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REVIEW ARTICLE

Barriers to treatment for visceral leishmaniasis in hyperendemic areas: India, Bangladesh, Nepal, Brazil and Sudan

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Abstract

Context: Visceral leishmaniasis (VL) is a severe and potentially fatal infection caused by the trypanosome parasite *Leishmania* sp. Over 90% of reported cases occur in India, Bangladesh, Nepal, Sudan, and Brazil, affecting mainly impoverished individuals and creating a significant economic burden through direct and indirect costs of treatment. *Objectives*: To identify the direct and indirect costs of VL treatment, compare these costs to household income, and identify the barriers to treatment in each of the five VL-endemic countries. *Methods*: Articles obtained through PubMed (US National Library of Medicine), EMBASE, and Cochrane Library were selected for relevance to VL treatment, costs for all forms of amphotericin B, miltefosine, paromomycin, and antimony compounds, and healthcare costs in India, Bangladesh, Nepal, Brazil, and Sudan. Healthcare statistics were obtained from the World Health Organization Statistical Information System, Médecins Sans Frontieres, and each country's national health ministry. *Results*: Per capita GDP, per capita GNI, cost of drugs, and hospitalization expenses differ by up to 10-fold in each of the five countries where VL is hyperendemic, resulting in unequal barriers to treatment. We found that the cost of specific drugs influences the choice of therapy. *Conclusions*: Poverty and VL treatment-related costs cause potential limitations in the provision of full and efficacious treatment, which may result in further dissemination of the disease. Effective nonparenteral antileishmania drugs would provide a significant advantage in reducing the barriers to VL treatment.

Key words: *Cost; kala-azar; patient management; treatment; visceral leishmaniasis*

Introduction

Leishmaniases are a collection of diseases of diverse clinical presentation that are caused by the interaction of various species of the protozoan genus *Leishmania,* a phlebotomine sandfly vector and reservoir hosts. The disease exhibits both zoonotic and anthroponotic cycles of transmission, with domestic dogs identified as the major nonhuman reservoir. Visceral leishmaniasis (VL) (also known as kala-azar) is the most severe form of this infection and is fatal if left untreated. According to the World Health Organization (WHO), there are approximately 500,000 new cases of VL and over 50,000 deaths from the disease per year[1]. More than 90% of reported cases occur in India, Bangladesh, Nepal, Sudan, and Brazil.

In the New World and the Mediterranean region, disease transmission is primarily zoonotic, with the domestic dog identified as the primary reservoir host. In these affected areas, most human VL cases are associated with immunocompromised patient populations and children. In Brazil, VL was traditionally known as a rural endemic, but since the 1980s, the majority of cases now originate in urban environments and the number of municipal epidemics is on the rise[2].

In south Asia and the Horn of Africa, disease transmission is mainly anthroponotic, with infected patients providing the primary reservoir for ongoing transmission

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(although close association with infected livestock may also contribute to the risk). However, epidemiological evidence from Sudan indicates that canids are playing a growing role in the transmission dynamics of VL[3], increasing the threat of infection and potential urbanization of the disease in east Africa. VL affects mainly people of the lowest socioeconomic status, which is significant given the potential economic burden of the disease in terms of both direct and indirect costs. Approximately 80% of all VL patients live on less than US$2 per day. The provision of subsidized health care in these countries ranges from emergency response treatment centers provided by organizations such as Médecins Sans Frontières (MSF) to socialized healthcare programs that cover all diagnostic and treatment costs. However, most cost of treatment analyses do not include the indirect costs of obtaining health services (such as travel costs, loss of income, costs of financing for out-of-pocket expenditures related to treatment). In this article, we have attempted to place the cost of treatment in the context of household income and identify barriers to treatment in each of the countries most affected by VL.

Drug regimens for visceral leishmaniasis

A range of treatment options for VL is available; all but one is administered parenterally. For over six decades, the primary treatment for VL involves either intravenous (IV) or intramuscular (IM) administration of pentavalent antimony (Sb^v) salts, available in two branded products and one generic form. Meglumine antimoniate (Glucantime®; Aventis Pharma, Bridgewater, NJ, USA) and sodium stibogluconate (Pentosam®; GlaxoSmithKline, Uxbridge, Middlesex, UK) have been used extensively in doses of 18–20 mg/kg daily for 21–30 days, with initial response rates exceeding 90–95%[4]. Generic sodium stibogluconate from Indian manufacturers (Albert David Ltd., Kolkata, India) has been reported to be equally efficacious but at ~14-fold lower cost[5–7].

