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Drug policy for visceral leishmaniasis: a cost-effectiveness analysis

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Summary

OBJECTIVE To facilitate the choice of the best visceral leishmaniasis (VL) treatment strategy for first-line health services in (VL)-endemic areas, we compared in a formal decision analysis the cost and the cost-effectiveness of the different available options.

METHODS We selected four drug regimens for VL on the basis of frequency of use, feasibility and reported efficacy studies. The point estimates and the range of plausible values of effectiveness and cost were retrieved from a literature review. A decision tree was constructed and the strategy minimizing the cost per death averted was selected.

RESULTS Treatment with amphotericin B deoxycholate was the most effective approach in the baseline analysis and averted 87.2% of all deaths attributable to VL. The least expensive and the most cost-effective treatment was the miltefosine regimen, and the most expensive and the least cost-effective was AmBisome® treatment. The cost of drug and medical care are the main determinants of the cost-effectiveness ranking of the alternative schemes. Sensitivity analysis showed that antimonial was competitive with miltefosine in the low-resistance regions.

CONCLUSION In areas with >94% response rates to antimonials, generic sodium stibogluconate remains the most cost-effective option for VL treatment, mainly due to low drug cost. In other regions, miltefosine is the most cost-effective option of treatment, but its use as a first-line drug is limited by its teratogenicity and rapid resistance development. AmBisome in mono- or combination therapy is too expensive to compete in cost-effectiveness with the other regimens.

keywords visceral leishmaniasis, drug policy, cost-effectiveness analysis

Introduction

Visceral leishmaniasis (VL), a fatal disease if left untreated, affects mainly people of the lowest socioeconomic status in developing countries who have minimal power to influence the political agenda and a very limited capacity to assume the costs of the disease (Desjeux 1996). Clinical cases of VL suffer from prolonged fever, anaemia, weakness, splenomegaly and, to a lesser extent, lymphadenopathy and malaise. At the advanced stage, wasting is prominent, but once a patient responds well to treatment, disability is averted. The World Health Organization (WHO) estimates the incidence of VL at 500 000 new cases per year (UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases 1997), half of which are occurring in India (Jha *et al.* 1998). The global figure does not reflect the real importance of VL in affected communities, because VL has a focal distribution. Reported incidence rates of kala-azar in endemic areas vary between 2/1000 person-years in Kenya (Schaefer *et al.* 1995), 14/1000 person-years in Ethiopia (Ali & Ashford 1994) and 40/1000 person-years in a community in eastern Sudan (Zijlstra *et al.* 1994). Despite the considerable burden, there has been little attempt to quantify the economic consequences of the disease in these communities. Adhikari and Maskay (2003) estimated that the total cost of a kala-azar episode for a household in Nepal may be as much as US$ 210, which is 2.5 times an average annual per capita household income (US$ 82). Thakur (2000) related that 75% of VL patients in Bihar, India, lived below the poverty threshold of less than US$ 1 income per capita per day. This seriously compromises the prognosis of VL, because in some countries patients have to pay for diagnostics, drugs and hospital care out of their own pockets. Other countries, such as Nepal, provide the drugs free of charge to confirmed VL patients through public health services.

Leishmaniasis has recently garnered attention as one of the diseases 'most neglected' by drug research and development, as there is a lack of effective, affordable and easy-to-use drugs (Yamey & Torreele 2002; Morel 2003). The WHO-recommended treatment regimen is a 30-day course of antimonials (intramuscular or intravenous), which, for an average 35-kg patient, costs between US$ 120 and 150 per course in the branded version (Glucantime® or Pentostam®) to US$ 28 per course in the generic version (stibogluconate) (Sundar *et al.* 2000a; Murray 2001). Griekspoor *et al.* (1999) estimated the cost-effectiveness ratio of VL care based on Pentostam in a relief programme in Sudan at US$ 18.40 per disability adjusted life year (DALY) averted, and judged it as 'very good value for money' and among the most cost-effective health interventions. Antimonials are not an ideal drug; they have to be administered parenterally over a period of 28–30 days, generally requiring hospitalization. Antimonials have shown rare but serious side effects, such as cardio, pancreas and liver toxicity (Gasser *et al.* 1994; Sundar *et al.* 1998c; Thakur *et al.* 1998; Rijal *et al.* 2003), whose importance increases if the patient is coinfected with HIV (Delgado *et al.* 1999; Laguna *et al.* 1999). Resistance to antimonials has been reported in up to 65% of patients in some villages of Bihar, India (Sundar 2001). In these areas, the current first-line treatment is amphotericin B deoxycholate. AmBisome® (a lipid formulation of amphotericin B) is recommended in most endemic countries as the second-line therapy, but is unaffordable for most patients (US$ 1747 per course for a person weighing 35 kg).

