%), elevation of AST (5 cases,0.75%),ALT (4 cases,0.6%) and creatinine (1 case,0.15%), rigors (23 cases from 2 studies,3.35%), suffocation (4 cases,0.6%), cellulites, thrombophlebitis,

fever(22 cases,3.3%), metallic taste(8 cases, 1.2%), neuritic pain (3 cases,0.45%) etc. (see Table 5)

b Paromomycin

The adverse events registered with Paromomycin include ototoxicity (11 cases from 3 studies,1.6%), nephrotoxicity (4 cases,0.6%), elevated AST (40 cases,5.9%) and ALT (14 cases,2%), vomiting (5 cases from 3 studies,0.75%), pain at injection site (276 cases,40%) and fever (13 cases,1.9%). (See Table 5)

c Paromomycin + Sodium stibogluconate

One case of myocarditis was reported (1%). Ototoxicity could not be evaluated as only 19 of 100 patients had audiometric assessment. (See Table 5)

d Miltefosine

SAEs reported with Miltefosine were mainly vomiting (261 cases from 5 studies,15%), diarrhea (180 cases from 5 studies including 1 death from acute diarrhea,10.4%,0.06% respectively), 1 death from abdominal pain and swelling (0.06%), elevation of AST (253 cases from 4 studies,14.6%), ALT elevation (195 cases from 3 studies,11.25%,),elevated BUN (8 cases,0.45%), high creatinine, pneumonia, renal failure, Steven Johnson syndrome, rigors (1 case each,0.06% for each

e Amphotericin B deoxycholate

The main adverse events reported were diarrhea (13 cases from 2 studies,0.65%), vomiting (27 cases from 2 studies,1.3%) elevated AST (84 cases from 3 studies,4.1%), ALT elevation(62 cases from 3 studies,3%), high

creatinine (85 cases,4.1%) and elevated BUN (43 cases,2.1%), hepatotoxicty (2 cases from 2 studies,0.1%), nephrotoxicity (43 cases from 2 studies,2.1%) and thrombocytopenia (1 case,0.05%). One incidence of death due to gastroenteritis and diahorrea occurred in the study(0.05%) (Sundar AmphB vs Par2007) Rashes, anorexia, (8 cases each, 0.4%)) fever and chills related to infusion (94 cases, 4.6%), hypothermia (1 case,0.05%) were also reported. (See Table 5)

f Liposomal Amphotericin B (AmBisome®)

The most common adverse event was infusion related fever (49 episodes in 25 patients, 10.3%), fever and chills related to AmBisome infusion (29 cases, 6%). Other adverse events reported include rigors (49 cases from 2 studies, 10.3%), vomiting (34 cases from 3 studies, 7.15%) and backache (10 cases from 2 studies, 2.1%). (See Table 5)

VI Discussion

1 General discussion

For this systematic review to be relevant to the Elimination Campaign, we decided to limit our analysis to recent trials (from 1990) of Sodium Stibogluconate, Amphotericin B deoxycholate, liposomal Amphotericin B AmBisome®, Miltefosine and Paromomycin. We therefore excluded older studies and drugs like Pentamidine, Sitamaquine, Amphotericin B Colloidal Dispersion (ABCD), Amphotericin B Lipid Complex (ABLC) and formulations of liposomal Amphotericin B other than AmBisome as they are either obsolete or will be of no particular avail to the elimination campaign.

There is little information outside India; clinical research is essentially done in Bihar. Most of the clinical trials in this review were done in India (20 of 23, 87%) with only two from Nepal and one from Bangladesh (the latter was published in 1993 but conducted during 1888-1990 and was included in this review as it was the only trial we were able to identify for VL from this country.) All studies outside India were on Sodium Stibogluconate - no clinical trials for the other drugs reviewed (AmBisome®, Amphotericin B, Miltefosine and Paromomycin).

Amphotericin B deoxycholate is very effective but impractical as it requires 15 injections and 30 days in the hospital and is associated with both infusion-related and delayed toxicities. AmBisome® is safer than plain Amphotericin B and is very effective. Miltefosine is as effective as Amphotericin B and is the only drug that has been tested in a Phase 4 study; in these conditions, effectiveness was lower than efficacy. Paromomycin is effective both alone and combined with Sodium Stibogluconate and was shown to be not different from Amphotericin B using a non-inferiority trial design (the direct comparison used here may not be appropriate.)

Sodium Stibogluconate is clearly lost to parasite resistance in Bihar but recent data from other areas are not available.

Extracting full information on the quality of studies and methods was not always easy. Not all studies were giving sufficient information on patient attrition as to numbers enrolled and those that were evaluable (intent to treat versus per protocol analysis). Safety was also unevenly reported.

2 Implications of findings for policy

This systematic review is relevant to the initiative of the governments of these three countries which signed a Memorandum of Understanding (MOU) to eliminate Visceral Leishmaniasis as a Public Health problem by 2015 in May 2005 in Geneva. This is the first systematic reviews for clinical studies done in the Indian Subcontinent including Nepal and Bangladesh. We believe that systematic reviews are a valid tool to assist and inform decisions in terms of policy, practice and research.

This systematic review confirms that safe and efficacious treatment options are available now in India and should also be made available in Nepal and Bangladesh.

The findings of this review indicate that treatment policies should consider the use of AmBisome®, Miltefosine and Paromomycin. It is interesting to note that all these three drugs are a result of effective public private partnerships (PPP).The partnership was between Gilead Sciences and WHO/TDR for AmBisome®; Zentaris, the Indian Council of Medical Research (ICMR) and WHO/TDR for Miltefosine and Institute for One World Health (IOWH) and WHO/TDR in the case of Paromomycin.

AmBisome® was approved for treatment for VL with clinical studies done by the public sector which were coordinated by WHO/TDR. Its main advantage is its high effectiveness and the option of being given in a single dose; its major disadvantage is

its high price. Initially the cost per treatment ranged from ca. US$1600 for children to ca. US$ 2800 for adults. In May 2007, Gilead Sciences, Inc, the manufacturers of AmBisome®, announced a reduction in the price of AmBisome® to US$20 per vial to Public Sector Agencies of all Developing Countries (3, 37). While this reduces the cost of treatment to ca. US$160 for children and US$280 for adults (i.e. one tenth of the earlier price), (37, 40) it is still too high for the poor in the endemic areas of the Indian subcontinent where the average daily income of a family is around US$1. Additional costs incurred like hospitalization, injection devices and others add to the financial burden. It would be tempting to consider a single infusion of either 5mg/kg or 7mg/kg for ease and affordability, but we learnt from Sodium Stibogluconate that a single agent in low doses will select for resistant organisms (5), though there is no evidence yet of resistance to Amphotericin B. Instead, a single dose AmBisome® combined with either a full or shortened course of a companion drug should be considered. The quick onset of action and high efficacy of AmBisome® will be leaving behind only a fraction of the parasite population which will be dealt by the combination drug. (47)

Miltefosine is the only oral drug and India was the first country to approve its use in 2002. (38). The Phase 4 clinical trial published in June 2007 supports its use in an outpatient setting where VL is endemic. (26) A change to ambulatory setting from the current inpatient treatment for VL patients in India would allow reaching out for more patients who would otherwise receive no or inappropriate treatment -.a major factor for the success of the elimination program. Oral bioavailability is both a blessing and drawback of Miltefosine, as it will facilitate coverage but also misuse which may be deleterious to safety and therapeutic lifespan (44). Hence Miltefosine should never be released without properly educating prescribers and without a form of supervision. Currently a few days' supply of Miltefosine could be bought from retail medical shops without a prescription.(5,38) The poor patients will not be made aware of the

consequences of not completing treatment, contraindications and adverse effects, and will tend to buy just a few days worth of medication and discontinue as soon as the symptoms abate (44), which will inevitably lead to resistance and toxicity (45). The cost of therapy was US$ 145 for a full adult course in the private sector (5, 44). A special discount (US$ 64 for a full course treatment) was obtained for the WHO for approximately 20,000 treatments. (38) However, there is not yet a definitive agreement on pricing.

Paromomycin was approved for use in India in August 2006 based on the results of the pivotal phase III trial (17) and earlier studies reviewed here. The final phases of development were conducted through a PPP funded by the Bill and Melinda Gates Foundation. (5) The main advantage of Paromomycin is the very competitive price (US$10 for an adult treatment), its main drawback is the three weeks of daily injections (though costs can be reduced by treating on outpatient basis.) (5)

There are both theoretical foundations and clinical evidence in favor of the use of combination therapies which are expected to protect antileishmanial drugs especially in areas of anthroponotic transmission like the Indian Subcontinent where resistance could spread quickly. (46) Overall dose and duration of treatment can be reduced by combining two drugs which will result in lower direct and indirect cost to the patient. If an oral drug is part of the combination, hospitalization could be limited to the initial few days and then the patient can continue treatment at home and returning to the hospital for check up and weekly supply of medication using a tuberculosis-like DOT (directly observed treatment) strategy.

Drugs are not the only tool; other policy measures like active case finding and treatment, effective vector control, imparting patient education are paramount for the success of the Visceral Leishmaniasis elimination campaign. The elimination strategy includes early diagnosis and complete treatment, effective disease and vector

surveillance, vector control through integrated vector management including residual spraying, insecticide treated bed nets, social mobilization and implementation research. Currently, the primary health centers in the affected regions are insufficiently equipped, skilled personnel often not available and laboratory diagnosis not feasible. Vector control measures like residual insecticide spraying and insecticide-treated bed nets are mostly poorly implemented and often unaffordable.(3) The cost of VL diagnosis and treatment is largely borne by the patient's family, enforcing the vicious cycle of poverty and disease and preventing people from seeking care. (7)

Implementation research (also supported by WHO/TDR) is being undertaken by investigators of India, Nepal and Bangladesh to identify cost-effective strategies for active case finding and Primary Health Care based case management (Mondal et al., unpublished data) (3) as well as efficient high quality vector control interventions (Anand et al., unpublished data).

Adequate policies should be implemented as part of the elimination campaign so that the overloaded health systems and health workers in Bangladesh, India and Nepal will be able to cope with the workload represented by active case detection and treatment of VL. (3)

The number of patients who need treatment is bound to increase as more cases will be detected. Trans border flux of cases should also be managed by joint coordinated effort by the three nations. Investment of resources into transmission control, a strong integration of early diagnosis and treatment into the existing health services and improvement of access to diagnosis and treatment for the poor and marginalized will go a long way in eliminating of Visceral Leishmaniasis by 2015.

a Policy for Drug Resistance

At present there is no policy either at national or international level to prevent the emergence of resistance to antileishmanial drugs. (53). The spread and emergence of resistant parasites is related to a number of factors that are as yet insufficiently defined. Very little is known about the effects of drug resistance on the fitness and virulence of *Leishmania* parasites, including ability to transform, establish an infection in the vector or outgrow a non-resistant wild type. Unlike anti-bacterial drug resistance, no mathematical model has been developed to model the spatio-temporal spread of drug-resistant *Leishmania* parasites. Such a model would both help in our understanding, as has been shown for antibiotic resistance (54), and will be a tool for evaluation of control strategies to prevent drug resistance development.

A series of control measures can be introduced in the case of anthroponotic diseases, as shown in other infectious diseases for drug resistance control. These measures include monitoring and surveillance of clinical isolates, improved methods to observe patient adherence to treatment regimes, use of drug combinations and legal restrictions on drug accessibility.(52). Monitoring drug resistance can be done either through (i) phenotypic sensitivity of parasite isolates, or (ii) molecular changes indicating alterations in either the drug target or mechanisms that alter the intra-parasite level of active drug. (52)

b Cost Effectiveness Analysis

Cost Effectiveness Analysis (CEA) of the existing treatment regimens can help informing policy decisions. The latest CEA study was by Vanlerberghe et al published in 2007, and the previous one was published in 2002 Boelaert et al (51). Vanlerberghe et al (50) compared four regimens (Sodium Stibogluconate, AmphotericinB, Miltefosine and AmBisome) from the perspective of health service

provider. The point at which a patient comes for consultation with signs and symptoms of VL was considered as the starting point. The treatment regimen that averts the larger number of deaths was considered to be the most effective. The strategy minimizing the cost per death averted was considered the most cost-effective treatment regimen. The study concluded that treatment with Amphotericin B deoxycholate was the most effective approach as it was found to avert over 87% of all VL attributable deaths. The study also found that the least expensive and the most cost effective treatment was Miltefosine, and the most expensive and the least cost-effective was AmBisome. The cost of drug and medical care were the main determinants of the cost effectiveness ranking of the alternative schemes.

This cost effectiveness analysis was published in February 2007 while in May 2007 the price of AmBisome was reduced by circa one tenth (37), making the findings with respect to AmBisome obsolete.