Because of the emergence of Sb^v resistance in India, parenteral amphotericin B (AmB) is considered the first-line treatment in many areas. Four formulations of AmB are available. Treatment with the first-generation AmB formulation (AmB deoxycholate; Fungizone®) involves daily IV therapy for up to 40 days and is associated with drug-related side effects, such as nephrotoxicity and RBC hemolysis. Highly effective and less-toxic lipid-based formulations offer a shorter course of therapy (3–5 days; AmBisome®)[4]; however, the retail cost of the liposomal formulation is 30 times that of Fungizone, placing it out of reach of the majority of patients. Recent negotiations between Gilead, the manufacturer of AmBisome®, and both MSF and the WHO have secured a 10-fold price reduction for the treatment of VL with AmBisome; unfortunately, even the reduced cost of the drug is outside the means of most VL patients. Treatment of VL in developed countries is almost exclusively with liposomal AmB, illustrating the exclusion from treatment and the economic burden inflicted on VL patients in developing countries (Figure 1)[8].

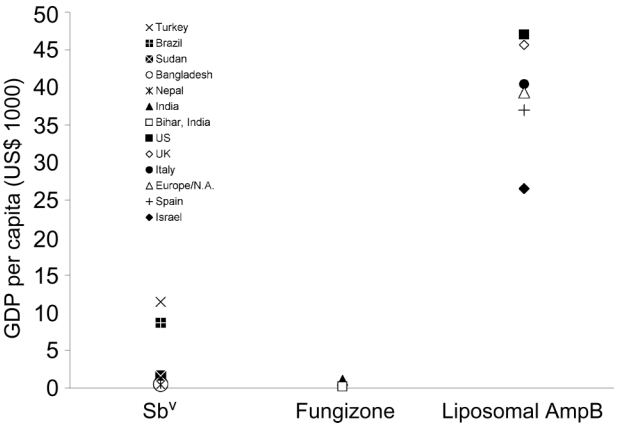

Figure 1. Per Capita GOP, GNI and costs of drugs and hospitalization expenses in five different countries for the Treatment of Visceral Leishmaniasis.

Two second-line therapies are also in use and are currently under investigation as cotherapies[9]. Pentamidine isoethionate is a general diamine antiparasitic drug that has demonstrated some efficacy against *Leishmania* sp. and was a second-line treatment for VL for over 40 years[10]. Unfortunately, the cure rate has declined from the early 1980s and clinical resistance to the drug has emerged as a primary obstacle to treatment. There is some evidence that pentamidine may be of benefit as a secondary prophylaxis in HIV/AIDS patients and current studies are underway.

Paromomycin (PM® by PharmaGland, Hyderabad, AP, India) is an aminoglycoside that exhibits efficacy against some protozoan parasites. In 2007, it was licensed in India for use as an effective, affordable, well-tolerated treatment for VL[11]. Current dosage recommendations are 11 mg/kg IM for 21 days. Adverse drug reactions include vestibular or cochlear disturbance and renal toxicity, but frequency of toxic reactions has been low (although ulceration and localized tissue damage at the site of injection are commonly observed)[12]. The drug is currently under further investigation for use against VL in Africa and India (Table 1), both as a monotherapy and in combination[11].

The only oral therapy that is currently approved for use against VL is miltefosine (Impavido®; Zentaris), a phosphorylcholine ester. Although it is affordable and

Table 1. Direct cost of medication and hospitalization for leishmaniasis in Bihar, India. WHO preferential pricing is indicated in parentheses (US$).

Characteristics	Amphotericin B deoxycholate (Sundar et al.)[14]	Liposomal amphotericin B (Sundar et al.)[14]	Miltefosine (Olliaro & Sundar)[15]		Paromomycin (Olliaro & Sundar)[15]	
Weight or patient (kg)	25	25	<25	≥25	25	
Length of hospitalization (days)	30	5	0	0	21	
Daily dosage (mg/kg)	1	2	50	100	15	
Length of treatment (days)	15 (alternate days)	5	28	28	21	
Total medication cost (US$)	49	800	75	150	5 (child)	10 (adult)
WHO preferential price (US$)	—	100	61.5	84.5	—	—
Total hospitalization cost (US$)	368	72	0	0	264	
Total treatment cost (US$)	417	872 (172)	75 (61)	150 (84.5)	269	274
% of Bihar GNI (31.8% of national per capita GNI)	138	288.65 (56.94)	24.83 (20.19)	49.65 (27.97)	89.04	90.70