Recently, a number of breakthroughs in VL chemotherapy have occurred: adoption of generic antimonials for VL control in East Africa (Veeken *et al.* 2000); clinical development of miltefosine as the first oral drug for VL (Sundar *et al.* 1998b, 2002a), which can be used safely in children (Sundar *et al.* 2003; Bhattacharya *et al.* 2004); development of low-cost lipid formulations of amphotericin B (Sundar *et al.* 2000a). Paromomycin phase III trials are in progress in India (Institute for One World Health) and East Africa (Drugs for Neglected Diseases initiative), and pharmaceutical manufacture has recently been secured (Thakur *et al.* 2000a; Croft & Coombs 2003).

The most important strategy for anthroponotic VL control is case detection and treatment (Boelaert *et al.* 2000), because no vaccine is available and vector control has limited efficacy and sustainability. If less complex and safer drug regimens could be adopted, more effective VL control could be achieved.

In this paper, we compared in a formal decision analysis the costs and the cost-effectiveness of the different actually available options for VL treatment in first-line health services in endemic areas, in order to facilitate the choice of the best strategy.

Methods

Clinical decision analysis is a quantitative method for evaluating the consequences of alternative strategies and permits the choice of the most effective or most cost-effective course of action in complex situations. The method requires the following:

- a decision tree describing possible alternative strategies;
- information on the probabilities attached to the events in each strategy and
- a judgement about the clinical and economic consequences of each intervention (Weinstein & Fineberg 1980).

We tried to answer the following question: what is the most cost-effective drug regimen in the management of VL in first-line health services in endemic regions?

Therapeutic strategies

We decided to compare the following four regimens, selected on the basis of frequency of use, feasibility and reported efficacy (Table 1).

Strategy A is the WHO-recommended one, antimonials (generic or branded version) 20 mg/kg/day intramuscularly for 30 days. In some countries, the duration of treatment is 28 days or/and the regimen is administered intravenously.
Strategy B is the Indian first-line regimen based on amphotericin B deoxycholate, 15 infusions of 1 mg/kg on alternate days.
Strategy C is the only existing oral treatment regimen, miltefosine 2.5 mg/kg/day, for 28 days.
Strategy D is a regimen of a lipid formulation of amphotericin B (liposomal amphotericin B or AmBisome, amphotericin B lipid complex) 2 mg/kg/day for five consecutive days, a frequently used second-line scheme in endemic areas (A variety of dosing schemes has been tested, ranging from single infusion up to 10 days treatment, with total dosages from 5 up to 20 mg/kg).

Decision tree structure

We constructed a decision tree to compare these strategies (Figure 1), taking a patient presenting with clinical signs and symptoms of VL as the starting point. After

Table 1 Effectiveness and cost estimates of currently available chemotherapy against VL in immunocompetent patients

Drug	Regimen	Total dose (MK)	Effectiveness† (%) (range)	Drug cost‡ (US$) (range)	Care cost (US$) (range)	References
Antimonials	20 MKD for 30 days IM	600	**92** (36–96)	**28** (28–149)	**143** (143–420)	Seaman *et al.* (1993), Griekspoor *et al.* (1999), Murray (2000, 2001), Sundar *et al.* (2000a), Veeken *et al.* (2000), Thakur *et al.* (2000b), Ritmeijer *et al.* (2001)
Amphotericin B deoxycholate	1 MKD, 15 infusions on alternate days	15	**97** (96–99)	**69** (69–255)	**279** (279–416)	Sundar *et al.* (1997, 2001, 2002a, 2004), Thakur *et al.* (1999), Murray (2000)
Miltefosine	2.5 MKD, *per os*, 28 days	70	**94** (88–94)	**140** (70§–198)	**40** (40–480)	Sundar *et al.* (2002a, 2003), Bhattacharya *et al.* (2004)
Lipid formulation of amphotericin B (AmBisome®, Abelcet®)	2 MKD, 5 days	10	**92** (90–96)	**1120** (455¶ –4138)	**90** (90–111)	Sundar *et al.* (1997, 2000a, 2004), Murray (2000)
	5 MK, single infusion	5	91 (70–91)	560 (230–658)	42	Sundar *et al.* (1998a, 2001)
	Various regimens	5–20	(78–100)	(230–4138)	(90–102)	Sundar *et al.* (1997, 1998a, 2001, 2002b, 2004), Murray (2000), Syriopoulou *et al.* (2003)

