Visceral leishmaniasis treatment in the Indian subcontinent: how to reach the most vulnerable

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"…interventions ensuring the most vulnerable communities have proper access to visceral leishmaniasis diagnosis and treatment will have medical and public health benefits."

Every year, approximately 1 – 1.5 million cases of different forms of leishmaniasis occur around the world. Visceral leishmaniasis (VL), also known as kala-azar, is the most severe type and is usually fatal if not treated. A large majority of VL cases are reported in India, Nepal and Bangladesh, and 200,000 to 400,000 new VL cases are estimated per year worldwide [1]. In the Indian subcontinent (ISC), VL is caused by *Leishmania donovani*, an intracellular protozoan transmitted from human to human by a sand fly vector (*Phlebotomus argentipes*). There is no animal reservoir, in contrast to VL caused by *Leishmania infantum*. VL is usually characterized by prolonged fever, enlarged spleen and pancytopenia evolving to cachexia and secondary complications.

In the absence of a vaccine, the current control strategy in the ISC is based on vector control and early case detection and treatment. However, although the trend in the number of new VL cases has been declining in the past few years, we are still far from the goal set by the governments to eliminate the disease by 2015 [101]. The reasons for this slow progress are multiple but are mainly due to the difficulties to promptly diagnose and treat all VL cases in the affected communities and to the low coverage and effectiveness of the sand fly control measures. Indoor residual spraying, which is the basis of *P. argentipes* control, is poorly implemented [2], and few alternative methods are available. Long-lasting impregnated nets do not seem to be a standalone alternative to indoor residual spraying [3]. Similarly, ensuring that each case of VL has access to prompt diagnosis and treatment is a huge challenge. VL tends to cluster in certain hamlets in remote rural villages where the access to quality healthcare services is limited. Furthermore, the communities affected tend to be extremely poor [4]. The cost of caring for a VL patient has a knock-on effect on the household economy, dragging the affected family into further poverty [5].

In the ISC, the burden of VL falls disproportionately on the most vulnerable. A number of studies indicate that VL is more prevalent in certain castes in India [6–10]. The increased risk of VL in these groups is not completely explained by their poorer economic status or housing conditions, so the social stratification itself seems to play a role [10]. The profound impact of sociocultural exclusion on the leishmaniasis transmission cycle is multifactorial [11]. VL patients belonging to the Scheduled Castes in India experienced longer delays between onset of symptoms and start of VL treatment than others [12]. Longer patient delays not only jeopardize individual prognosis but also put the household and community at increased risk, as the longer an infectious case remains in the community, the higher the risk of transmission of infection to other

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individuals. Thus, interventions ensuring the most vulnerable communities have proper access to VL diagnosis and treatment will have medical and public health benefits.

In the past 10 years, there have been major advances in the drugs and diagnostics to fight VL. A reliable rapid test for VL is now available, allowing diagnosis in the field and primary-care facilities such as the Primary Health Centers [13]. After 70 years, during which time pentavalent antimonials, a toxic class of drugs requiring long and painful treatments, were the only therapeutic option, a number of less toxic and more effective drugs are now available as monotherapy or combination therapy (i.e., liposomal amphotericin B, miltefosine and paromomycin [14]). The WHO has facilitated access to some of these VL drugs by negotiating the cost and availability of these with pharmaceutical companies [15]. Miltefosine, the first oral drug against VL, and paromomycin were registered in India in 2002 and 2006, respectively. Both drugs were later registered in Bangladesh and Nepal. For ease of use in programmatic conditions, miltefosine was recommended for the VL elimination program in the ISC in 2006. Recent evidence showed that the liposomal form of amphotericin B, the safest antileishmanial drug, was highly effective at a single dose of 10 mg/kg [16] and several short-course combination regimens attained similar safety and efficacy [17]. These shorter regimens have multiple proven or potential advantages in terms of cost, compliance and safety [18]. Single-dose liposomal amphotericin B is now listed as a recommended first-line regimen for the ISC by the WHO [14], and some authors suggested that it be used in active screen-and-treat campaigns in endemic villages until the incidence is reduced below 1/10,000. This attack phase would then be followed by a consolidation phase where combination therapies involving other antileishmanial drugs (i.e., miltefosine and paromomycin) could be used [19]. Using combination therapies is considered by WHO as "the best strategy for protecting medicines from resistance, if the available clinical evidence is confirmed in larger Phase IV trials" [14].

The governments in the region, the WHO and nongovernmental organizations have been renewing their control efforts capitalizing on recent breakthroughs. In India, to increase accessibility, miltefosine was made available in private pharmacies and practices between 2002 and 2006. From 2006 onwards, miltefosine was only available in governmental health facilities and charities and is provided for free. Similarly, in Nepal and Bangladesh, miltefosine is provided for free as part of the governmental VL control program. The Indian and Nepalese governments have put economic incentives in place to encourage VL patients to complete their treatment. Nongovernmental organizations such as Médecins Sans Frontières have treated thousands of Indian VL patients for free with liposomal amphotericin B with a high success rate [20]. However, these efforts may not be enough. The unrestricted distribution of miltefosine in India between 2002 and 2006 has contributed to its irrational use, and increasing failure rates with this drug are now reported [21]. Pentavalent antimonials, which are ineffective in large parts of India, were still in use instead of miltefosine in Primary Health Centers in endemic areas in Bihar until recently [22], and the supply of VL rapid diagnostic tests in those peripheral facilities is often interrupted. The free provision of VL drugs is still insufficient to make VL care affordable for all affected communities, as indirect costs remain huge. Structural inefficiencies in the public health system in India often preclude the access of VL patients to proper medical assistance and VL control program incentives [23].