reasonably well tolerated with mild to moderate gastrointestinal side effects, miltefosine has been shown to be teratogenic in animals and cannot be used in women at risk of pregnancy. The high oral bioavailability of this drug has been referred to as a paradoxical blessing and drawback—it can be used widely on an outpatient basis, which improves access but also exposes the drug to misuse and elevates the risk of developing resistant strains of VL[13]. As the half-life of miltefosine is prolonged (150–200 hours) and drug resistance is easily induced in vitro, directly observed therapy is recommended to both protect female patients of childbearing age and provide some degree of protection against the development of miltefosine-resistant strains of *Leishmania*.

Reports on the drug selection and cost of treatment of VL from the various VL-endemic regions are inconsistent and incomplete, making it difficult to assess the financial barriers to treatment. In this article, we have endeavored to summarize the available information regarding the cost of the prevalent drug treatment regimen by quantifying the cost of the drug as well as nondrug-related costs of treatment. By documenting the treatment expenses from the five primary countries with respect to the income level of the affected population, we are better able to identify the obstacles that prevent effective VL outcomes. In addition, we have tried to highlight the differences in treatment costs and thus the potential challenges each country faces in treating VL.

Cost of leishmaniasis treatment in India (Bihar region)

The state of Bihar in northern India carries the largest population of VL patients in the world, the majority of which are now infected with antimony-resistant *Leishmania.* With the removal of pentavalent antimonials from the drug arsenal, treatment with AmB has emerged as the first-line therapy. A 30-day IV course of treatment with first-generation AmB (Fungizone®) at 1 mg/kg every second day has an associated drug cost of US$49 ($6.50 per 50 mg vial; pricing is based on a 25 kg patient). Hospitalization, laboratory test, and treatment costs are estimated to be US$368[14]. Liposomal AmB (AmBisome®) retails at US$200, but with the MSF and WHO price reductions, the drug cost drops to US$20 per 50 mg vial. Recent studies indicate a short course of AmBisome® (daily for 5 days) at 2 mg/kg treatment yields significant efficacy and has an associated drug cost of US$100[15]. Combined with hospitalization and laboratory costs for a 5-day treatment (US$72), the total per-patient cost of AmB therapy is estimated to be ~US$417 for Fungizone and ~US$172 for AmBisome. However, Bihar region occupies the lowest position in the per capita income table for India, with individuals earning an annual income of US$142 (India Central Statistics Organisation report, 2005–2006); therefore, a 5-day course of AmBisome treatment would cost an individual the equivalent of more than 1 year's salary. There is little in the way of public funding for treatment, and many patients are referred to 'private' clinics, where the cost of treatment is borne entirely by the patient (Table 2).

Miltefosine is also in use for the treatment of VL in Bihar region. On the private market, the current cost of miltefosine is US$75 (patients <25 kg) or US$150 (patients ≥25 kg). WHO has negotiated preferential pricing for miltefosine treatment of VL in India (US$61.53 for patients <25kg and US$84.54 for patients ≥25 kg). Volume discounts are also available (US$63.8 and US$71.74, respectively) if more than 75,000 packs are ordered[15]. However, if patients have the opportunity, they will purchase less than a full course of medicine, which leads to the spread of resistance[16].

Paromomycin is administered as an IM injection at a dose of 15 mg/kg/day for 21 days (375 mg/day for 15

Table 2. Cost of Visceral leishmaniasis patient management in India (after Meheus et al.[17].

Category	Costs from the societal perspective (US$)	%	Costs from the household perspective (US$)	%
Medical costs				
Consulation fees	—	—	3.92	2
Accommodation costs (i.e., personnel costs, overhead costs, infrastructure)	63.04	18	—	
Investigations (diagnostic, laboratory tests)	62.21	18	4.15	2
Medicines				
Amphotericin B deoxycholate	49.77	14	49.77	23
Other drugs (miscellaneous, i.e., antibiotics, aspirin)	4.00	1	—	
Medical supplies	16.59	5	—	
Total medical costs	195.61	55	57.84	27
Nonmedical costs Transportation costs	10.60	3	10.60	5
Food costs	21.89	6	21.89	10
Total nonmedical costs	32.49	9	32.49	15
Indirect costs				
Loss of income to the patient	101.38	29	101.38	46
Loss of income to the attendant	20.74	5	20.74	10
Monthly interest on loans	4.61	1	4.61	2
Total indirect costs	126.73	36	126.73	59
Total Cost	354.83	100	217.06	100
% of per capita GNI (US$950)	37.35		22.85	

days; 7875 mg in total[12]). At a total drug cost of $10 for the entire treatment, it is an economically viable option, but the cost of hospitalization and loss of income deter from its attractive price point.