Values used in baseline analysis are given in bold. Range of plausible values between parentheses. MK, mg/kg; MKD, mg/kg/day.
†Effectiveness estimated as proportion cases with negative parasitology/no clinical signs at the end of 6-month follow-up period.
‡All drug cost values computed for a 35-kg patient.
§Purchase via Acteon Medeor, Germany.
¶Public sector price for Africa only.

performing a diagnostic test, and treating the test-positive patients, the branches of the decision tree lead to the following outcomes.

- 'VL – treated', i.e. a real case of VL is correctly diagnosed and treated accordingly.
- 'Erroneously treated', i.e. a person without VL is incorrectly diagnosed as VL and wrongly receives treatment for a disease he/she does not have.
- 'VL – untreated', i.e. a real case of VL is missed because of a false-negative test result and consequently, the VL case is not treated.
- 'Correctly ruled out', i.e. a person without VL in whom the disease is correctly ruled out and therefore does not receive treatment for VL.

Probabilities, effectiveness and cost assumptions

Table 1 shows the baseline probability estimates used in the decision analysis. A literature review (Medline search accessed between January 2004 and August 2004) provided a range of plausible values for those parameters about which uncertainty exists. In the absence of pooled estimates from systematic reviews of all endemic regions worldwide, we took the result of the clinical trial with the highest power as the baseline point estimate for effectiveness, and included the other effectiveness estimates in the range subjected to sensitivity analysis.

Effectiveness. The marginal health benefits or losses of a strategy and its utility, i.e. the patient's perceptions of the quality of life associated with a health state, were disregarded, and overall effectiveness was expressed as deaths averted relative to mortality in the absence of intervention. However, it should be noted that sequelae of VL do occur, as up to 50% of initially cured kala-azar patients can develop post-kala-azar dermal leishmaniasis (PKDL), a non-life-threatening dermatological complication which is difficult to cure and is considered to be a reservoir of transmission, as PKDL cases are highly infectious (Zijlstra *et al.* 2003). As the differential impact of the available treatments on the appearance of PKDL is not yet studied, we disregarded this sequel in our study.

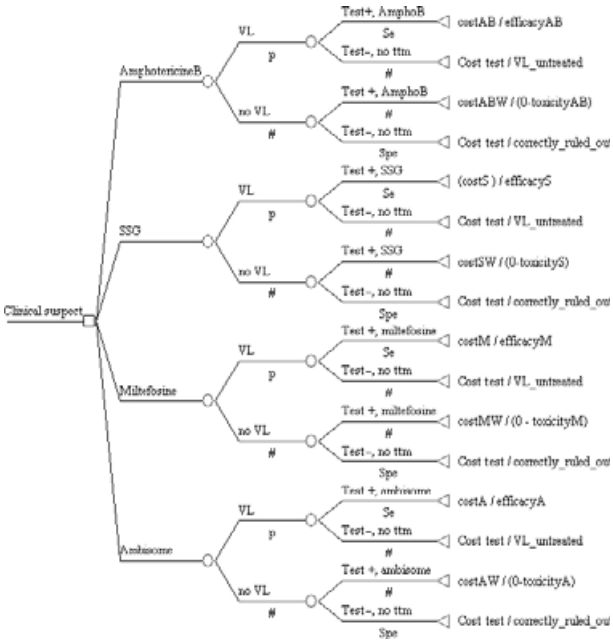

Figure 1 Decision tree.