To properly inform policy decisions, it will be important to update CEA and obtaining information also on indirect costs.

Specifically for the results of this systematic review, it is important to consider that the choice of regimens depends not only on efficacy and safety (that can be tested in clinical trials) but also on cost-effectiveness in real life and other variables which are more difficult to quantify. The collection of data contributing to this assessment, large real-life type implementation studies and continuous monitoring of effects will be paramount to the success of the campaign.

3 Implications for research

There is a clear need to document efficacy and safety of treatment options outside India. Only two studies were done in Nepal and none in Bangladesh during 1990-2006 (the study included from Bangladesh was published in 1993 but done earlier),

all on Sodium Stibogluconate. There is no information as to whether the efficacy of Sodium Stibogluconate has decreased here as well as it did in Bihar, and no information as yet on Miltefosine (which will be the choice treatment in the campaign) and other drugs like AmBisome® and Paromomycin.

It will also be important to test drug combinations in order to protect drugs against resistance, prolonging their lifespan of effective use.

Methodological quality and consistence of clinical trials is paramount, as well as more attention to the systematic collection of clinical and laboratory safety information

We need more data on the effectiveness of drugs when used in real life as conditions in practice are different from the controlled conditions of clinical trials. A strong, active and continuous pharmacovigilance is imperative when new drugs are deployed to document safety and rational use.

Despite the high efficacies of Miltefosine, Paromomycin and AmBisome, there is always the danger of resistance development with time. Therefore, short course multidrug regimens should be developed to ensure compliance and prolong the useful lifespan of effective use of the drugs. The price reduction of AmBisome® and Miltefosine (though the final price has not yet been decided for the latter) in addition to the affordable price of Paromomycin provides options for combination regimens. Clinical research based on this rationale should be done to develop effective short course treatment regimens.

There is certainly a place for a vaccine for leishmaniasis. Research for Leishmaniasis vaccines must be funded and encouraged. This is a daunting task even with funds and other resources as like Plasmodium; Leishmania is also a tricky organism to develop a vaccine against. There are good serodiagnostic tests that exist, but the problem is that it may not be suitable for on field use. In addition to show what is

happening to the parasite load tissue invasive tests are needed. Therefore the main need is for simple tests on either urine or saliva which contains leishmanial antigens. There should be more research and funds with both public and private sector support for also the development and improvement of reliable and affordable rapid diagnostic tests as these will be the ones of immense use in remote villages with little or no infrastructure where most visceral leishmaniasis cases occur.(13)

4 Limitations

In this systematic review only three studies done outside India could be identified, all on Sodium Stibogluconate, none recent and none of the three drugs (AmBisome®, Miltefosine and Paromomycin) that the review found potentially beneficial for the elimination campaign. While the results of this systematic review are up to date, comprehensive and informative for the elimination campaign in India, little more has been learnt for Bangladesh and Nepal in terms of current status of Sodium Stibogluconate responsiveness of leishmania isolates and in terms of efficacy and effectiveness of other leading drugs in those countries.

VII Conclusions

The findings of this systematic review indicate that treatment policies should consider the use of AmBisome®, Miltefosine and Paromomycin. The theoretical basis and evidence from both VL and other diseases support testing combination therapies to improve efficacy and adherence, reduce treatment duration and costs and prolong the drugs' useful lifespan by be protecting them from parasite resistance, particularly in areas of anthroponotic transmission like the Indian Subcontinent where resistant parasites could spread quickly.

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IX REFERENCES

1. World Health Report (2002) Reducing Risks, Promoting HealthyLife. World Health Organization, Geneva, Switzerland. pp. 186–192.
2. Business plan: Business line 10–Visceral leishmaniasis elimination Draft Business Plan for JCB , May, 2007,WHO/TDR http://www.who.int/tdr/about/strategy/pdf/bl10.pdf. Accessed online, June 16, 2008.
3. Sundar S, Mondal D, Rijal S, Bhattacharya S, Ghalib H, Kroeger A, Boelaert M, Desjeux P, Richter-Airijoki H, Harms G. Implementation research to support the initiative on the elimination of kala azar from Bangladesh, India and Nepal--the challenges for diagnosis and treatment. Trop Med Int Health. 2008 Jan;13(1):2-5.
4. Jeffrey Witsoe, “Challenges and Opportunities Facing India's Poorest State” Center for the Advanced Study of India, University of Pennsylvania. http://casi.ssc.upenn.edu/print_pages/pdf/print_Witsoe.pdf Accessed online, July 2, 2008.
5. Olliaro PL, Guerin PJ, Gerstl S, Haaskjold AA, Rottingen JA, Sundar S. Treatment options for visceral leishmaniasis: a systematic review of clinical studies done in India, 1980-2004. Lancet Infect Dis. 2005 Dec;5(12):763-74.
6. Singh SP, Reddy DC, Rai M & Sundar S (2006) Serious underreporting of visceral leishmaniasis through passive case reporting in Bihar, India. Tropical Medicine and International Health 11,899–905.
7. Alvar J, Yactao S & Bern C (2006) Leishmaniasis and poverty. Trends in Parasitology 22, 552–557.

8. Visceral Leishmaniasis Fact Sheet ,Institute for One World Health www.oneworldhealth.org/pdf/Leishmaniasis%20Fact%20Sheet.pdf Accessed online, June 14, 2008.
9. WHO/TDR. Press release: Elimination of kala-azar from endemic Countries in the south-east Asia region. Health ministers' sign Memorandum of understanding. Geneva/New Delhi, May 18, 2005. http://www.who.int/tdr/diseases/leish/press_release.htm Accessed online June 10, 2008
10. Kala Azar: Why Kala Azar Elimination is Possible in South Asia Countries? http://www.searo.who.int/en/Section10/Section2163_11671.htm Accessed online , June 10 , 2008
11. Davidson RN. Practical guide for the treatment of leishmaniasis. *Drugs* 1998; **56:** 1009–18.
12. Murray HW. Treatment of visceral leishmaniasis (kala-azar): a decade of progress and future approaches. *Int J Infect Dis* 2000;**4:**158–77.
13. Guerin PJ, Olliaro P, Sundar S, et al. Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. *Lancet Infect Dis* 2002; **2:** 494–501.
14. Jha TK, Olliaro P, Thakur CP, Kanyok TP, Singhania BL,Singh IJ, Singh NKP, Akhoury S, Jha S. Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India : BMJ. 1998 Apr 18;316(7139):1200-5.
15. Mishra M, Biswas UK, Jha AM, Khan AB. Amphotericin versus sodium stibogluconate in first-line treatment of Indian kala-zar: Lancet. 1994 Dec 10;344(8937):1599-600.
16. Singh UK, Prasad R, Mishra OP, Jayswal BP. Miltefosine in children with visceral leishmaniasis: a prospective, multicentric, cross-sectional study. :Indian J Pediatr. 2006 Dec;73(12):1077-80.

17. Sundar S, Jha TK, Thakur CP, Sinha PK, Bhattacharya SK. Injectable paromomycin for Visceral leishmaniasis in India : N Engl J Med. 2007 Jun 21;356(25):2571-81.
18. Sundar S, Mehta H, Suresh AV, Singh SP, Rai M, Murray HW. Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations: Clin Infect Dis. 2004 Feb 1;38(3):377-83. Epub 2004 Jan 13.
19. Thakur CP. A single high dose treatment of kala-azar with Ambisome (amphotericin B lipid complex): a pilot study: Int J Antimicrob Agents. 2001 Jan;17(1):67-70.
20. Sundar S, Jha TK, Thakur CP, Engel J, Sindermann H, Fischer C, Junge K, Bryceson A, Berman J. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med. 2002 Nov 28; 347(22):1739-46.
21. ThakurCP,Sinha GP,Sharma V,Pandey AK, Kumar M, Verma BB .Evaluation of amphotericin B as a first line drug in comparison to sodium stibogluconate in the treatment of fresh cases of kala-azar.:Ind J Med Res (A)97,July 1993,170-175
22. Thakur CP, Narayan S.A comparative evaluation of amphotericin B and sodium antimony gluconate, as first-line drugs in the treatment of Indian visceral leishmaniasis.Ann Trop Med Parasitol. 2004 Mar;98(2):129-38.
23. Thakur CP, Kanyok TP, Pandey AK, Sinha GP, Messick C, Olliaro P. Treatment of visceral leishmaniasis with injectable paromomycin (aminosidine). An open label randomized phase II clinical study.:TRSTMH 2000;94,432-433.
24. Thakur CP, Kanyok TP, Pandey AK, Sinha GP, Zaniewski AE, Houlihan HH, Olliaro P.A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin (aminosidine) plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. TRSTMH 2000;94,429-431.

25. Bhattacharya SK, Jha TK,Sundar S,Thakur CP,Engel J, Sindermann H,Junge K,Karbwang J, AnthonyD M, Bryceson A, Berman J D Efficacy and Tolerability of Miltefosine for Childhood Visceral Leishmaniasis in India:CID 2004;38:217-21
26. Bhattacharya SK, Sinha PK, Sundar S, Thakur CP, Jha TK, Pandey K, Das VR, Kumar N, Lal C, Verma N, Singh VP, Ranjan A, Verma RB, Anders G, Sindermann H, Ganguly NK. Phase 4 trial of miltefosine for the treatment of Indian visceral leishmaniasis: J Infect Dis. 2007 Aug 15;196(4):591-8. Epub 2007 Jun 29.
27. Rijal S, Chappuis F, Singh R, Bovier PA, Acharya P, Karki BM, Das ML, Desjeux P, Loutan L, Koirala S. Treatment of visceral leishmaniasis in south-eastern Nepal: decreasing efficacy of sodium stibogluconate and need for a policy to limit further decline: Trans R Soc Trop Med Hyg. 2003 May-Jun;97(3):350-4.
28. SundarS,Jha TK,ThakurCP,Mishra M,Singh VP, Buffels R. Single-dose liposomal amphotericin B in the treatment of visceral leishmaniasis in India: a multicenter study. :Clin Infect Dis. 2003 Sep 15;37(6):800-4. Epub 2003 Aug 28.
29. Chowdhury M, A J, Alam M N Hussain A, Uddin A K M Rahman. A study on the treatment of Bangladeshi Kala-azar patients with different dosage regiments of sodium antimony gluconate: Bangladesh J of Medicine 1993; 4 (1): 1-5.
30. Jha TK, Sundar S,Thakur CP,Bachmann P,Karbwang J,Fischer C,Voss A, Berman J. Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis: N Engl J Med. 1999 Dec 9;341(24):1795-800.
31. Karki P,.Koirala S,Parija SC, Hansdak SG and DasML. A thirty day course of Sodium Stibogluconate for Treatment of Kala Azar in Nepal:South East Asian J Trop Med Pub Health 1998,Mar;29(1):154-8

32. Sundar S, Agrawal G,Rai M,Makharia MK, Murray HW. Treatment of Indian visceral leishmaniasis with single or daily infusions of low dose liposomal amphotericin B: randomised trial:BMJ 2001, 323:419-22
33. Sundar S, Jha TK,Thakur CP,Mishra M, Singh VR, Buffels R. Low-dose liposomal amphotericin B in refractory Indian visceral leishmaniasis: a multicenter study : Am J Trop Med Hyg. 2002 Feb;66(2):143-6.
34. Sundar S, Chakravarty J, Rai VK, Agrawal N, Singh SP, Chauhan V, Murray HW.Amphotericin B treatment for Indian visceral leishmaniasis: response to 15 daily versus alternate-day infusions: Clin Infect Dis. 2007 Sep 1;45(5):556-61. Epub 2007 Jul 23.
35. Sundar S, Jha TK, Sindermann H, Junge K, Bachmann P, Berman J. Oral miltefosine treatment in children with mild to moderate Indian visceral leishmaniasis: Pediatr Infect Dis J. 2003 May;22(5):434-8.
36. Thakur CP, Pandey AK, Sinha GP, Roy S, Behbani K, Olliaro P Comparison of three treatment regimens with liposomal amphotericin B (AmBisome) for visceral leishmaniasis in India: a randomized dose-finding study: TRSTMH 1996, 90: 319-322.
37. [e-drug] Price reductions for drugs for leishmaniasis.essentialdrugs.org http://www.essentialdrugs.org/edrug/archive/200705/msg00062.php Accessed online, July 2, 2008.
38. Sundar S, Olliaro PL, “Miltefosine in the treatment of leishmaniasis: Clinical evidence for informed clinical risk management” Ther Clin Risk Manag. 2007 Oct;3(5):733-40
39. Press Release. June 21, 2007 “Research on New Treatment for Neglected Disease Published in The New England Journal of Medicine.” http://www.oneworldhealth.org/media/details.php?prID=175 Accessed online, July 2, 2008.

