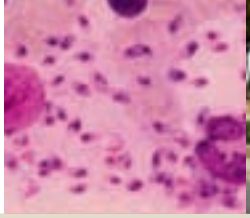


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DND*i*'s *outlook*

Drugs for Neglected Diseases *Initiative*

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For Visceral Leishmaniasis, drug supply and cost remain a major barrier to access to treatments

VL affects the most impoverished and neglected populations, inexorably leading to further destitution and death

VL is estimated to affect approximately 500,000 people and kills over 50,000[1]. The disease is fatal, if left untreated, and among parasitic diseases only malaria is more deadly[2]. Most cases (>90%) occur in just six countries: Bangladesh, India, Nepal, Sudan, Ethiopia and Brazil. Half of patients worldwide live in the Indian state of Bihar[3], one of the poorest states of India. Two thirds of VL cases occur in the Indian subcontinent where northeast India borders Bangladesh and Nepal. The second largest focus is East Africa, which is also an epidemic-prone region[1].

VL is transmitted by the sandfly, and in Africa and Asia usually affects the most impoverished people living in small clusters in areas with poor access to health services. This vector-borne disease is linked to poor housing, as shown in the Indian subcontinent. Households often sell their assets and take loans to pay for health care and expensive drugs, leading to further impoverishment as demonstrated in studies from Nepal and India[4,5,6,7,8,9]. The social and economic impact of VL in affected communities is profound, and treatment and vector control measures for such a deadly disease need to be subsidized or provided free to most households living in VL-affected areas.

There is some political commitment to support the present VL elimination initiative in the Indian subcontinent. Early diagnosis and treatment are essential for both individual patients and the community, as untreated VL patients act as a reservoir for parasites and contribute to disease transmission in anthroponotic VL areas in South Asia and East Africa[1].

In the past 10 years, remarkable progress led to new chemotherapies

The old established treatment for VL has been based on pentavalent antimonial drugs, such as sodium stibogluconate (Pentostam®, GSK) and generic sodium stibogluconate (SSG, Albert David, India) or meglumine antimoniate (Glucantime®, Sanofi-Aventis). They are given intramuscularly or intravenously for four weeks and have some associated adverse events. Antimonials are no longer effective in Bihar, India, where they cure less than 50% of the patients[10]. This has led to the recommendation and use of amphotericin B as an alternative treatment in India. This treatment has some associated toxicity, is difficult to administer in the field and is expensive. Progress has been made in the past 10 years with the availability of

KEY ISSUES

→ VL affects the most impoverished living in the most remote areas, inexorably leading to further destitution and death; if not treated, the disease mortality is 100%

→ New cost-effective treatments have been developed for the management of VL in East Africa & South Asia

→ These treatments offer excellent efficacy and safety; however, they remain unaffordable to the individual patient

→ Cost projections on drug costs for these new treatments show that they are affordable for governments and donors, provided that manufacturers make a further commitment to preferential pricing

→ Changes in drug pricing could significantly improve affordability; by offering better preferential pricing, manufacturers can play a fundamental role in making control activities affordable

→ The total drug cost to treat 100,000 VL patients with new treatments amounts to less than US$ 8 million per year

rapid diagnostic tests and new chemotherapies: liposomal amphotericin B (L-AmB, Gilead, US), miltefosine (MF; Impavido®, Paladin, Canada) and paromomycin (PM; Gland Pharma, India & iOWH). Each drug has significant limitations, including lack of compliance (miltefosine is a 28-day long treatment), poor feasibility (paromomycin requires 21 days of injection; AmBisome® requires an intravenous infusion), toxicity (miltefosine is teratogenic) and high cost. Furthermore, parasite resistance can be induced experimentally to both miltefosine and paromomycin[11] and is expected to emerge naturally if optimal adherence cannot be ensured[12]. Combination therapy is a possible strategy to delay the occurrence of resistance and has successfully been used to prevent resistance to malaria and TB drugs[13].

In the last 12 months, significant breakthroughs have been made in the management of VL. In a study by Sundar and colleagues, a single dose of 10mg/kg of AmBisome® was demonstrated to be safe, with 95% efficacy in India. As a single dose treatment, compliance to this treatment is expected to be 100%[14]. Recently, DND*i* successfully completed two pivotal phase III clinical trials. The VL COMBO0-07 trial in India involved 627 patients and tested the following combinations: miltefosine and paromomycin both for 10 days, single dose (5mg/kg) AmBisome® and miltefosine for 7 days and single dose (5mg/kg) AmBisome® and paromomycin for 10 days. All these combinations were demonstrated to be very safe and efficacious (>97.5%). The LEAP 0104 study in East Africa showed that a combination of SSG and paromomycin is as safe and effective as SSG alone with the clear benefit of reducing treatment time from 30 to 17 days, increasing patient turnover (particularly useful in epidemic situations) and reducing costs.