Our decision analysis started from a person with clinical signs and symptoms of VL (prolonged fever and splenomegaly). For the baseline analysis, we assumed that the diagnostic test used was the rK39 dipstick, as proposed by Chappuis *et al.* (2006) with a sensitivity of 90.1% [95% confidence interval (CI): 85.7–94.6] and a specificity of 93.1% (95% CI: 87.5–98.6) (Boelaert *et al.* 2004), and that every rK39-positive individual was subsequently treated. We evaluated the robustness of our conclusions by changing the values of sensitivity and specificity of rK39 to the lowest (85.7% for sensitivity and 87.5% for specificity) and highest (respectively 94.6% and 98.6%) values of the above-mentioned 95% CI.

We derived the effectiveness value of a true-positive diagnosis (treating a true case of VL) directly from the efficacy estimates of the drug obtained in clinical trials, evaluated at 6 months interval after the start of treatment. As fatal toxicity of a drug is already reflected in the efficacy figures of randomized controlled trials, we did not have to add toxicity estimates to this outcome. We assigned an effectiveness value of 0 to a false-negative diagnosis (i.e. a missed diagnosis of a true case of VL), as the eventual outcome, death, would be the same as when the disease was allowed to follow its natural course. We also assigned an effectiveness of 0 to a true-negative diagnosis (the correct ruling out of VL), because it does not directly avert deaths (although it may off-course lead to psychological benefit in such patients). A false-positive diagnosis exposes a person to a relatively toxic treatment, and therefore we considered the effectiveness of a false-positive outcome as (0 – toxicity of drug). Moreover, it delays correct diagnosis and any other potentially life-saving treatment, but this was disregarded in the valuation of this outcome. Data on serious adverse events in healthy people in field contexts are very scarce for the drugs we studied. For the iatrogenic death rate of antimonials, we used the same estimate as Boelaert *et al.* (1999) at 1 death per 1000 healthy individuals treated. It has been demonstrated in India that the case–fatality rate is significantly higher in VL patients treated with antimonials than in those treated with an alternative drug (Thakur 2004). This gives an indication that also in healthy individuals, the toxicity could be much higher than the estimate of 0.001; therefore, we put the range up to 0.07 deaths/treatment, which was the figure found by Sundar *et al.* (2000b) in a cohort of VL patients under antimonial treatment. For the other drugs, we used information from drug trials. The toxicity of miltefosine is estimated at 0.0003 deaths/treatment based on the occurrence of Stevens–Johnson syndrome in one patient among 299 treatments with miltefosine (Sundar *et al.* 2002a), which has a mortality of 1–15% (Schopf *et al.* 1991; Ghislain & Roujeau 2002). The toxicity of amphotericin B deoxycholate has been estimated at 0.003 deaths/treatment by Thakur *et al.* (1999), and according to the FDA, there is comparative safety information on amphotericin B deoxycholate and lipid formulations of amphotericin B (Meyerhoff 1999). Olliaro *et al.* (2005) reported more frequent (mostly minor) adverse events during treatment with amphotericin B deoxycholate, and we included a range up to 0.01 deaths/treatment in the sensitivity analysis.

Costs. The total cost of VL care for one patient comprises the cost of the diagnostic test, the specific anti-leishmanial drug, the cost of possible retreatment episodes, ancillary drugs and patient care during the treatment course until cure was obtained. We estimated the cost of rK39 dipstick at US$ 1/test (Chappuis *et al.* 2006). The point estimates of the drug costs are computed for an 'average' 35-kg patient and were provided by the Campaign for Access to Essential Medicines of 'Médecins Sans Frontières' in March 2006. The costs of care are based on the prices in the treatment centres, as published elsewhere (Table 1) (Meyerhoff 1999; Murray 2000, 2001; Boelaert *et al.* 2002). Unit costs were adjusted for inflation to year 2004 prices, using the Indian consumer price index (the last year for which the consumer price indices were available at the time of this study). (Source: Indian Central Statistical Office; http://labourbureau.nic.in/cpi%20iw%202004%20table%204%20p.htm, accessed 7 August 2006).

The range is based on the most extreme prices found in the literature. For retreatment, we assumed that AmBisome®, 3 mg/kg/day, for 5 days would be given as second-line treatment to every failure in the first-line treatment (Sundar *et al.* 2000a). Cost of this regimen is estimated at US$ 1747 for a 35-kg patient, care included (Murray 2000; Sundar *et al.* 2000a).