In addition to the cost of drug and associated treatment, hospitalization, and laboratory testing, there are nonmedical costs that provide barriers to the availability of treatment. Nonmedical costs include transportation, food, monthly interest payment on loans, and loss of income for both the patient and the requisite caregiver (hospitalization costs in India are for the bed only; patients are required to supply their own caregivers, food, linens, etc.)[15,17]. Families surveyed were using available cash/savings, selling assets, renting land, or taking loans to pay for treatment[17].

Cost of leishmaniasis treatment in Bangladesh

Bangladesh is the home of the first described case of VL. From 1824 onwards, historical records describe the classical picture of VL and detail the development of progressive emaciation, prolonged irregular fever, and enlargement of the hepato- and splenomegaly. The disease spread to other parts of Bengal throughout the 1800s, moving westward into Bihar in 1872[18]. As VL in Bangladesh is anthroponotic, living in proximity to another individual with VL is the highest risk factor for disease transmission. The Bangladesh national guidelines for the treatment of VL recommend Sb^v at 20 mg/kg IM for 20 days as the first-line treatment; second-line treatments are rarely available. Since 2000, endemic districts in Bangladesh have experienced severe shortages of Sb^v. The official price of an adult course of Sb^v is US$20; however, in 2002, market prices up to 3 times higher were observed[19]. Data from a 2006 survey on the economic impact of VL in Bangladesh estimated the median direct expenditure for treatment to be US$87[18] (Table 3). This figure encompasses costs for provider expenses (consultation and diagnostic fees, supplemental medications), drug costs, informal payments, and miscellaneous costs related to food, transport, and patient comfort. The long- and short-term costs of VL to a household (which often include traditional healer consultation and local village 'doctor' visits prior to

Table 3. Direct costs of visceral leishmaniasis treatment in Bangladesh (after Sharma et al.[20].

Type of expenditure	Median cost US$ (range)
Provider charges	23 (1–206)
Sodium antimony gluconate treatment (SAG purchase cost plus injection charges)	28 (1–96)
Informal payments	2 (0–37)
Miscellaneous costs	23 (4–386)
Monthly household income <US$70	84 (21–386)
Monthly household income >US$70	91 (25–690)
% of GNI for Bangladesh (US$470)	5.32–146.81

diagnostic confirmation at a private clinic or hospital as well as loss of income) are estimated to be US$85–500 (5000–30,000 Taka)[19]. Households had to borrow money (median of US$53) or sell (rent) land and animals to collect money for diagnosis and treatment[20].

Cost of leishmaniasis treatment in Brazil

In Brazil, leishmaniasis is a notifiable disease. For more than 40 years, the Brazilian control program has been based on the provision of free delivery of specific drug therapy, culling of seropositive dogs, and vector control. However, despite these control strategies, a marked increase in the incidence of VL in Brazil had occurred over the last few decades[21,22]. From 1980 to 2003, a total of 51,222 cases were officially notified (Brasil Ministerio da Saude)[23]. The geographic spread and increased urbanization of VL sets it apart from other endemic countries, where the disease is largely associated with rural populations. The first-line treatment for Brazilian VL is pentavalent antimony. Glucantime® is commercially available in Brazil in 5 mL vials containing 405 mg Sb^v, with the recommended treatment of 20 mg/kg/day IV or IM for 20 days (maximum treatment is 40 days). The cost of a sufficient course of treatment is US$189.60 (Table 4)[23,24].