40. Interview with Mari Carmen Viñoles, MSF General Coordinator Bihar, India. "New kala azar project in India: The disease of the 'untouchables'" http://www.msfindia.in/Bihar.htm Accessed online, July 2, 2008.

41. Sundar S, Sinha PR, Agrawal NK, et al. A cluster of cases of severe lot of sodium antimony gluconate. *Am J Trop Med Hyg* 1998; **59:** 139–43.

42. Rijal S, Chappuis F, Singh R, et al. Sodium stibogluconate cardiotoxicity and safety of generics. *Trans R Soc Trop Med Hyg* 2003; **97:** 597–98.

43. Sundar S, Thakur BB, Tandon AK, et al. Clinicoepidemiological study of drug resistance in Indian kala-azar. *BMJ* 1994; **308:** 307.

44. Sundar S, Murray HW. Availability of miltefosine for the treatment of kala-azar in India. *Bull World Health Organ* 2005; **83:** 394–95.

45. Seifert K, Matu S, Javier Perez-Victoria F, et al. Characterisation of *Leishmania donovani* promastigotes resistant to hexadecylphosphocholine (Miltefosine). *Int J Antimicrob Agents* 2003; **22:** 380–87.

46. Bryceson A. A policy for leishmaniasis with respect to the prevention and control of drug resistance. *Trop Med Int Health* 2001; **6:** 928–34.

47. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. Adv Parasitol. 2006;61:223-74.

48. Trends of Kala Azar in India. /www.searo.who.int/LinkFiles/Kala_azar_Trends_India.pdf Accessed online July 2, 2008.

49. Trends of Kala Azar in Bangladesh

http://www.searo.who.int/LinkFiles/Kala_azar_Trends_Bangladesh.pdf

50. Vanlerberghe V, Diap G, Guerin PJ, Meheus F, Gerstl S, Van der Stuyft P, Boelaert M. Drug policy for visceral leishmaniasis: a cost-effectiveness analysis. Trop Med Int Health. 2007 Feb;12(2):274-83.

51. Boelaert M, Le Ray D, Van Der Stuyft P. How better drugs could change kala-azar control. Lessons from a cost-effectiveness analysis. Trop Med Int Health. 2002 Nov;7(11):955-9.

52. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. Adv Parasitol. 2006;61:223-74.

53. Bryceson, A.. A policy for leishmaniasis with respect to the prevention and control of drug resistance. Tropical Medicine & International Health 2001, 6, 928–934.

54. McCormick, A.W., Whitney, C.G., Farley, M.M., Lynfield, R., Harrison, L.H., Bennett, N.M., Schaffner, W., Reingold, A., Hadler, J., Cieslak, P., Samore, M.H. and Lipsitch, M. Geographic diversity and temporal trends of antimicrobial resistance in Streptococcus pneumoniae in the United States. Nature Medicine 2003, 9, 424–430.

X Tables (Annex I)

XI Figures (Annex II)

ANNEX I

TABLES

Table 1 Patients enrolled in different types of trials overall and by treatment

	comparative		dose finding		non comparative		Grand Total	
Drug	N	%	N	%	N	%	N	%
Paromomycin + sodium stibogluconate	100	1.7%		0.0%		0.0%	100	1.7%
AmBisome	68	1.2%	205	3.6%	203	3.5%	476	8.3%
Paromomycin	681	11.9%		0.0%		0.0%	681	11.9%
Sodium stibogluconate	285	5.0%	281	4.9%	120	2.1%	686	12.0%
Miltefosine	363	6.3%	159	2.8%	1212	21.2%	1734	30.3%
AmphoB	568	9.9%	1485	25.9%		0.0%	2053	35.8%
Grand Total	2065	36.0%	2130	37.2%	1535	26.8%	5730	100.0%

ANNEX I

Table 2, Patients enrolled total and by treatment contributing to the Intent to Treat and Per Protocol datasets

	enrolled (ITT)		evaluable (PP)		
	N	%	N	%	%ITT
AmBisome	476	8.3%	474	8.8%	99.6%
AmphoB	2053	35.8%	2012	37.4%	98.0%
Miltefosine	1734	30.3%	1560	29.0%	90.0%
Paromomycin	681	11.9%	676	12.6%	99.3%
Paromomycin + sodium stibogluconate	100	1.7%	100	1.9%	100.0%
Sodium stibogluconate	686	12.0%	558	10.4%	81.3%
Total	5730	100.0%	5380	100.0%	93.9%

ANNEX I

Table 3 Efficacy results: 6-month cure rates

References	N enrd	N evble	N cd	95UCI ITT	95LCI ITT	CR ITT	95UCI PP	95LCI PP	CR PP
Sundar AmBi,3 regimens 2002	28	28	25	100.0%	77.8%	89.3%	100.0%	77.8%	89.3%
Thakur AmBi,3 regimens 1996	10	9	9	100.0%	71.4%	90.0%	100.0%	100.0%	100.0%
Sundar AmBi non comp 2003	203	203	183	94.2%	86.0%	90.1%	94.2%	86.0%	90.1%
Sundar AmBi single vs daily 2001	46	46	42	99.4%	83.2%	91.3%	99.4%	83.2%	91.3%
Sundar AmBi,3 regimens 2002	28	28	26	100.0%	83.3%	92.9%	100.0%	83.3%	92.9%
Sundar AmBi single vs daily 2001	45	45	42	100.0%	86.0%	93.3%	100.0%	86.0%	93.3%
Sundar AmphB,Conv vs lipid 2004	51	50	49	100.0%	90.8%	96.1%	100.0%	94.1%	98.0%
Sundar AmBi,3 regimens 2002	28	28	27	100.0%	89.6%	96.4%	100.0%	89.6%	96.4%
Thakur AmBi vs AmphB 2001	17	17	17	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Thakur AmBi,3 regimens 1996	10	10	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Thakur AmBi,3 regimens 1996	10	10	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Singh AmphB vs Milt 2006	23	21	21	100.0%	79.8%	91.3%	100.0%	100.0%	100.0%
Singh AmphB vs Milt 2006	38	35	35	100.0%	83.5%	92.1%	100.0%	100.0%	100.0%
Sundar AmphB,15d vs alt day 2007	244	234	225	95.6%	88.9%	92.2%	98.6%	93.7%	96.2%
Sundar AmphB,15d vs alt day 2007	245	241	234	98.1%	92.9%	95.5%	99.2%	95.0%	97.1%
Sundar AmphB,15d vs alt day 2007	496	487	476	97.7%	94.2%	96.0%	99.1%	96.4%	97.7%
Sundar AmphB,Conv vs lipid 2004	51	51	49	100.0%	90.8%	96.1%	100.0%	90.8%	96.1%
Sundar AmphB,15d vs alt day 2007	500	491	483	98.2%	95.0%	96.6%	99.5%	97.3%	98.4%
Sundar AmphB vs Milt 2002	99	96	96	100.0%	93.6%	97.0%	100.0%	100.0%	100.0%
Sundar AmphB vs Par2007	165	164	163	100.0%	97.1%	98.8%	100.0%	98.2%	99.4%
Mishra AmphB vs SB 1994	40	40	40	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Thakur AmBi vs AmphB 2001	17	17	17	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Thakur AmphB vs SB 1993	75	75	75	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Thakur AmphB vs SB 2004	60	60	60	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Bhattacharya Phase 4 Milt 2007	1132	971	927	84.1%	79.6%	81.9%	96.8%	94.2%	95.5%
Sundar Milt 2003	18	17	15	100.0%	66.1%	83.3%	100.0%	72.9%	88.2%
Sundar Milt 2003	21	21	19	100.0%	77.9%	90.5%	100.0%	77.9%	90.5%
Singh AmphB vs Milt 2006	44	42	41	100.0%	85.7%	93.2%	100.0%	93.0%	97.6%
Jha Milt 1999	30	30	28	100.0%	84.4%	93.3%	100.0%	84.4%	93.3%
Jha Milt 1999	30	30	28	100.0%	84.4%	93.3%	100.0%	84.4%	93.3%
Bhattacharya Milt 2004	80	79	75	99.1%	88.4%	93.8%	99.8%	90.1%	94.9%
Sundar AmphB vs Milt 2002	299	291	282	96.9%	91.7%	94.3%	98.9%	94.9%	96.9%
Singh AmphB vs Milt 2006	20	19	19	100.0%	85.4%	95.0%	100.0%	100.0%	100.0%
Jha Milt 1999	30	30	29	100.0%	90.2%	96.7%	100.0%	90.2%	96.7%
Jha Milt 1999	30	30	29	100.0%	90.2%	96.7%	100.0%	90.2%	96.7%
Jha PM vs SB 1998	30	30	23	91.8%	61.5%	76.7%	91.8%	61.5%	76.7%
Thakur PM vs SB 2000	30	27	24	94.3%	65.7%	80.0%	100.0%	77.0%	88.9%
Thakur PM vs SB 2000	30	29	25	96.7%	70.0%	83.3%	98.8%	73.7%	86.2%
Thakur PM vs SB 2000	30	30	27	100.0%	79.3%	90.0%	100.0%	79.3%	90.0%
Jha PM vs SB 1998	30	29	28	100.0%	84.4%	93.3%	100.0%	89.9%	96.6%
Sundar AmphB vs Par2007	501	501	474	96.6%	92.6%	94.6%	96.6%	92.6%	94.6%
Jha PM vs SB 1998	30	30	29	100.0%	90.2%	96.7%	100.0%	90.2%	96.7%
Thakur PM+SB vs SB 2000	52	52	48	99.6%	85.1%	92.3%	99.6%	85.1%	92.3%
Thakur PM+SB vs SB 2000	48	48	45	100.0%	86.9%	93.8%	100.0%	86.9%	93.8%
Chowdhury SB 1993	59	25	17	40.4%	17.3%	28.8%	86.3%	49.7%	68.0%
Chowdhury SB 1993	55	24	20	49.1%	23.7%	36.4%	98.2%	68.4%	83.3%
Chowdhury SB 1993	60	27	23	50.6%	26.0%	38.3%	98.6%	71.8%	85.2%
Chowdhury SB 1993	53	29	21	52.8%	26.5%	39.6%	88.7%	56.1%	72.4%
Thakur AmphB vs SB 2004	60	60	28	59.3%	34.0%	46.7%	59.3%	34.0%	46.7%
Thakur PM+SB vs SB 2000	50	49	26	65.8%	38.2%	52.0%	67.0%	39.1%	53.1%

ANNEX I

Mishra AmphB vs SB 1994	40	40	25	77.5%	47.5%	62.5%	77.5%	47.5%	62.5%
Jha PM vs SB 1998	30	30	19	80.6%	46.1%	63.3%	80.6%	46.1%	63.3%
Thakur PM vs SB 2000	30	29	20	83.5%	49.8%	66.7%	85.8%	52.1%	69.0%
Thakur AmphB vs SB 1993	75	75	57	85.7%	66.3%	76.0%	85.7%	66.3%	76.0%
Karki SB 1998	27	27	21	93.5%	62.1%	77.8%	93.5%	62.1%	77.8%
Rijal SB 2003	120	116	99	89.3%	75.7%	82.5%	91.8%	78.9%	85.3%
Karki SB 1998	27	27	25	100.0%	82.7%	92.6%	100.0%	82.7%	92.6%

ANNEX I

Table 4 Efficacy in comparative trials

Study	fail/enrolled Amphotericin B	fail/enrolled Miltefosine	Weight %	RR (fixed) 95%CI
SinghMF(naive)06	2/23	1/20	8.69	1.74 [0.17, 17.78]
SinghMF(SBfail)06	3/38	3/44	22.59	1.16 [0.25, 5.40]
SundarMF02	1/33	17/299	68.72	0.53 [0.16, 1.78]
Total (95% CI)	***8/160***	***21/363***	***100***	***0.78 [0.33, 1.84]***
Test for heterogeneity:	Chi^2 = 1.09, df = 2 (P = 0.58), I^2 = 0%			
Test for overall effect:	Z = 0.57 (P = 0.57)			
		Paromomycin		
SundarPM07	2/165	27/501	100	0.22 [0.05, 0.94]
Total (95% CI)	***2/165***	***27/501***	***100***	***0.22 [0.05, 0.94]***
Test for heterogeneity:	not applicable			
Test for overall effect:	Z = 2.05 (P = 0.04)			
		AmBisome		
SundarAB04	2/51	2/51	100	0.67 [0.12, 3.82]
ThakurAB01	0/17	0/17	0	Not estimable
Total (95% CI)	***2/68***	***3/68***	***100***	***0.67 [0.12, 3.82]***
Test for heterogeneity:	not applicable			
Test for overall effect:	Z = 0.46 (P = 0.65)			
		Sodium Stibogluconate		
MishraSB94	0/40	15/40	23.31	0.03 [0.00, 0.52]
ThakurSB93	0/75	18/75	27.82	0.03 [0.00, 0.44]
ThankurSB04	0/60	32/60	48.87	0.02 [0.00, 0.25]
Total (95% CI)	***0/175***	***65/175***	***100***	***0.02 [0.00, 0.11]***
Test for heterogeneity:	Chi^2 = 0.15, df = 2 (P = 0.93), I^2 = 0%			
Test for overall effect:	Z = 4.63 (P < 0.00001)			
total patients	**568**	**1107**	**1675**	