The costs of patient care incurred under the different regimens are presented from the perspective of the health service, as in most countries the government subsidizes the VL case management. Information on cost of patient care is scarce and highly variable depending on the context. In this study, our data were based on initial cost estimations of Sundar and Murray from previous studies in India (Murray 2000; Sundar *et al.* 2000a). Cost of patient care included: cost of hospitalization day [baseline estimate US$ 4 (range 2–100)], ancillary drugs and adjuvant treatment for the side effects of the chosen strategy, injection material and – fee, routine laboratory and other complementary tests and fees for medical doctor visits.

The duration of hospital admission depends on the strategy. In endemic countries, patients treated by antimonials are generally admitted for 1 week, and continue injections on an ambulatory basis afterwards. We assumed that miltefosine, as it is an oral drug with side effects that last for 1–2 days (Sundar *et al.* 2002a), would only need a mean of 2 days of inpatient care to supervise possible adverse reactions of the patient to the drug. Amphotericin B deoxycholate gives a lot of side effects that persist in 63% of the cases even at the 10th infusion (day 20) (Sundar *et al.* 2004) and needs a good hydration of the patient; therefore ambulatory treatment is excluded. The AmBisome® regimen studied here requires infusions during 5 days, which we counted as the period of hospitalization.

Analysis

We analysed efficiency from the perspective of the health service and used the patient consulting with signs and symptoms for VL as starting point to address the question of most efficient therapeutic approach. The expected effectiveness of each strategy was estimated by calculating the sum of the effectiveness values of each possible outcome of the strategy weighted by their probability of occurring. The strategy averting most deaths was considered to be the most effective. A cost-effectiveness analysis was then performed and the strategy minimizing the cost per death averted was considered the most cost-effective therapeutic strategy.

Subsequently, one-way and two-way sensitivity analyses were performed on those parameters of probability and cost that were subject to appreciable uncertainty: cost and efficacy of drugs, sensitivity and specificity of the diagnostic test, toxicity, care and hospitalization costs. The analysis was performed using DATA™ v.3.0 software (TreeAge, Williamstown, MA, USA).

Results

Cost, effectiveness and cost-effectiveness of the different strategies

Table 1 shows that the reported efficacy of regimens does not differ much, ranging between 91% (lipid formulation of amphotericin B, single infusion) and 97% (amphotericin B deoxycholate). Treatment with amphotericin B deoxycholate is the most effective approach in the baseline analysis. This strategy averts 349 deaths per 1000 clinical suspects enrolled, or 87.2% of all deaths attributable to VL in a group of clinical suspects with a prior probability of 0.40 of having the disease (Table 2). Miltefosine treatment ranks second, followed by antimonials (in antimonial-sensitive regions) and AmBisome® with comparable effectiveness (avoiding 83–84% of VL deaths).

The cost of the four strategies (taking into account effectiveness, toxicity and retreatment need) ranged from US$ 111.1 to 537.5 per clinical suspect enrolled. The least expensive treatment strategy is the most recently intro-

Table 2 Comparison of the cost, effectiveness and cost-effectiveness ratio of the different therapeutic strategies in baseline analysis

Strategy	Cost (US$ per clinical suspect enrolled)	Effectiveness (deaths averted per 1000 clinical suspects)	Cost-effectiveness (US$/death averted)	Marginal cost-effectiveness ratio (US$/death averted)
Antimonials (SSG)	120.1	332	362.2	Dominated by miltefosine strategy
Miltefosine	**111.1**	339	**327.9**	Dominant strategy
Amphotericin B deoxycholate	159.7	**349**	457.0	4543.3
AmBisome®	537.5	331	1621.8	Dominated by amphotericin B deoxycholate

Strategies ranked by increasing cost and best-ranked values are given in bold.

duced regimen of miltefosine and the most expensive is the AmBisome® treatment scheme. If we use the point estimates of Table 1, the most cost-effective scheme is the miltefosine strategy with a cost of US$ 327.9 per death averted. There is a striking contrast between the first three strategies (A, B and C) with a range of US$ 327.9–457.0 per death averted and the US$ 1621.8 per death averted for the lipid formulations of amphotericin B (AmBisome®) strategy. We observe that cost is the main determinant in this cost-effectiveness comparison as the range of effectiveness is quite narrow, but prices of drugs and cost of care are very divergent.

The cost of care is mainly determined by the supportive treatment and the different medical and laboratory examinations necessary for all strategies (73–77% of total care cost) except for amphotericin B, where the hospitalization days are responsible for just over 50% of the care costs.