For patients over 50 years of age, or those diagnosed with cardiac complications, kidney or liver disease, or in patients positive for Chagas disease, the use of second-line therapies are indicated by the Brazilian Health Ministry. These include IV liposomal, colloidal or deoxycholate formulations of amphotericin B, pentamidine, and immunomodulators (interferon or granulocyte macrophage colony stimulating factor), although the latter two treatments are currently under investigation and not in common use. Recommended dosage for AmB deoxycholate (Fungizone®) is 1 mg/kg/day for 14 consecutive days (cost for a 70 kg patient would be US$228.73). Although AmBisome® is regarded as superior to other AmB formulations because of the reduction in renal toxicity, the excessive cost limits its use to patients who are either Sb^v-resistant, in end-stage VL, or exhibiting renal insufficiency or cardiac toxicity. For these patients, AmBisome® is used at a recommended dose of 3 mg/kg/day for 7 days. A course of treatment with Amphocil® is 30% less costly, but the risk of renal complications is significantly higher than with AmBisome®[24].

In Brazil, poverty plays a significant role in disease transmission through lack of education, presence of poor housing conditions, lack of sanitation, and proximity to refuse, vermin, and livestock. Elimination of infected canines alone may not decrease the incidence of serological conversion, as humans provide a substantial reservoir for the perpetuation of the disease[25]. Despite free treatment being provided through the public health system, Brazilians suffer disproportionately from neglected tropical diseases[26]. Brazil has one of the greatest disparities between wealthy and poor people anywhere in the world, and this disparity creates a situation whereby the treatment is available, but the information, education, and resources required to access medical care are lacking[27].

Cost of leishmaniasis treatment in Nepal

At present, VL in Nepal is confined to the 12 southeastern districts that border the Bihar state in India. For the last three decades, the Government of Nepal has had VL control programs in place[28]. The primary treatment for VL in Nepal is sodium antimony gluconate. Diagnosis, drugs, and treatment services are provided free of charge in public hospitals. In some circumstances (i.e., shortage of medicines in public hospitals or absence of laboratory technicians), patients have to rely on private institutions, further increasing the burden of treatment. Despite the free treatment services provided by public hospitals, one of the largest contributors to the cost of care is medical costs not covered by the public system[29]. The cost of VL treatment has a catastrophic impact on

Table 4. Drug and hospital costs of government-provided visceral leishmaniasis treatment in Brazil (US$).

Drug	Unit	Daily cost (Amato et al.)[24]	Treatment (Brazil Ministeria da Saude)[23]	Total drug cost	Tertiary Hospital costs (UN 2005)	Total cost
Pentavalent Antimonial	1 ampole = 5 ml of 85 mg/ml Sb	6.32	20 mg/kg/day; max 30 days	189.60	3302.40	3492.00
Amphotericin B deoxycholate (Fungizone)	1 ampole = 50 mg	11.67	1 mg/kg/day; 14 days	163.38	1541.12	1704.50
Liposomal amphotericin B (AmBisome)	1 ampole = 50 mg	205.00	2 mg/kg/day; 7 days	3444.00	770.56	4214.56
Colloidal dispersion of amphotericin B (Amphocil)	1 ampole = 50 mg	139.00	2 mg/kg/day; 7 days	2335.20	770.56	3105.76

Table 5. Direct and indirect costs of visceral leishmaniasis treatment in Nepal.

Direct costs		Healthcare costs	Other costs	Both costs
First-line care	Mean (US$)	28.28	3.32	31.60
	Median (US$)	8.34 (2.78–51.56)	1.6 (0.56–4.72)	9.87 (3.51–54.14)
Referral-level care	Mean (US$)	9.52	18.74	28.26
	Median (US$)	4.17 (1.5–6.34)	19.59 (7.54–24.36)	22.86 (12.32–28.44)
Subtotal	Mean (US$)	37.80	22.06	59.86
	Median (US$)	10.11 (6.34–56.94)	21.61 (9.97–24.64)	29.19 (26.69–82.17)
Indirect costs				
			Mean (US$)	58.73
			Median (US$)	39.96 (15.12–94.87)
Total costs				
			Mean (US$)	113.64
			Median (US$)	84.41 (50.09–139.50)

Source: Rijal et al.[29]

households, consuming approximately 17.5% of average annual household income[30]. The average total direct cost of kala-azar episode treatment was US$95.62 (7076 NPRs). This includes supply of services costs, costs incurred before diagnosis, and frequent lack of public resources (i.e., the absence of a technician, shortages of IV sets, fluids, food, travel). The total indirect costs for the household, such as loss of income, are US$147.43 (10,910 NPRs), for a total cost per household of US$243.05 (17,986 NPRs). Over 80% of households surveyed had borrowed money to pay for treatment, with an average debt load of US$87.32 (6462 NPRs[30]).