Table 5 Safety Outcomes

Study ID	Interventions	Outcomes: safety
Bhattacharya Milt 2004	MF: 2.5 mg/kg /d x 28 days	MF: Vomiting: 21(26%) CTC Gr 3-4: 2(2.6%) Diarrhea:20(25%)CTC Gr 3: 3(1.3%) AST elevation:44(55%) CTC Gr3:1(1%) No AE to discontinue therapy.
Bhattacharya Phase 4 Milt 2007	MF: 2.5 mg/kg /d x 28 d	MF: 3 deaths during Rx phase.1 after acute diarrhea,1 after abdominal pain& swelling,1 in a car accident. Vomiting:90, CTC Gr3-4:5 .Diarrhea:69 ,CTC Gr: 3-4:10 Hospitalised:13(1%); 1 with penumonia& RF,1 each for oral bleeding,anasarca,elevated liver enzymes,macular skin arsh,epistaxis & hemoptysis,nausea & vomiting;2 undefined events.reason unrecorded for 1. Creatinine elevations;CTC Gr3:7.
Chowdhury SB 1993	SB: 10 mg/kg/d x 20 d single bd, 10 mg/kg/d x 10 d single bd, 20 mg/kg/d x 10 d od, 20 mg/kg/d x 20 d single od	SB: 5 deaths.1 in groupA of unexplained shock.3in group C,1 from severe bleeding,1 from splenic infraction & 1 sudden death on last day of injection.1 in group D from severe bleeding.Fever:28;Bleeding manisfestation:22;splenic infraction:4; Arthralgia:8;Icterus:2;Rash:8;Anorexia:2;Rigor:1;Suffocation:4;Pain in calf muscle:1;Vomiting:1. SAE & drug withdrawal in C(6.4%) & D(12.8%)
Jha Milt 1999	MF: 50mg/d x 6w, 50mg/d x 1w + 100mg/d x 3wk, 100mg/d x 4w, 100mg x 1wk + 150mgd x 3wk	MF: 2 drug discontinuation.1 due to elevated AST,1 due to elevated creatinine.62% had GI SE viz vomiting &diarrhea.
Jha PM vs SB 1998	PM: 20 mg/kg x 21 d, 12mg/kg x 21 d, 20 mg/kg x 21 d, SB: 20 mg/kg/d x 30 d.	PM 12mg/kg/day:Vomiting:1. PM 20mg/kg/day:Ototoxicity Gr2-3:1. Gr1:1 SB 20mg/kg/day:myocarditis (drug related):2; epilepsy(dug unrelated):1 No Rx discontinuation in any case.
Karki SB 1998	SB: 20 mg/kg/d x 20 d 20 mg/kg/d x 30 d	SB: Arthralgia:5;Cellulitis & abcess:2;pain at inj site:31 No cardivascular,respiratory or other SE reported.
Mishra AmphB vs SB 1994	AmpB: 0•5 mg/kg ,14 doses, alt d SB: 20 mg/kg in 2 div dose x 40 d	AmpB & SB: No SAE were reported.Fever & chills were common with AmpB infusion.Managed with paracetamol.
Rijal SB 2003	SB 20 mg/kg/d x 30 d (40 d if + parasitology)	SB: 4 deaths(3.3%) during Rx.Cardiotoxicity:2;Septic shock:1,Suicide:1. 2 had cardiotoxicity & shifted to AmpB.Thus 3.3% incidence of cardiotoxicity

Singh AmphB vs Milt 2006	AmpB: 1 mg/kg, cumulative dose 15mg/kg, MF: 2.5 mg/kg/d x 28 d	MF: 2.5mg/kg/day (Group1& 2) Vomiting:23;Diarrhea:26,Anorexia:7;Elevations of ALT :39; AST :31;BUN:8. Rashes :2 AmpB:1mg/kg/day (Group 3& 4): Anorexia:8;Elevations of :ALT :32; AST :34;BUN:43. Rashes :8.
Sundar AmBi non comp 2003	AB: 7.5mg/kg single infusion	AB: infusion related fever & rigor(9.8%),chills(3%),vomiting (3.5%) & backache(1.5%).None required any medication.
Sundar AmBi single vs daily 2001	AB: 5 mg/kg as single infusion, 1 mg/kg x 5 d	AB: 5 mg/kg as single infusion : fever:3;chills:1;fever&chills:18;vomiting:2 AB:1 mg/kg for 5 days: fever:4;chills:1;fever&chills:18;vomiting:2;back pain:2
Sundar AmBi,3 regimens 2002	AB: 3.0 mg/kg/dx 5 d 1.5 mg/kg/d x 5 d 0.75 mg/kg /d x 5 d	AB: infusion related rigors:46 episodes(37 patients).91% were of mild intensity.Fever:49 episodes (25 patients),34 mild,11 moderate.Lumbosacral pain:8; 2 severe. Vomiting:7(1 episode) No SAR, hepatotoxicity or bone marrow toxicity.
Sundar AmphB vs Milt 2002	MF: 2.5 mg/kg/d x 28 d; AmpB: 1mg/kg, 15 infusions, alt d	MF:6 SAEs. Convulsion due to cranial cyst(2),abrrupt anemia due to bleeding hemorroids(1),P.vivax malaria(1),Gram - ve meningitis (1) resulting in death.SJ syndrome(1),attributed to MF. 4 discontinued Rx.Diarrhea:(1)arthritis & skin rash(1), increased bilirubin(1),AST,thrombocytopenia(1) Other AEs :Vomiting:113(38%);CTC Gr2:34 (11%) Diarrhea:61(20%),CTC Gr.4:1;Rigors:1.(<1%) High AST :177(58%);High ALT:155(51%) AmpB: Vomiting:20(20%);CTC Gr2:4(4%) Diarrhea:6(6%),CTC G r.4:0; Rigors:90(90%) High AST :47(47%);High ALT:29(29%)
Sundar AmphB vs Par2007	AmphB: 1 mg/kg, alt d x 30 d PM: 11 mg/kg for 21 days	PM:Deaths:2;1 before admin of PM,2 others were unrelated to PM.1 due to alcoholism,other due o septicemia. Pain at inj site:276(55%);fever:13(3%),Vomiting:3(1%),Nephrotoxicity:4(1%); Ototoxicity:7(1%), High AST:40(8%); High ALT:14(3%) AmpB:Deaths:1,due to gastroenteritis & diarrhea;Fever:94(57%),Vomiting:16(10%),Nephrotoxicity:42(25%);High AST:3(2%); High ALT:1(1%).12 patients discontnued Rx.
Sundar AmphB,15d vs alt day 2007	AmphB: 0.75 mg/kg,15 inf,alt d, 1 mg/kg,15 inf,alt d 0.75 mg/kg ,15 inf d, 1 mg/kg,15 inf alt d	AmphB:0.75 mg/kg,15 infusions,alternate days: Removed from study:3;Vomiting/diarrhea:1;hepatotoxicity:1;Infusion reaction:1;High creatinine:8 AmpB:1 mg/kg,15 infusions,alternate days: Removed from study:2;Vomiting/diarrhea:1;severe thrombocytopenia:1High creatinine:11 AmpB: 0.75 mg/kg ,15 infusions, daily: Removed from study:4;Vomiting/diarrhea:3,hepatotoxicity:1;High creatinine:29 AmpB:1 mg/kg,15 infusions, daily: Removed from study:4;Vomiting/diarrhea:2,nephrotoxicity:1; hypothermia:1;High creatinine:37

ANNEX I

Sundar AmphB,Conv vs lipid 2004	AmpB: 1 mg/kg, alt d x 30d, AB: 2 mg/kg/d x 5 d	AmpB: 1 mg/kg, alternate days x 30d:Fever& rigors:50(98%); AB:2 mg/kg/d x 5 d: Fever& rigors:15(29%)
Sundar Milt 2003	MF: 2.5 mg/kg/d x 28 d, 1.5 mg/kg/d x 28 d	MF:2.5 mg/kg/day x 28 d: Vomiting:7(33.3%);Diarrhrea,Anorexia,Nausea, high ALT: 1 each(4.8%) MF:1.5 mg/kg/day x 28 d: Vomiting:7(38.9%);Diarrhrea:3(16.7%)
Thakur AmBi vs AmphB 2001	AB: 15 mg/kg, single dose AmpB: 1mg/kg/d x 20d	AB:Shivering:3(17%);nausea:1(6%) AmpB: Shivering:11(65%);nausea:9(53%),chill:3 (17%); high creatinine:4(23%);anorexia:12(70%)
Thakur AmBi,3 regimens 1996	AB: 2mg/kg days 1-6 & 10 2mg/kg days 1-4 & 10 2mg/kg days 1, 5 & 10	AB:rigor:3,1 died of an unrelated illness after 2 months of clinical & parasitological cure.
Thakur AmphB vs SB 1993	AmpB: 1mg/kg,stng wt 0.05mg/kg,alt d,till 20mg/kg is given SB: 20 mg/kg daily for 30 days	AmpB: shivering,rigor& fever:75(100%),thrombophelbitis:2(3),anorexia:16 (21%);neuritic pain:2 (3%),high BUN:13(17%),hypokalemia:14(19%) SB: pain at inj site:75(100%),anorexia:12(16%),metallic taste:8(11%),neuritic pain:3(4)
Thakur AmphB vs SB 2004	SB: 20 mg/kg/d x 4 wks, AmpB: 1 mg/kg/d x 20 d	SB: Cardiotoxicity:9(15%);death(cardiotoxicity):2(3.3%);anorexia:6(10%);Hiigh:Creatinine:1(1.7%);ALT:4.(6.7%), AST:5(8.3%) AmpB: rigor&fever:22(36.6);anorexia:9(15%) Hiigh:Creatinine:1(1.7%);ALT:1(1.7%)
Thakur PM vs SB 2000	PM: 16mg/kg/d x 21d, 20 mg/kg/d x 21d, 12mg/kg/d x 21d, SB: 20 mg/kg/d x 30d	PM 12mg/kg/day:Vomiting:1. PM 20mg/kg/day:Ototoxicity Gr2-3:1. Gr1:1 SB 20mg/kg/day:myocarditis (drug related):2; epilepsy(dug unrelated):1.No Rx discontinuation in any case.
Thakur PM+SB vs SB 2000	PM12mg/kg + SB20 mg/kg/d x 21d, PM18mg/kg + SB 20 mg/kg/d x 21 d, SB: 20 mg/kg/d x 30d	SB:Myocarditis:1(2%) PM:only 19 of 100 patients had full audiometric assessment,so ototoxicity analysis is impossible.