Incremental costs

We compared miltefosine treatment with the amphotericin B deoxycholate regimen, which is the only more effective one, to determine the incremental cost to save an additional life, which elevates to US$ 4543.3 per death averted.

Sensitivity analysis

When allowing for changes, respectively, in the efficacy of antimonials (>93.9%) (Figure 2), as well as in the drug efficacy (<92.5%), in the drug cost (>US$ 168.9), and cost of medical care (>US$ 68.9) of miltefosine, all within the range found in literature, antimonials become competitive with the miltefosine strategy. The AmBisome® strategy approaches the cost and cost-effectiveness of amphotericin B deoxycholate treatment only when the preferential pricing that is currently available to the public sector in Africa, is applied together with a single infusion regimen of 5 mg/kg total dose.

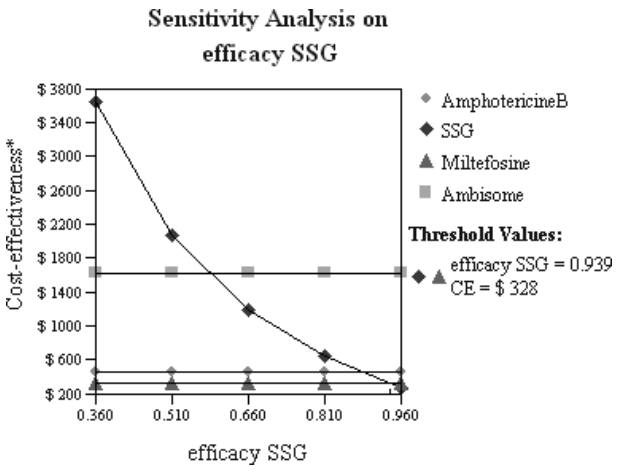

Figure 2 Sensitivity analysis on efficacy antimonials. *US$/death averted.

A sensitivity analysis for the other variables in the model did not lead to a different choice of the most cost-effective strategy. There were only changes in the ranking of cost-effectiveness of the different regimens. When the drug price of antimonials rises to US$ 100 per course, amphotericin B deoxycholate becomes the most cost-effective treatment after miltefosine.

The sensitivity analysis on the cost of a hospitalization day did not change the choice of most cost-effective strategy, as miltefosine does not require long hospitalization. When the hospitalization day price rises to US$ 50, amphotericin B deoxycholate treatment becomes less cost-effective than AmBisome® treatment.

The conclusions on cost-effectiveness were also robust when changing the sensitivity and specificity of the diagnostic test to lower values. We observed slight differences in effectiveness and cost, showing among others, that more sensitivity leads to strategies with higher effectiveness but also higher cost, because of more true patients to treat.

Discussion

Cure rates of the currently available first-line drug regimens for VL are high and range between 91% and 97%, except in Bihar State in India, where antimonials cure less than 50% of the patients. However, the drug cost of those different regimens varies between US$ 28 and 1120 per average treatment course and this is, together with the cost of patient care, the main determinant for the efficiency of a therapeutic strategy. In our analysis, in areas with a certain level of drug resistance patterns to antimonials, a miltefosine-based strategy is the most cost-effective at US$ 328 per death averted. Miltefosine has a cure rate of 94%, requires a short hospitalization period as it is an oral drug, gives few major side effects and has a balanced price (in comparison with the alternative regimens). In areas where antimonials remain highly effective, with cure rates above 93.9% antimonials compete with miltefosine and are in the same range of cost-effectiveness.

Amphotericin B deoxycholate is the most effective drug, but because of its prolonged hospitalization requirement, it becomes slightly less cost-effective than the first two options. AmBisome®-based treatment is not competitive with the other regimens because of its current high drug cost. Even at the preferential pricing for the

public sector in African countries, the cost of a treatment course is almost double the price of the other regimens.

The question whether miltefosine is a valid substitute for the antimonials is not easy to answer. Antimonials are problematic drugs because of their toxicity and need for parenteral administration. The painful injections and long hospitalization period add to the burden from the patient's perspective. Miltefosine has the clear advantage of oral administration, and this is more than an issue of patient comfort and cost. Singh *et al.* (2000) pointed out the risk of transmitting blood-borne infections such as HIV, Hepatitis B and C, with parenteral treatment of VL because of unsafe injection practices. The main disadvantage is the potential teratogenicity of this drug, which complicates its use as first-line treatment for women of reproductive age. Non-supervised treatment with this drug may leave VL patients with sub-therapeutic doses, and this, given its long half-life, implies a high risk of development of resistance. Moreover, the figures of the cure rates used in this analysis came from controlled clinical trials and we have to be careful with their extrapolation to effectiveness, as irregular intake of drugs and interruption of treatment are likely in real life.