In anthroponotic areas of transmission such as India, Nepal and Bangladesh, treatment of cases is an important tool, together with vector control, to help achieve VL elimination targets set by the VL elimination programme. The objective is to lower the number of VL cases in endemic areas to under 1 case per 10,000 people. The new treatment modalities developed (combination treatments, single dose AmBisome®) could play an extremely important role in meeting that target through the following:

> Shift away from older, toxic and less cost-effective monotherapy regimens involving SSG and amphotericin B
> Promote patients' health-seeking behavior and increased confidence in the public sector through the use of more effective and feasible treatment regimens
> Therefore, improve the likelihood that elimination targets set could be achieved

As no new compound is expected in the near future to treat VL, there is an immediate need for strategies:

1. Improving the compliance to treatment
2. Practical in the field
3. Highly cost-effective
4. Delaying or preventing the emergence of resistance

Today these new treatment strategies can be implemented and need to be made widely available to patients in order to have a significant impact. This is an urgent priority and requires an increased and sustained commitment from all implementing and funding partners.

Cost-effective treatments exist but the supply and cost of drugs remain a major barrier for their implementation

A study from Meheus and colleagues evaluated the cost-effectiveness of various monotherapies and combination VL treatment strategies in the Indian subcontinent. **With a cost of US$ 91 per death averted, the combination of miltefosine with paromomycin for 10 days appeared the most cost-effective because of its high effectiveness and low cost — US$ 72.9 per patient treated** (cost inclusive of drug cost, other direct medical cost such as contraceptives, administration, etc., as well as non-medical and indirect cost).

While treatment regimens including L-AmB were found to be highly effective, the preferential drug price of US$ 20 per vial in 2008 resulted in a higher average cost-effectiveness[15]. Moreover, L-AmB requires a cold chain and the cost per patient treated and per death averted may have been under-estimated as the cost of the cold chain was not included.

Over the years, Gilead made substantial efforts to lower the price of AmBisome®, offering today a preferential price of US$ 18/vial to treat VL patients in the public sector. However, although more affordable, this price is still too high for L-AmB-containing treatments to be cost-effective or to be made widely available. The total cost of a single infusion of 10mg/kg for a 35-kg patient in Bihar was US$ 162 in 2008 (US$ 140 for the drug plus US$ 22 for 1 day of in-hospital care) while outpatient treatment cost US$ 148 at a US$ 20 AmBisome® vial price[14].

Meheus study results show that **to be cost-effective in India, a vial of L-AmB needs to be priced at or below US$ 13 in a combination therapy with paromomycin, and US$ 10 for a 10mg/kg single dose L-AmB treatment.**

Miltefosine can be ordered through WHO at a preferential price of US$ 79 per pack of 56 50-mg capsules or US$ 1.41 per capsule for use in the public sector[15] (the comparative market price was US$ 2.68 per capsule). Miltefosine was sold to Paladin in 2008; ensuring long-term availability of this treatment at a preferential price for VL patients in the public sector is paramount. In addition, there is a single manufacturer of paromomycin, and agreeing on a back-up supply strategy is critical in the event of problems in supply. Paromomycin is priced at US$ 0.71 per 700-mg ampoule. Securing the long-term availability of these two treatments for VL patients in the public sector is therefore essential: given the current limited demand and unlikely scenario of two manufacturers for each of those products, a buffer stock may be a possible option in the short term.

Table 1 shows a theoretical scenario estimating yearly demand and cost of these various treatments during the period 2012-2014. These estimates are theoretical, based upon current treatments registered or used, or future use of treatment regimen recently developed. Future use is estimated based upon information available, and is by definition inaccurate; these estimates do not necessarily represent the treatments recommended by DND*i*. Estimated demand for each treatment is based upon the following assumptions:

> In the Indian subcontinent, 1/3 of patients may receive a combination

Table 1 - YEARLY ESTIMATES IN 3-YEAR PERIOD

	Indian sub-continent	East Africa	Latin America
% cases treated in the region/global	87%	10%	3%
n patients treated (pts)	87,000	10,000	3,000
Assumptions re: treatments used	1) MF 7 days/PM 10 days* – 33%	1) PM + SSG combo 17 days – 80%	1) Glucantime® mono 20 days – 80%
	2) AmB single shot 10mg/kg – 33%	2) AmB multi dose 30mg/kg – 10%	2) AmB multi dose 20mg/kg – 20%
	3) MF mono 28 days – 33%	3) MF mono 28 days – 10%	
AmBisome®			
% (n) patients treated with AmBisome® in the region	33% (29,000 pts)	10% (1,000 pts)	20% (600 pts)
n AmBisome® vials (cost for US$ 18/vial)	201,000 (7 vials/35kg-pt) **US$ 3,617,000**	21,000 (21 vials/35kg-pt) **US$ 378,000**	12,000 (20 vials/50kg-pt) **US$ 216,000**
Miltefosine			
% (n) patients treated with MF	66% (57,000 pts)	10% (1,000 pts)	–
MF n units (cost for US$ 1.41/capsule) 2/day × Combo 7 OR Mono 28 days	2,010,000 **US$ 2,834,000**	56,000 **US$ 79,000**	–
Paromomycin			
% (n) patients treated with PM in the region	33% (29,000 pts)	80% (8,000 pts)	–
PM n units (cost for US$ 0.71/vial) 10 vials per patient	287,000 **US$ 204,000**	80,000 **US$ 57,000**	–
SSG/Glucantime®			
% (n) patients treated with SSG/Glucantime® in the region	–	80% (8,000 pts)	80% (2,400 pts)
SSG n units (cost for US$ 7/vial)	–	32,000 (4 vials/35kg-pt) **US$ 224,000**	
Glucantime® n units (cost for US$ 1.2/vial) 1 vial per day × 20 days	–		48,000 **US$ 58,000**
Total treatment cost in 2012	**US$ 6,655,000**	**US$ 738,000**	**US$ 274,000**

* This treatment combines 2 MF tablets for 7 days and 1 injection of PM per day for 10 days.

Table 2 - YEARLY ESTIMATES OF TOTAL VL DRUG COSTS WITH:

	Indian sub-continent	East Africa	Latin America	Total	% of current drug cost
Drugs with current prices	US$ 6,655,000	US$ 738,000	US$ 274,000	**US$ 7,667,000**	100%
AmBisome® priced at US$ 10/vial	US$ 5,047,000	US$ 570,000	US$ 178,000	US$ 5,795,000	76%
Miltefosine priced at US$ 1/capsule	US$ 5,831,000	US$ 715,000	US$ 274,000	US$ 6,820,000	89%
Both drugs reduced to above preferred prices	US$ 4,224,000	US$ 547,000	US$ 178,000	**US$ 4,949,000**	65%
200,000 patients treated/year with current prices	US$ 13,310,000	US$ 1,476,000	US$ 548,000	US$ 15,334,000	200%
200,000 patients treated/year and improved preferential prices for miltefosine (US$ 1/tablet) and AmBisome® (US$ 10/vial)	US$ 8,448,000	US$ 1,094,000	US$ 356,000	US$ 9,898,000	130%

of paromomycin and miltefosine, 1/3 AmBisome® single dose at 10mg/kg and 1/3 miltefosine monotherapy

> In East Africa, it is estimated that 80% of patients may receive a combination of paromomycin and SSG, and 20% miltefosine or AmBisome® monotherapy

> In Latin America, 80% of the patients may be treated with Glucantime® monotherapy and 20% with AmBisome® multi dose

It is also assumed that Amphotericin B is gradually replaced by AmBisome® and phased out.

The total drug cost to treat VL patients amounts to approximately US$ 7.7 million per year with current drug prices. The total AmBisome® cost to treat VL patients may amount to approximately US$ 4.2 million per year for a US$ 18 vial price, or 55% of the total drug cost. The total miltefosine cost may amount to US$ 2.9 million, or 38% of total drug cost, and paromomycin to US$ 260,000.

These estimates can be subject to a sensitivity analysis, including a change in the estimated number of patients treated each year in each region. For instance, a doubling of patients treated with AmBisome® in Africa (e.g. 2,000 a year) would result in a total annual AmBisome® treatment course of around US$ 760,000. Variable prices for AmBisome® or miltefosine result in the treatment costs shown in Table 2. Our model analysis shows that with a significant reduction in the prices of AmBisome® and miltefosine, the drug cost decrease to treat VL patients with AmBisome® priced at US$ 10 instead of US$ 18 and miltefosine priced at US$ 1 instead of US$ 1.41 amounts to US$ 2.7 million/year, or 35% of current cost (Table 2).

Conclusion

Although cost-effective treatments are available, most afflicted patients cannot afford them, and strategies including relatively expensive drugs such as AmBisome® are not accessible to most individuals unless governments, manufacturers and donors are willing to subsidize these treatments. Importantly, significant reductions in the price of AmBisome® and miltefosine would also encourage Control Programs and implementers to move towards effective and safe treatments, including AmBisome®-based treatments. Why are we waiting to strengthen **our partnerships with manufacturers and further secure continuous supply of these drugs at a preferential price for the public sector? Why are we waiting to treat VL patients?**

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