ANNEX I

Table 6. Treatment Regimens Used in the Included Studies

References	Sdy	Drug	Route	Dosage and Schedule	country	year(s) of study
Sundar AmBi,3 regimens 2002	DF	AB	IV inf	0.75 mg/kg/ d x 5d	India	2002
Thakur AmBi,3 regimens 1996	DF	AB	IV inf	2mg/kg on d 1,2,3,4 & 10	India	1996
Sundar AmBi non comp 2003	NC	AB	IV inf	7.5mg/kg single infusion	India	2003
Sundar AmBi single vs daily 2001	DF	AB	IV inf	5 mg/kg single infusion	India	2001
Sundar AmBi,3 regimens 2002	DF	AB	IV inf	1.5 mg/kg/d x 5 d	India	2002
Sundar AmBi single vs daily 2001	DF	AB	IV inf	1 mg/kg/dx 5d	India	2001
Sundar AmphB,Conv vs lipid 2004	CP	AB	IV inf	2 mg/kg/dx 5 d	India	2001
Sundar AmBi,3 regimens 2002	DF	AB	IV inf	3.0 mg/kg/dx 5 d	India	2002
Thakur AmBi vs AmphB 2001	CP	AB	IV inf	15 mg/kg,single dose	India	2000
Thakur AmBi,3 regimens 1996	DF	AB	IV inf	2mg/kg on d 1, 5 & 10	India	1996
Thakur AmBi,3 regimens 1996	DF	AB	IV inf	2mg/kg on d 1,2,3,4,5,6,&10	India	1996
Singh AmphB vs Milt 2006	CP	AMB	IV inf	1 mg/kg ,cum d 15mg/kg	India	2003-2005
Singh AmphB vs Milt 2006	CP	AMB	IV inf	1 mg/kg ,cum d 15mg/kg	India	2003-2005
Sundar AmphB,15d vs alt day 2007	DF	AMB	IV inf	0.75 mg/kg,15 inf,alt d	India	2003-2006
Sundar AmphB,15d vs alt day 2007	DF	AMB	IV inf	1 mg/kg,15 inf,alt d	India	2003-2006
Sundar AmphB,15d vs alt day 2007	DF	AMB	IV inf	0.75 mg/kg , inf od x15d	India	2003-2006
Sundar AmphB,Conv vs lipid 2004	CP	AMB	IV inf	1 mg/kg ,alt d x30 d	India	2001
Sundar AmphB,15d vs alt day 2007	DF	AMB	IV inf	1 mg/kg, inf od x15d	India	2003-2006
Sundar AmphB vs Milt 2002	CP	AMB	IV inf	1mg/kg,15 inf,alt d	India	1999-2000
Sundar AmphB vs Par2007	CP	AMB	IV inf	1 mg/kg ,alt d x 30 d	India	2003-2005
Mishra AmphB vs SB 1994	CP	AMB	IV inf	0•5 mg/kg inf,14 doses,alt d	India	1994
Thakur AmBi vs AmphB 2001	CP	AMB	IV inf	1 mg/kg/d x 20d	India	2000
Thakur AmphB vs SB 1993	CP	AMB	IV inf	1 mg/kg,wt 0.5mg/kg,alt d,till 20mg/kg	India	1993
Thakur AmphB vs SB 2004	CP	AMB	IV inf	1 mg AMB/kg/d x20d	India	2004
Bhattacharya Phase 4 Milt 2007	NC	MF	PO	2.5 mg/kg /day for 28 d	India	2006
Sundar Milt 2003	DF	MF	PO	2.5 mg/kg/d x14 d	India	1999-2000
Sundar Milt 2003	DF	MF	PO	1.5 mg/kg/d x 28 d	India	1999-2000
Singh AmphB vs Milt 2006	CP	MF	PO	2.5 mg/kg/dx 28 d	India	2006
Jha Milt 1999	DF	MF	PO	50 mg/d x1wk+ 100mg/d x3 w	India	1999
Jha Milt 1999	DF	MF	PO	50 mg/ d x 6 w	India	1999
Bhattacharya Milt 2004	NC	MF	PO	2.5 mg/kg /dx 28d	India	2001-2002
Sundar AmphB vs Milt 2002	CP	MF	PO	2.5 mg/kg/dx28 d	India	1999-2000
Singh AmphB vs Milt 2006	CP	MF	PO	2.5 mg/kg/d x28 d	India	2006
Jha Milt 1999	DF	MF	PO	100 mg/dx 1w + 150mg/d x 3w	India	1999
Jha Milt 1999	DF	MF	PO	100 mg/d x 4 w	India	1999
Jha PM vs SB 1998	CP	PM	IM	12mg/kg x 21 d	India	1993-1995
Thakur PM vs SB 2000	CP	PM	IM	16mg/kg x 21 d	India	1996
Thakur PM vs SB 2000	CP	PM	IM	20 mg/kg x 21d	India	1996
Thakur PM vs SB 2000	CP	PM	IM	12mg/kg x 21d	India	1996
Jha PM vs SB 1998	CP	PM	IM	16mg/kg x 21d	India	1993-1995
Sundar AmphB vs Par2007	CP	PM	IM	11 mg/kg x 21d	India	2003-2004
Jha PM vs SB 1998	CP	PM	IM	20 mg/kg x 21 d	India	1993-1995
Thakur PM+SB vs SB 2000	CP	PM+ SB	IM	PM12mg/kg + SB20 mg/kg/d x21d	India	1996
Thakur PM+SB vs SB 2000	CP	PM+ SB	IM	PM18mg/kg + SB 20 mg/kg/d x 21d	India	1996
Chowdhury SB 1993	DF	SB	IV	10 mg/kg/d x 20d single bd	Bangladesh	1988-1990
Chowdhury SB 1993	DF	SB	IV	10 mg/kg/d x 10 d single bd	Bangladesh	1988-1990
Chowdhury SB 1993	DF	SB	IV	20 mg/kg/d x10 d single od	Bangladesh	1988-1990
Chowdhury SB 1993	CP	SB	IV	20 mg/kg/d x20 d single daily ds	Bangladesh	1988-1990
Thakur AmphB vs SB 2004	CP	SB	IM	20 mg SAG/kg/d x 4 w	India	2004

ANNEX I

Thakur PM+SB vs SB 2000	CP	SB	IM	20 mg/kg /d x 30 d	India	1996
Mishra AmphB vs SB 1994	CP	SB	IM	20 mg/kg in 2 div ds/d x40d	India	1994
Jha PM vs SB 1998	CP	SB	IM	20 mg/kg/d x30 d.	India	1993-1995
Thakur PM vs SB 2000	CP	SB	IM	20 mg/kg x28 d	India	1996
Thakur AmphB vs SB 1993	CP	SB	IM	20 mg/kg/d x 30 d	India	1993
Karki SB 1998	DF	SB	IM	20 mg/kg/d x 20 d	Nepal	1998
Rijal SB 2003	NC	SB	IM	20 mg/kg/d x 30 d	Nepal	1999-2001
Karki SB 1998	DF	SB	IM	20 mg/kg/d x30 d	Nepal	1998

ANNEX I

Table 7, Study Characteristics

Study ID	Sdy Typ	N arms	N pts	Methods	Interventions	Type of participants	Outcomes: efficacy
Bhattacharya Milt 2004	NC	1	80	not applicable	MF: 2.5 mg/kg /day x 28 days	INCLUDE: M&F; 2-11y; +ve splenic aspirate; EXCLUDE: severe disease	primary failure + relapse at 6months follow-up
Bhattacharya Phase 4 Milt 2007	NC	1	1132	not applicable	MF: 2.5 mg/kg /day x 28 days	INCLUDE:M&F; 2-65y; +ve splenic aspirate. EXCLUDE:pregnancy,lactation,HIV+,refusal to use contraception during study and 2 months after.	primary failure + relapse at 6months follow-up
Chowdhury SB 1993	DF	4	227	randomised: method not specified, concealment: none, open-label	SB: 10 mg/kg/day for 20 days single twice daily, 10 mg/kg/day for 10 days single twice daily, 20 mg/kg/day for 10 days single daily dose, 20 mg/kg/day for 20 days single daily dose,	INCLUDE:M&F; 13-60y; EXCLUDE:TB,pneumonia,jaundice,renal or cardiac disease,prior antileismanial Rx,Hb below 30g/l.	primary failure + relapse at 6months follow-up
Jha Milt 1999	DF	4	120	sequential groups	MF: 50mg/d x 6w, 50mg/d x 1w + 100mg/d x 3wk, 100mg/d x 4w, 100mg x 1wk + 150mgd x 3wk	M&F; 12-50y; ≥2+ splenic aspirate; EXCLUDE: pregnancy, HIV, severe disease	primary failure + relapse at 6months follow-up

Jha PM vs SB 1998	CP	4	120	randomised: computer generated, concealment: none, open-label	PM: 20 mg/kg x 21 days, 12mg/kg x 21 days, 20 mg/kg x 21 days, SB: 20 mg/kg/day x 30 days.	INCLUDE:M&F; 6-50y;+ splenic,bone marrow aspirate;EXCLUDE: pregnancy,lactation, severe disease,allergy to aminoglycosides,prior antilesihmanial Rx,refusal to come for all followups,critically ill with leishmaniasis.	final cure at 6 months followup
Karki SB 1998	DF	2	54	randomised,concealment:none,open label	SB: 20 mg/kg/day x 20 days 20 mg/kg/day x 30 days	EXCLUDE: pregnancy,cardiac and liver diseases,RF,Earlier Rx with Pentamidine,Amphotercin B,SAG	final cure at 6 months followup
Mishra AmphB vs SB 1994	CP	2	80	randomised: method not specified, concealment: none, open-label	AmpB: 0•5 mg/kg infused in 5% dextrose, 14 doses, alternate days SB: 20 mg/kg in 2 divided doses daily x 40 days	INCLUDE:+ bone marrow aspirate. EXCLUDE: patients with cardiac,renal,pulmonary or hepatic complications.	final cure at 12 months folowup.
Rijal SB 2003	NC	1	120	not applicable	SB 20 mg/kg/d x 30 d (40 d if + parasitology)	INCLUDE:parasitologically proven cases with no prior treatment with SB. EXCLUDE:patients not from neigbouring 3 districts of treatment center.	primary failure + relapse at 6months follow-up
Singh AmphB vs Milt 2006	CP	4	125	randomised: slips, concealment: none, open-label	AmpB: 1 mg/kg, cumulative dose 15mg/kg, MF: 2.5 mg/kg/day x 28 days	INCLUDE:children 1-14y,+ splenic aspirate. EXCLUDE:coexisting malaria or HIV,Bleeding disorders,incomplete course of SB	primary failure + relapse at 6months follow-up

Sundar AmBi non comp 2003	NC	1	203	not applicable	AB: 7.5mg/kg single infusion	INCLUDE:M&F all ages,+splenic,bone marrow aspirate. EXCLUDE:pregnancy,lactation,HIV+,concomittant antileishmanial Rx.	final cure at 6 months followup
Sundar AmBi single vs daily 2001	DF	2	91	randomised: computer generated, concealment: yes, open-label	AB: 5 mg/kg as single infusion, 1 mg/kg for 5 days	INCLUDE:M&F all ages,+splenic aspirate. EXCLUDE:pregnancy,lactation,HIV+,TB,bacterial pneumonia,Hb less than 40g/l.	final cure at 6 months followup
Sundar AmBi,3 regimens 2002	DF	3	84	randomised: computer generated, concealment: yes, double-blinded	AB: 3.0 mg/kg per day for 5 days (cumulative dose, 15.0 mg/kg), 1.5 mg/kg per day for 5 days (cumulative dose, 7.5 mg/kg), 0.75 mg/kg per day for 5 days (cumulative dose, 3.75 mg/kg)	INCLUDE:M&F all ages,+splenic,bone marrow aspirate. EXCLUDE:HIV+,pregnancy, lactation,IV Drug abusers	apparent cure+final cure at 6 months followup
Sundar AmphB vs Milt 2002	CP	2	398	randomised: block (3:1 ratio), concealment: none, open-label	MF: 2.5 mg/kg/day x 28 days; AmpB: 1mg/kg, 15 infusions, alternate days	INCLUDE:M&F;12yrs and older. EXCLUDE:major illness,previous AmpB Rx,pregnancy, lactation,refusal to use contraception during study and 2 months after.	primary failure + relapse at 6months follow-up
Sundar AmphB vs Par2007	CP	2	666	randomised: not specified, concealment: none, open-label	AmphB: 1 mg/kg, alternate days x 30 d PM: 11 mg/kg for 21 days	INCLUDE:M&F 5-55y,+splenic,bone marrow aspirate. EXCLUDE:pregnancy,lactation,HIV+,VL Rx during 2 wks before enrollment,hypersensitivity to aminoglycosides,prior Rx with AmphB without response,severe disease.	final cure at 6 months followup

Sundar AmphB,15d vs alt day 2007	DF	4	1485	randomised: computer generated, concealment: none, open-label	AmphB: 0.75 mg/kg,15 infusions,alternate days, 1 mg/kg,15 infusions,alternate days, 0.75 mg/kg ,15 infusions, daily, 1 mg/kg,15 infusions, daily	INCLUDE:M&F 2-65y,+splenic aspirate. EXCLUDE:pregnancy,lactation,HIV+,TB,bacterial pneumonia,Hb less than 3.5g/dl.	primary failure + relapse at 6months follow-up
Sundar AmphB,Conv vs lipid 2004	CP	2	102	randomised: computer generated, concealment: yes, open-label	AmpB: 1 mg/kg, alternate days x 30d, AB: 2 mg/kg/d x 5 d (ABLC not included in this analysis)	INCLUDE:M&F,+splenic aspirate. EXCLUDE:pregnancy,lactation,HIV+,TB,bacterial pneumonia.	final cure at 6 months followup
Sundar Milt 2003	DF	2	39	sequential groups	MF: 2.5 mg/kg/day x 28 d, 1.5 mg/kg/day x 28 d	INCLUDE:M&F 2-11y,+splenic aspirate. EXCLUDE:,HIV+,concomittant renal,hepatic,malignant,retinal& infectious disease.	relapse at 6months follow-up
Thakur AmBi vs AmphB 2001	CP	2	34	randomised: not specified (matched by age, sex), concealment: none, open-label	AB: 15 mg/kg, single dose AmpB: 1mg/kg/d x 20d	INCLUDE:M&F 12-60,+splenic aspirate. EXCLUDE:pregnancy,lactation,HIV+,TB,renal,hepatic,cardiac diseases,unable to follow protocol in all study phases.	final cure at 6 months followup
Thakur AmBi,3 regimens 1996	DF	3	30	randomised: computer generated, concealment: none, open-label	AB: 2mg/kg days 1-6 & 10 (total 14mg/kg) 2mg/kg days 1-4 & 10 (total 10mg/kg) 2mg/kg days 1, 5 & 10 (total 6mg/kg)	INCLUDE:M&F,+splenic,bone marrow aspirate. EXCLUDE:,HIV+,TB,severe disease,AmphB Rx in last 12 months,allergic to AmphB	final cure at 12 months followup