Is AmBisome® a realistic alternative for the first-line health services, regardless of its cost? The answer is not straightforward because of regional variation of its effectiveness. In Brazil, the regimen studied (2 mg/kg during 5 days) was insufficient, and a total dose of 20 mg/kg was needed to attain the acceptable effectiveness (Berman *et al.* 1998). The FDA recommends a total dose of 21 mg/kg, given on 7 days over a 21-day period (Meyerhoff 1999). The lack of sufficiently powered clinical trials of shorter regimens compared with the standard FDA regimen and the huge variety of dosage schemes reported (from 3.75 mg/kg total dose to 30 mg/kg total dose and from single infusion up to 21 days of treatment) make any therapeutic recommendation on shorter regimens difficult. An equivalence or non-inferiority study could bring guidance in the best choice of regimen and the minimal dose needed.

In countries with high hospitalization costs, such as the *Leishmania infantum* endemic areas in the Mediterranean basin, any approach that reduces hospital stay can offset the cost of expensive drugs. Pagliano *et al.* (2003) reported in Italy that the cost of AmBisome® 3 mg/kg/day given on an inpatient basis during five consecutive days with a sixth dose on day 10 (at € 4100), compared favourably to the € 4200 for a 21-day inpatient course of meglumine antimoniate (Glucantime®). Similarly, in Greece, where cost of hospitalization was € 88 per day, the total cost of short regimens of AmBisome® compared favourably to that of inpatient treatment with Glucantime® (Syriopoulou *et al.* 2003). However, one should remember that, from the patient's perspective, the AmBisome® and miltefosine regimens present advantages that were not taken into account in our analysis, as a shorter time period of loss of income for both the diseased persons and their attendants.

How useful are the results of cost-effectiveness analysis when it comes to the formulation of drug policy recommendations? The conclusions of this analysis are applicable in all VL endemic regions, on condition that the point estimates of effectiveness and cost are comparable to local figures. The decision analytic model used as the basis for the cost-effectiveness analysis is a simple one-period model, which does not capture longer term benefits and risks of treatment strategies. The main benefit, impact on transmission, and the main risk, drug pressure with the probability of subsequent resistance development, are not well-studied subjects and therefore difficult to take into account in an analysis. Moreover, if the emergence of drug resistance is to be prevented, monotherapies should be avoided, and combination therapies have to be considered.

In our analysis, we saw that the drug price is the main determinant in the ranking of cost-effectiveness in the typical *Leishmania donovani* areas, where hospitalization is relatively cheap. From the viewpoint of the cost issues, antimonials, miltefosine and amphotericin B deoxycholate are valid candidates to insert in combination therapies, but the inclusion of AmBisome®, even if it was a single dose, would raise the price of treatment to unacceptable levels.
In *L. infantum* areas, where hospitalization is relatively expensive, antimonials and amphotericin B deoxycholate are not very attractive drugs for combination therapies unless the duration of treatment is considerably shortened.

Croft (2001) and Bryceson (2001) proposed a combination therapy of sodium stibogluconate and paromomycin. Paromomycin monotherapy, applicated parenterally during 21 days, showed promising efficacy results in Phase II trials and could become a valuable alternative treatment in the future because of its low price and relatively low toxicity (Jha *et al.* 1998; Thakur *et al.* 2000a).

Another factor to be taken into consideration when making therapeutic recommendations is the emergence of HIV–*Leishmania* coinfection. These patients present more serious and frequent side effects than patients infected only with *Leishmania* (Delgado *et al.* 1999). Their response to treatment is also poor: antimonials, amphotericin B deoxycholate and amphotericin B lipid complex are showing an effectiveness of around 60–70% (Laguna 2003), and similar figures have been reported for miltefosine (Sindermann *et al.* 2004).