In the 2009 survey, the average annual per capita income was reported to be US$83.20 (6157 NPRs). Cost of disease changes this variable and after deducting medical costs, medical and travel costs, and total direct costs, the average post-payment per capita income is US$19.59 (1450 NPRs), US$11.07 (819 NPRs), and US$ –12.42 (–918.83 NPRs), respectively[30].

Survey performed by Rijal et al. estimated the median annual per capita household income to be US$81.07, whereas the total cost incurred by patients was on average US$113.64 (patients treated with 20 mg/kg/day sodium stibogluconate). Indirect costs are estimated on loss of earnings for days lost because of illness or to being a caretaker (Table 5)[31].

Cost of leishmaniasis treatment in Sudan

For the last 50 years or so, VL has been a major health problem in northeastern and southern Sudan, and by 1984, VL reached epidemic proportions. Health coverage in this country is so minimal that some patients must walk for several days to obtain the most basic of services[32]. Ongoing civil war and unrest have had a devastating effect on healthcare delivery; however, a Comprehensive Peace Agreement between northern and southern Sudan was signed in 2005[32]. Survey data from three VL endemic regions indicated that the majority of the population-at-risk is from subsistence farming households, where disposable income is almost nonexistent. Almost 90% of the interviewed heads of households had no formal education, and the knowledge of VL was minimal. Treatment options are limited, with some private health clinics or aid organizations offering assistance. Before receiving professional care, patients would seek out traditional remedies, followed by self-treatment with basic drugs bought on local markets.

The recommended treatment in Western Upper Nile region of Sudan is Sb^{v}[5]. In the MSF program, Pentosam® (sodium stibogluconate) is used as first-line treatment[33]. Patients from Sudan prefer the MSF facilities, as treatment provided is free. However, as most are subsistence farmers and over 60% of households do not have any means of transport, even the cost of travel to a clinic may be a sufficient barrier to treatment. In the dry season, the median cost to reach the closest health facility by public transport is US$1.12 (290 SDD)[34]; private transport is 2–3 times higher. There is no public transport during rainy season and patients must either walk to the nearest health unit or hire private transport[34]. The lack of healthcare access causes delays in appropriate diagnosis and treatment leading to increase in morbidity and mortality[35].

Conclusions and next steps

Despite the significant differences in per capita GDP, household income, and the cost of treatment in each of the five countries examined, some similarities exist in the form of common barriers to treatment. Regardless of country, the majority of VL patients suffer from poverty

and lack of education, leading to delays in treatment resulting in further dissemination of the disease. Travel costs for many are prohibitive and proximity to medical centers influences the decision to seek treatment. As the majority of drug regimes are parenteral, the need for the presence of a caregiver for the duration of treatment is also recognized as a significant cost.

Educational programs and the availability of an affordable oral VL therapy would alleviate a significant number of barriers. Miltefosine represents a fundamental advance in VL therapy, as it is a novel chemical entity as well as the first oral agent against VL[36]. Miltefosine had a 95–97% final cure rate in large phase III and IV trials in India[37]. However, its teratogenic potential and long half-life are significant drawbacks. With a half-life of 150–200 hours, the risk of resistant parasite emergence is significantly elevated[38]. Gastrointestinal side effects and mild-moderate elevations in liver enzyme levels are frequent, and the drug is contraindicated in women of childbearing age, necessitating direct observed therapy[39]. Advances in drug discovery have resulted in a number of promising leads, but many have failed to produce the efficacy required to move forward to clinical trials. The reformulation of amphotericin B for oral administration shows significant efficacy against VL in a mouse model with no evidence of toxicity[40]. This reformulation of AmB provides a promising lead in the development of effective, affordable oral antileishmanial treatments for VL[41].

Thus, a strategy of 'one size fits all' does not apply when it comes to treating VL. We need to recognize this and work with governments and healthcare professionals in these countries to address their specific needs. This is a multifaceted problem that encompasses many barriers. The current failure in providing treatments for neglected global diseases, such as VL, is due to the fact that medicines have not been discovered or adequately developed to treat these diseases and those that are discovered and developed in research laboratories are not actually reaching the people in need. The reasons for this comprise a multifaceted set of issues ranging from a lack of funding to perform and deliver the outcomes of neglected disease research to the poor understanding of the diseases, target populations, and underlying socioeconomic and political issues, and involve all stakeholders (i.e., from the researchers who discover and develop the medicines to the personnel in the target communities who deliver and administer these interventions).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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