Thakur AmphB vs SB 1993	CP	2	150	randomised,method not specified.	AmpB: 1 mg/kg,starting with 0.05mg/kg,alternate days,till 20mg/kg is given SB: 20 mg/kg daily for 30 days	INCLUDE:M&F,+ splenic,bone marrow aspirate. EXCLUDE:TB,pneumonia,renal,hepatic,cardiac diseases,unable to come for monthly followup,prior VL Rx.	final cure at 6 months followup
Thakur AmphB vs SB 2004	CP	2	150	allocation not specified (matched by age, sex), concealment: none, open-label	SB: 20 mg/kg/d x 4 wks, AmpB: 1 mg/kg/d x 20 days	INCLUDE:M&F,+ splenic,bone marrow aspirate. EXCLUDE:TB,pneumonia,HIV+,diabetes, jaundice,renal,hepatic,cardiac diseases.	clinical cure+ relapse at 6months follow-up
Thakur PM vs SB 2000	CP	4	120	randomised: computer generated, concealment: yes, open-label	PM: 16mg/kg/d x 21, 20 mg/kg/d x 21d, 12mg/kg/d x 21d, SB: 20 mg/kg/d x 30d	INCLUDE:M&F; 6-50y;+ splenic,bone marrow aspirate ;EXCLUDE: pregnancy,lactation, severe disease,allergy to aminoglycosides,prior antilesihmanial Rx,refusal to come for all followups,critically ill with leishmaniasis.	final cure at 6 months followup
Thakur PM+SB vs SB 2000	CP	3	150	randomised: computer generated, concealment: none, open-label	PM12mg/kg + SB20 mg/kg daily x 21d, PM18mg/kg + SB 20 mg/kg daily x 21 d, SB: 20 mg/kg daily x 30d	INCLUDE:M&F; 6-50y;+ splenic,bone marrow aspirate ;EXCLUDE: pregnancy,lactation, severe disease,allergy to aminoglycosides,prior antilesihmanial Rx,refusal to come for all followups,critically ill with leishmaniasis.	final cure at 6 months followup

FIGURES

Figure 1. Study and patient attrition

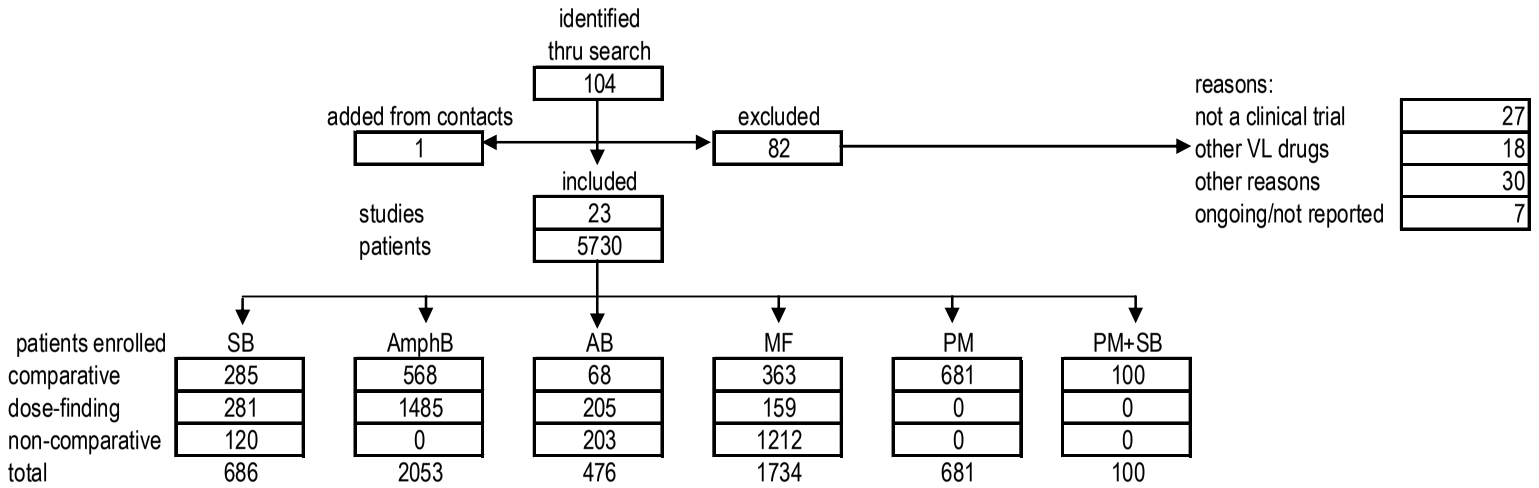


Figure 2.

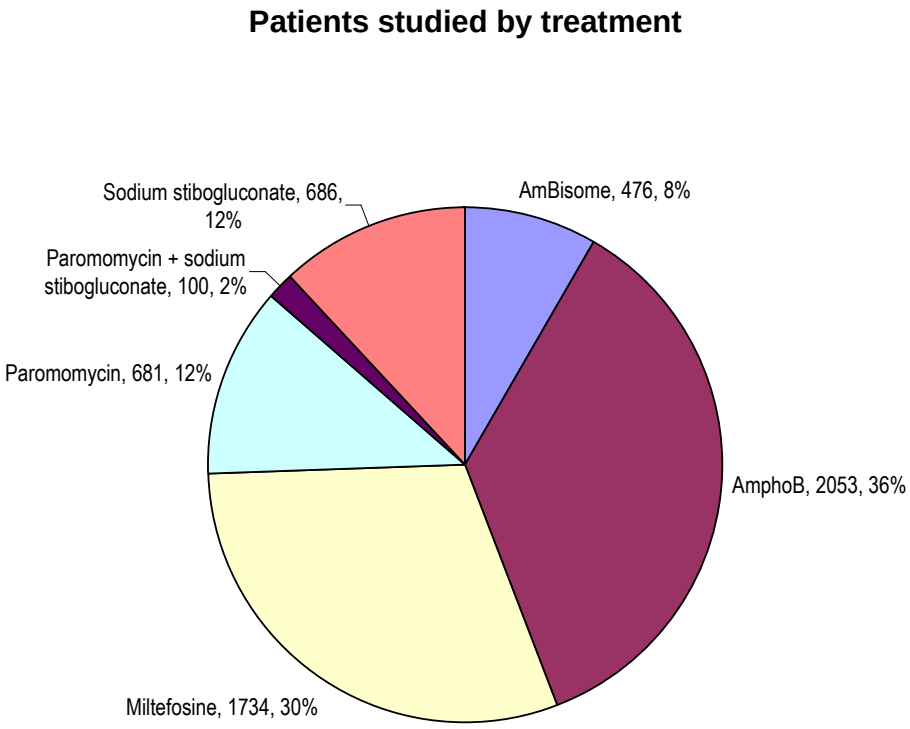

Patients studied by treatment
Sodium stibogluconate, 686, 12%
AmBisome, 476, 8%
Paromomycin + sodium stibogluconate, 100, 2%
Paromomycin, 681, 12%
AmphoB, 2053, 36%
Miltefosine, 1734, 30%

Figure 3.

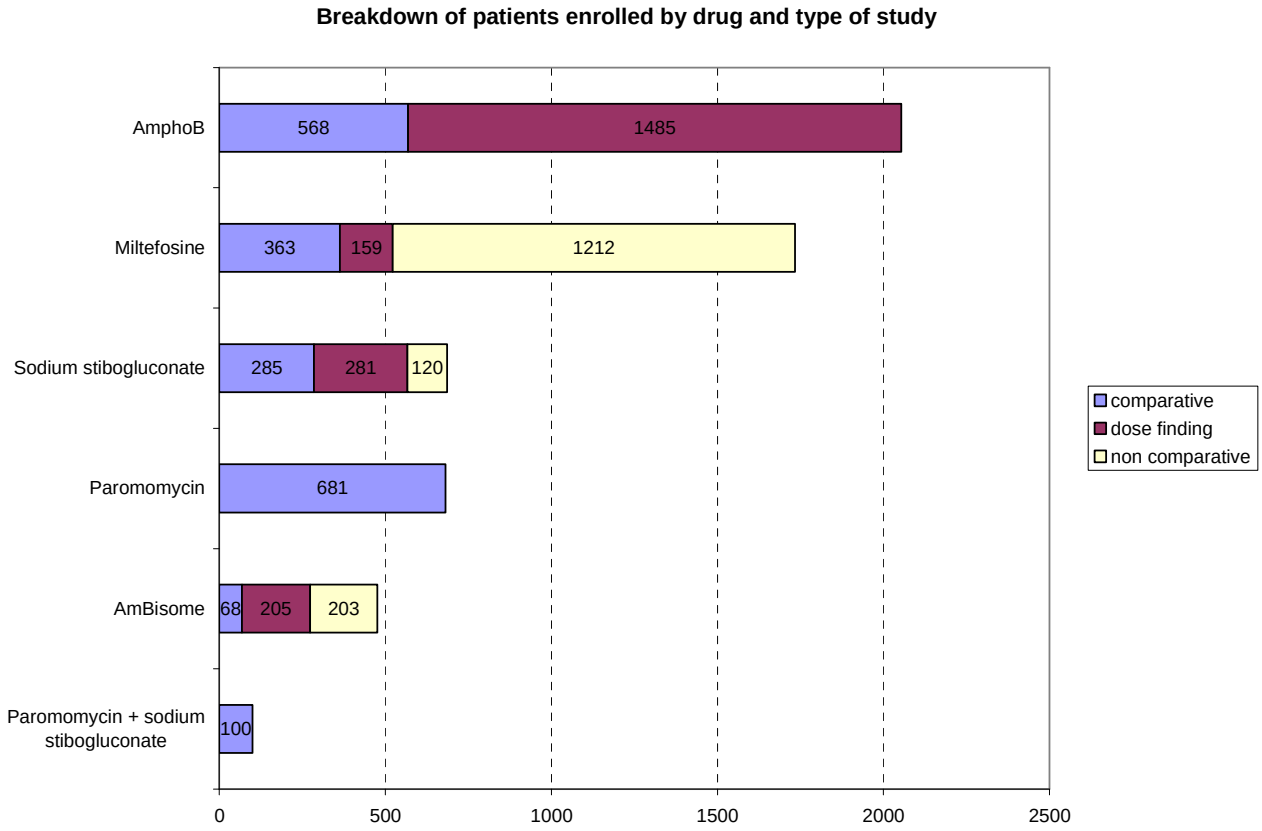
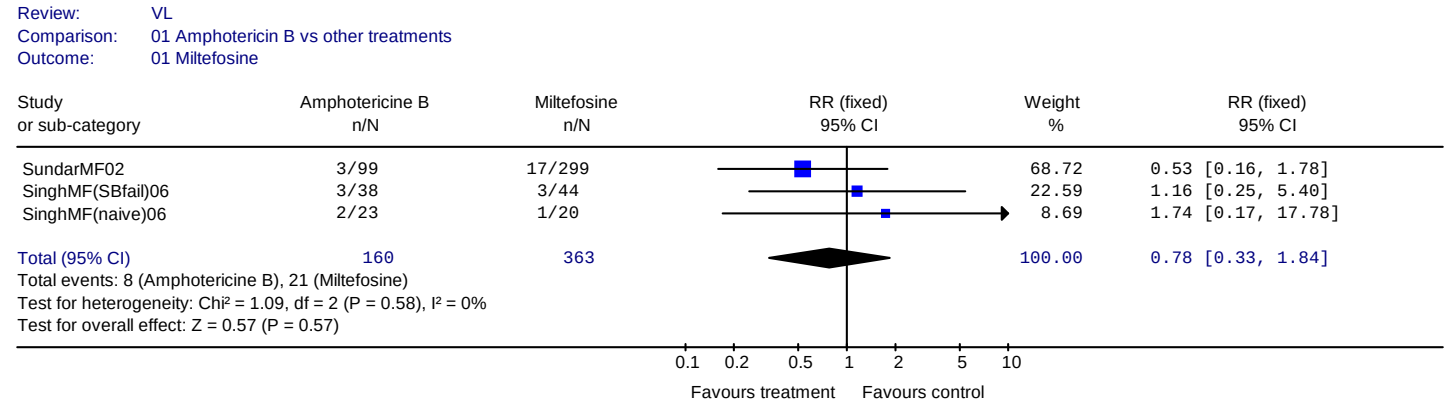
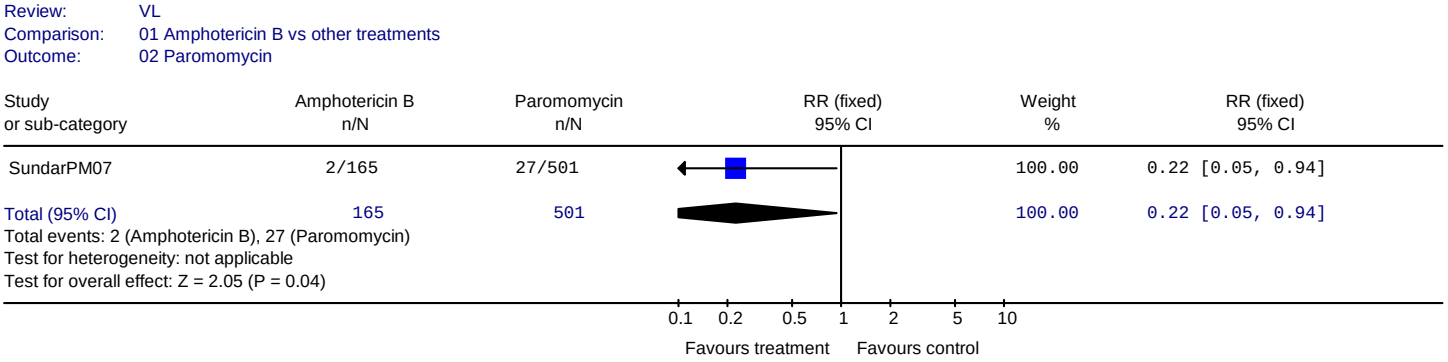
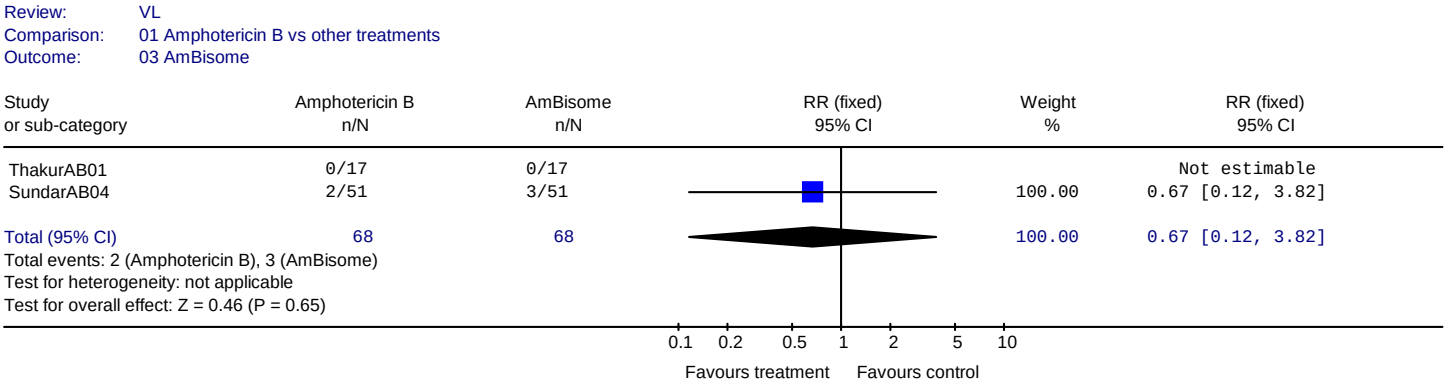