In the future, the challenge is not only to reduce the price of the treatment of this highly lethal disease that affects mainly the poorest, but also to adequately use and protect the few existing drugs, as there are no other new drugs in the pipeline of the pharmaceutical industry. Meanwhile, price reductions of lipid formulations of amphotericin B would relieve a bottleneck in the treatment of kala-azar patients.

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Politique des médicaments contre la leishmaniose viscérale: une analyse de coût efficacité

OBJECTIF Pour faciliter le choix de la meilleure stratégie de traitement de la leishmaniose viscerale (LV) dans les services de santé de 1ère ligne dans des zones endémiques nous avons comparé dans une analyse formelle de décision le coût et le coût-efficacité de différentes options disponibles.
MÉTHODE Nous avons choisi quatre régimes de médicaments contre la LV sur base de la fréquence d'utilisation, la faisabilité et les études d'efficacité rapportées. L'estimation ponctuelle et l'amplitude des valeurs plausibles de l'efficacité et du coût ont été tirés d'une revue de littérature. Un arbre de décision a été construit et la stratégie réduisant au minimum le coût par décès évité a été choisie.
RÉSULTATS Le traitement au désoxycholate d'amphotéricine B était l'approche la plus efficace dans l'analyse de ligne de base en évitant 87,2% de tous les décès attribuables à la LV. Le traitement le moins cher et le plus coût-efficace était celui au Miltefosine et le plus cher et moins coût-efficace était celui à l'AmBisome®. Le coût du médicament et des soins médicaux était le déterminant principal dans le classement de coût-efficacité des schémas alternatifs. L'analyse de sensibilité a démontré que les antimoniés ētaient en compétition avec le Miltefosine dans les zones de résistance basse.
CONCLUSION Dans les zones avec des taux de réponse >94% aux antimonios, le générique de stibogluconate sodique demeure l'option la plus rentable pour le traitement de la LV, principalement due au faible coût du médicament. Dans d'autres zones, le miltefosine constitue l'option de traitement la plus coût-efficace, mais son utilisation comme médicament de 1ère ligne est limitée par sa tératogénicité et le développement rapide de résistance. L'AmBisome® en monothérapie ou en combinaison est trop coûteux pour concurrencer les autres traitements en terme de coût efficacité.

mots clés leishmaniose viscérale, politique sur les médicaments, analyse de la rentabilité, analyse de coût-efficacité

Política de medicamentos para la Leishmaniasis Visceral: análisis de costo-efectividad

OBJETIVO Con el fin de facilitar la elección de la estrategia de tratamiento de leishmaniasis visceral más adecuada para los servicios sanitarios de primera línea en áreas endémicas, hemos comparado en un análisis formal de decisiones el costo y la costo-efectividad de las diferentes opciones disponibles.
MÉTODO Hemos seleccionado cuatro regimenes de medicamentos para la LV, basándonos en la frecuencia de uso, la viabilidad y los estudios de eficacia publicados. Los estimaciones puntuales y el rango de valores plausibles de costos y efficacia se basaron en una revisión bibliográfica. Se construyó un árbol de decisión y se seleccionó la estrategia que minimizaba el costo por muerte evitada.
RESULTADOS El tratamiento con desoxicolato de Amfotericina B era la estrategia más efectivo en el análisis basal y prevenía un 87.2% de todas las muertes atribuibles a LV. El tratamiento más barato y costo-efectivo era el régimen con Miltefosine, mientras que el más costoso y menos costo-efectivo era aquel con AmBisome®. El costo de los medicamentos y tratamiento médico son los principales determinantes del rango de costo-efectividad de las diferentes estrategias. Los análisis de sensibilidad mostraban que el antimonial era competitivo con Miltefosine en las regiones con baja resistencia.
CONCLUSIÓN En áreas con tasas de respuesta a antimoniales de >94%, el estibogluconato sódico genérico continúa siendo la opción más costo-efectiva para el tratamiento de la LV, principalmente debido al bajo costo del medicamento. En otras regiones, Miltefosine es la opción de tratamiento más costo-efectiva, pero su uso como primera línea de tratamiento es limitada por su teratogenicidad y el rápido desarrollo de resistencias. El AmBisome®, bien en mono-dosis o como terapia de combinación, es demasiado costoso para competir desde un punto de vista de costo-efectividad con otros regímenes.

palabras clave leishmaniasis visceral, política de medicamentos, análisis de costo-efectividad