Breakdown of patients enrolled by drug and type of study
AmphoB
568
1485
Miltefosine
363
159
1212
Sodium stibogluconate
285
281
120
Paromomycin
681
AmBisome
68
205
203
Paromomycin + sodium stibogluconate
100
0
500
1000
1500
2000
2500
comparative
dose finding
non comparative

Figure 4 Funnel plots of of 6-month ITT failure rates in trials comparing Amphotericin B to other drugs with Relative Risk and 95% Confidence Intervals







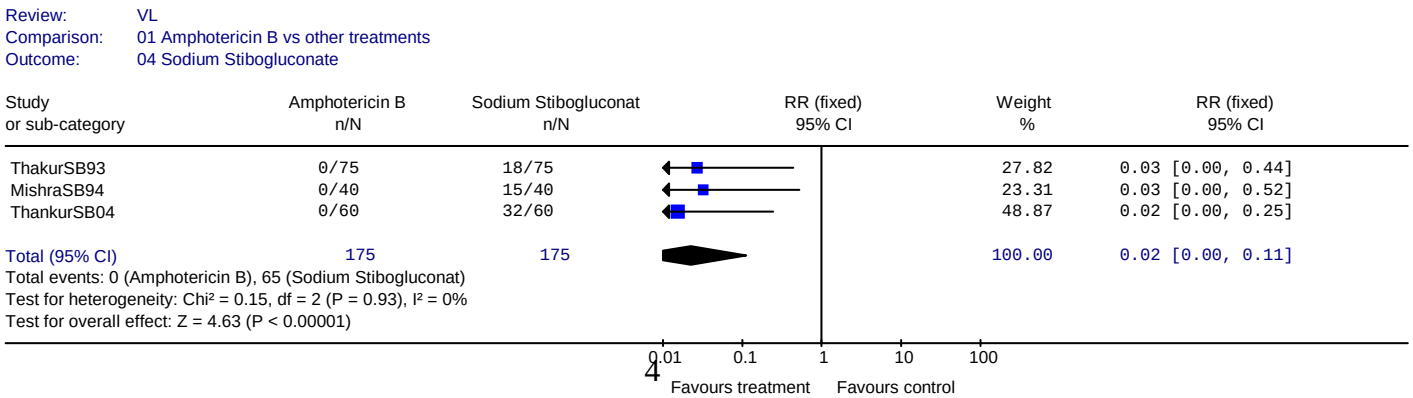


Figure 5 Cure rates after 6 months with Sodium Stibogluconate.

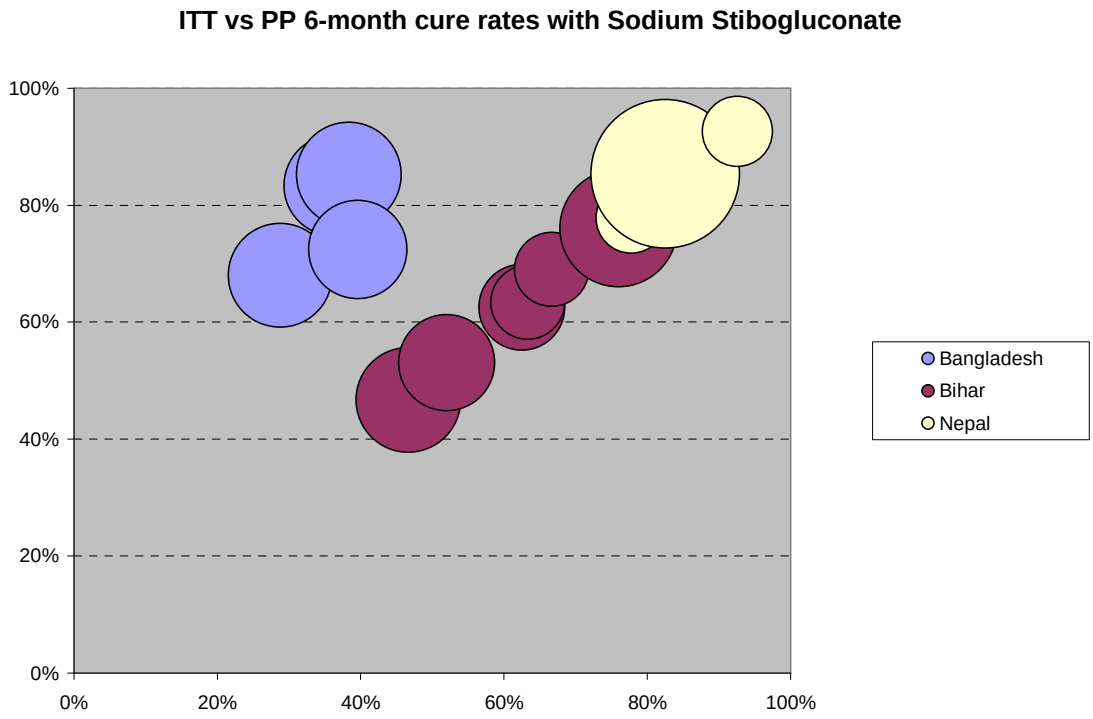


Figure 6

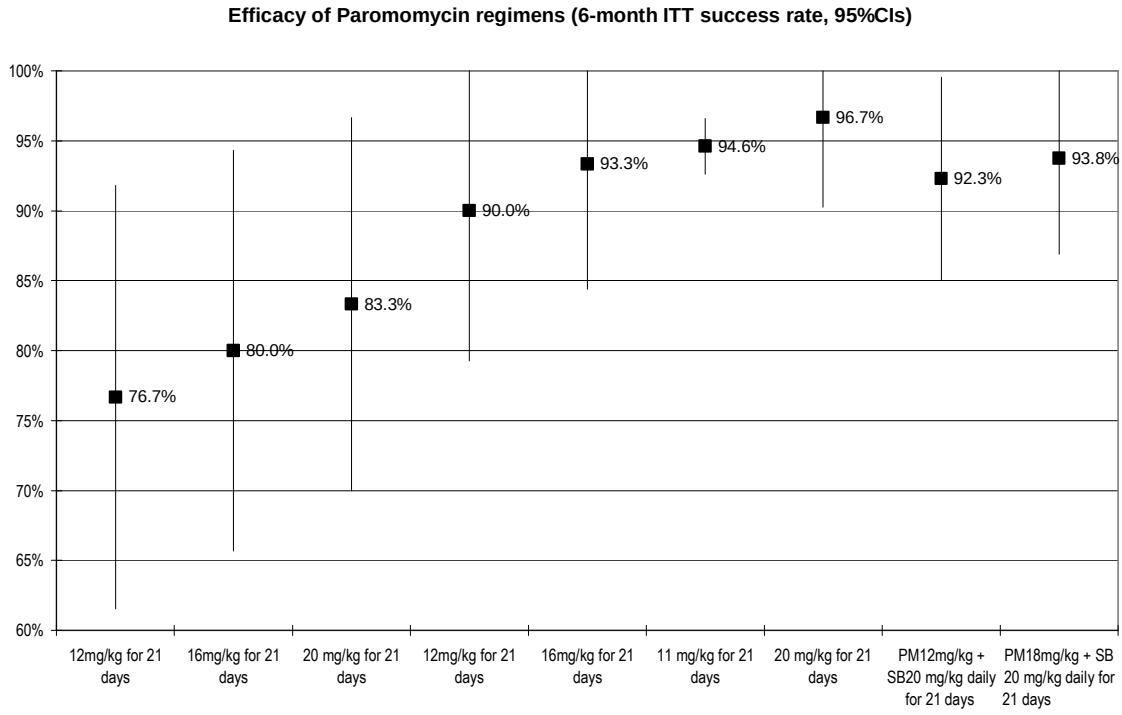

Efficacy of Paromomycin regimens (6-month ITT success rate, 95%CIs)
100%
95%
90%
85%
80%
75%
70%
65%
60%
76.7%
80.0%
83.3%
90.0%
93.3%
94.6%
96.7%
92.3%
93.8%
12mg/kg for 21 days
16mg/kg for 21 days
20 mg/kg for 21 days
12mg/kg for 21 days
16mg/kg for 21 days
11 mg/kg for 21 days
20 mg/kg for 21 days
PM12mg/kg + SB20 mg/kg daily for 21 days
PM18mg/kg + SB 20 mg/kg daily for 21 days

Figure 7 ITT vs PP: 6 Month cure rates with Miltefosine.

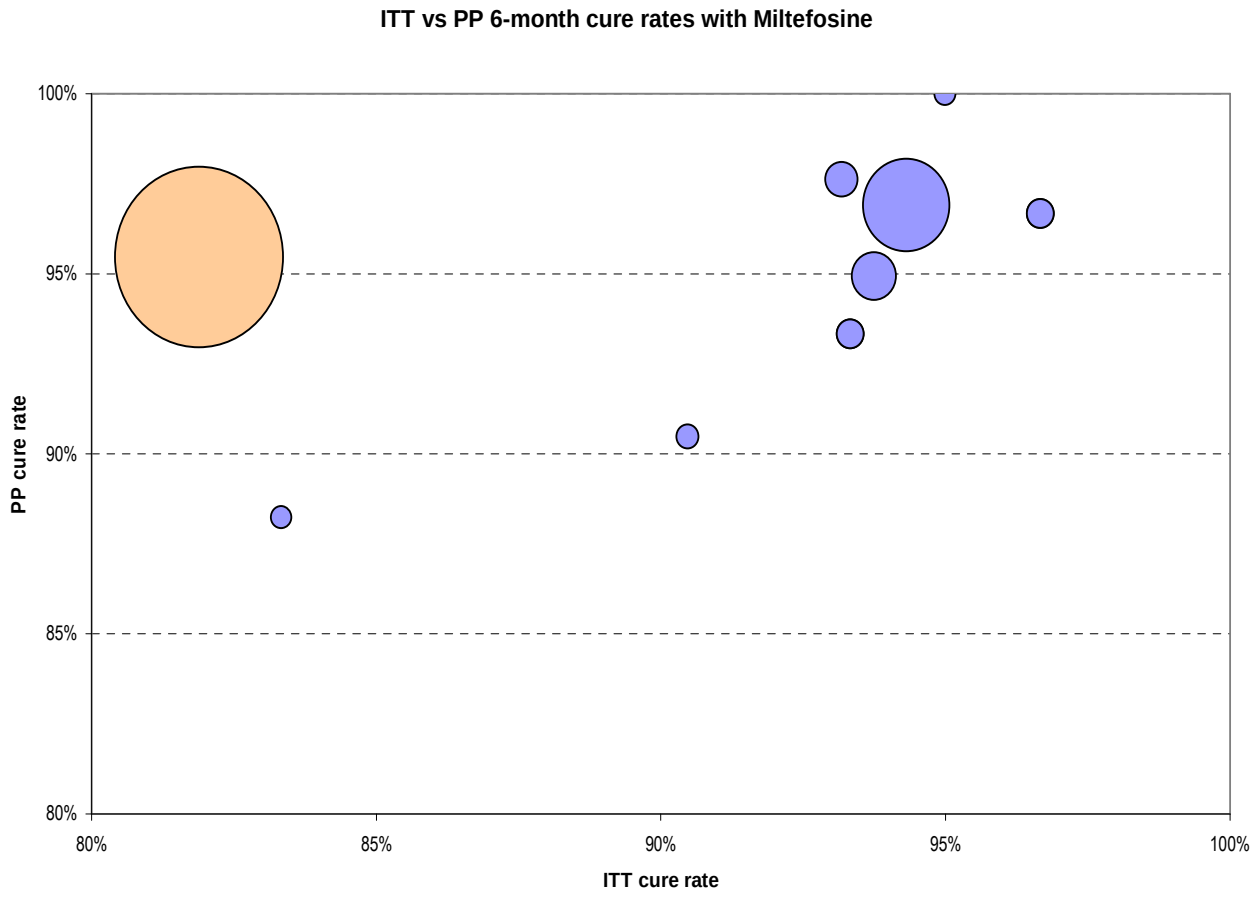


Figure 8

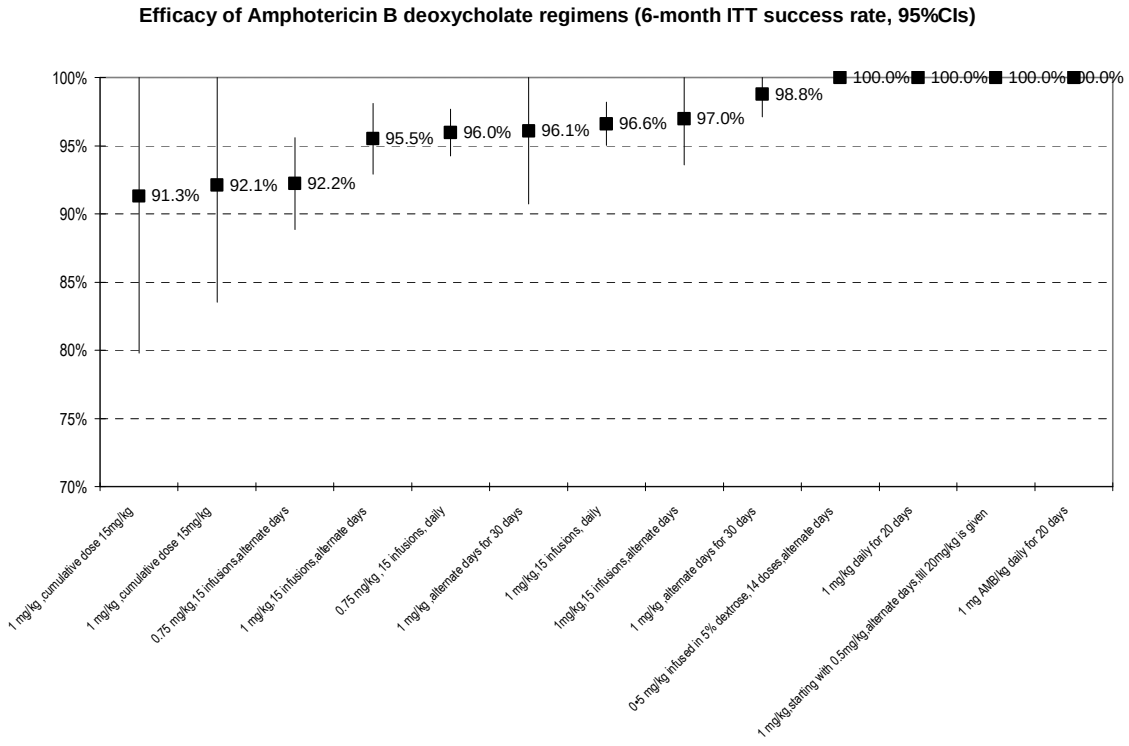

Efficacy of Amphotericin B deoxycholate regimens (6-month ITT success rate, 95%CIs)
100%
95%
90%
85%
80%
75%
70%
91.3%
92.1%
92.2%
95.5%
96.0%
96.1%
96.6%
97.0%
98.8%
100.0%
100.0%
100.0%
100.0%
1 mg/kg, cumulative dose 15mg/kg
1 mg/kg, cumulative dose 15mg/kg
0.75 mg/kg,15 infusions,alternate days
1 mg/kg,15 infusions,alternate days
0.75 mg/kg, 15 infusions, daily
1 mg/kg, alternate days for 30 days
1 mg/kg,15 infusions, daily
1mg/kg,15 infusions,alternate days
1 mg/kg, alternate days for 30 days
0-5 mg/kg infused in 5% dextrose, 14 doses,alternate days
1 mg/kg daily for 20 days
1 mg/kg,starting with 0.5mg/kg,alternate days,till 20mg/kg is given
1 mg AMB/kg daily for 20 days

Figure 9. L'Abbé plot of 6-month ITT cure rates in trials comparing Amphotericin B to other drugs

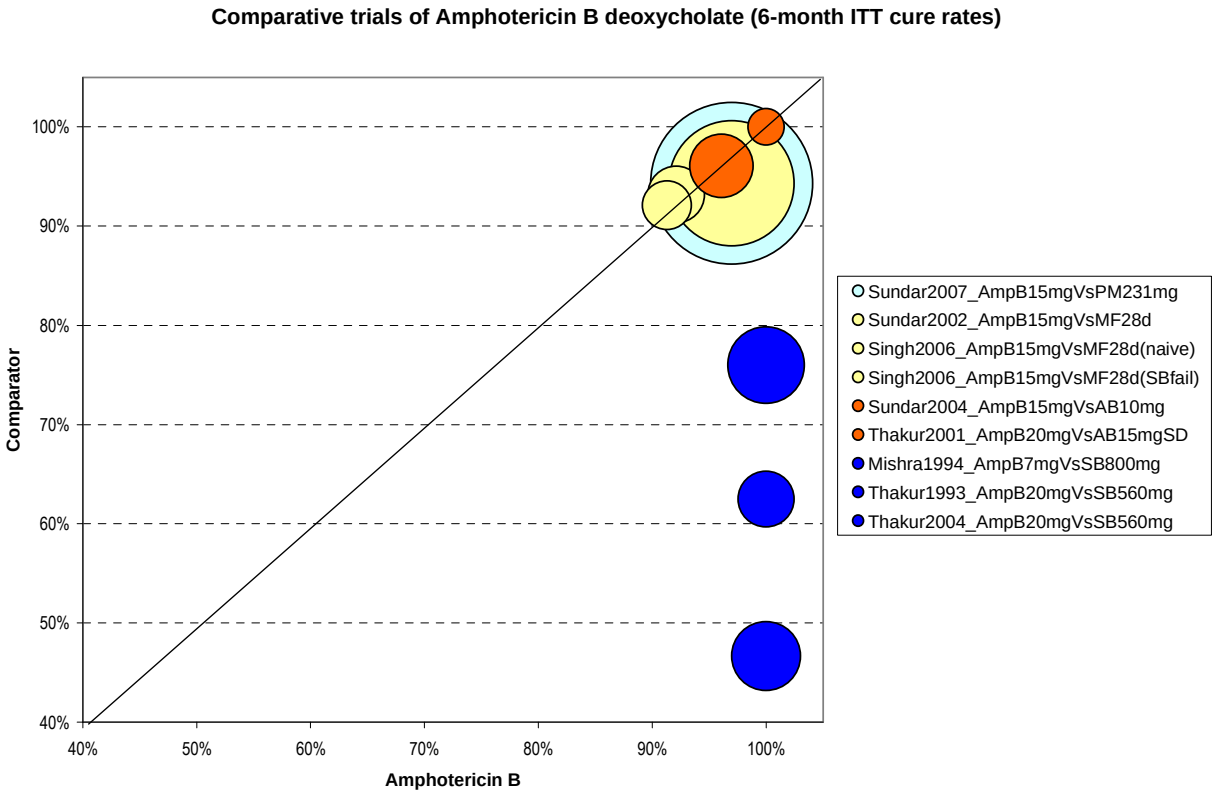


Figure 10 VL endemic regions in India. (48)

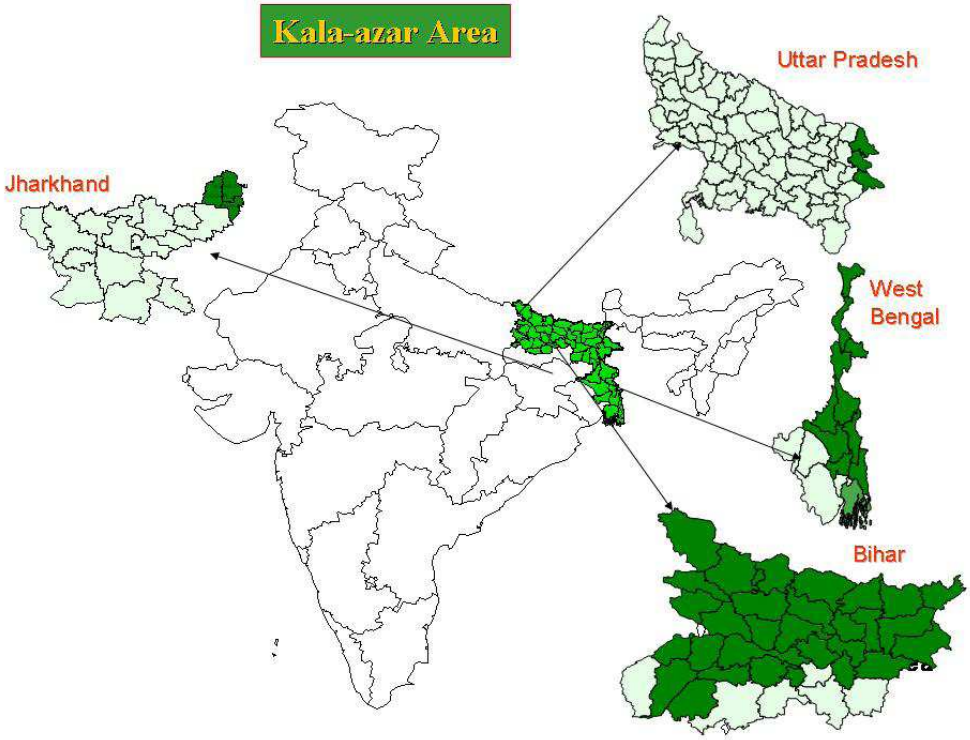


Figure 11 VL endemic regions in Bangladesh. (49)