We observe that the measures currently in place may still be inadequate to reach the most vulnerable. As the reasons of their exclusion are not entirely economical, a comprehensive intersectorial approach is required. The VL elimination program should work within these most vulnerable communities, which are easily identifiable, and link up with community-based programs. Since poor housing is one of the main risk factors for VL [24], programs, such as the Indira Awaas Yojana in India aiming to improve the living conditions of the poorest in endemic areas, could be reinforced and will have other benefits beyond VL. Moreover, access to healthcare in general, and VL care in particular, should be improved among the most vulnerable. Interventions are needed to ensure that affected communities are aware of the disease characteristics and can seek timely care [25]. Accredited Social Health Activists in India and their counterparts in Nepal and Bangladesh could play a pivotal role in promoting identification, early diagnosis, patient adherence and adequate follow-up at community level and link communities with the health services. Health services serving rural communities should be strengthened and supplied with the required personnel, diagnostic tools and drugs to diagnose and treat VL. Complete, safe, efficacious and free short-course treatment should be provided to all VL patients. Developing the public health system in the ISC will primarily benefit socioeconomically disadvantaged communities that cannot afford private care and seems essential to ensure all VL cases are treated. Getting the socially excluded communities onboard the VL control efforts in the ISC is an essential step toward achieving VL elimination in the region.

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References

1 Alvar J, Vélez ID, Bern C *et al.* The WHO Leishmaniasis control team. Leishmaniasis worldwide and global estimates of its incidence. *PLoS ONE* 7(5), e35671 (2012).

2 Chowdhury R, Huda MM, Kumar V *et al.* The Indian and Nepalese programmes of indoor residual spraying for the elimination of visceral leishmaniasis: performance and effectiveness. *Ann. Trop. Med. Parasitol.* 105(1), 31–35 (2011).

3 Picado A, Singh SP, Rijal S *et al.* Longlasting insecticidal nets for prevention of *Leishmania donovani* infection in India and Nepal: paired cluster randomised trial. *BMJ* 341, c6760 (2010).

4 Boelaert M, Meheus F, Sanchez A *et al.* The poorest of the poor: a poverty appraisal of households affected by visceral leishmaniasis in Bihar, India. *Trop. Med. Int. Health* 14(6), 639–644 (2009).

5 Adhikari SR, Maskay NM, Sharma BP. Paying for hospital-based care of kala-azar in Nepal: assessing catastrophic, impoverishment and economic consequences. *Health Policy Plan.* 24(2), 129–139 (2009).

6 Singh S, Kumar J, Singh R, Dwivedi SN. Hepatitis B and C viral infections in Indian kala-azar patients receiving injectable anti-leishmanial drugs: a community-based study. *Int. Soc. Infect. Dis.* 4(4), 203–208 (2000).

7 Sharma BP, Maskay NM, Adhikari SR *et al.* Socio-economic determinants of kala-azar in Nepal. *J. Nepal Health Res. Council* 2(1), 35–42 (2004).

8 Shah H. Prevalence of visceral leishmaniasis associated with the behaviors of the people in rural areas. *J. Nepal Med. Assoc.* 44(160), 116–120 (2005).

9 Thakur CP. Kala-azar may break out in epidemic form. *The Times Of India*, 27th April, (2005).

10 Hasker E, Singh SP, Malaviya P *et al.* Factors associated with visceral leishmaniasis in rural Bihar, India; a multilevel analysis. *Trop. Med. Int. Health* (Suppl. 2), 55–62 (2010).

11 Alvar J, Yactayo S, Bern C. Leishmaniasis and poverty. *Trends Parasitol.* 22(12), 552–557 (2006).

12 Pascual Martínez F, Picado A, Roddy P, Palma P. Low castes have poor access to visceral leishmaniasis treatment in Bihar, India. *Trop. Med. Int. Health* doi:10.1111/j.1365-3156.2012.02960.x (2012) (Epub ahead of print).

13 Chappuis F, Rijal S, Soto A, Menten J, Boelaert M. A meta-analysis of the diagnostic performance of the direct agglutination test and rK39 dipstick for visceral leishmaniasis. *BMJ* 333(7571), 723 (2006).

14 World Health Organization. Control of the leishmaniases. *World Health Organ. Tech. Rep. Ser.* (949), xii–xiii, 1–186, back cover (2010).

15 den Boer M, Argaw D, Jannin J, Alvar J. Leishmaniasis impact and treatment access. *Clin. Microbiol. Infect.* 17(10), 1471–1477 (2011).

16 Sundar S, Chakravarty J, Agarwal D, Rai M, Murray HW. Single-dose liposomal amphotericin B for visceral leishmaniasis in India. *N. Engl. J. Med.* 362(6), 504–512 (2010).

17 Sundar S, Sinha PK, Rai M *et al.* Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. *Lancet* 377(9764), 477–486 (2011).

18 van Griensven J, Boelaert M. Combination therapy for visceral leishmaniasis. *Lancet* 377(9764), 443–444 (2011).

19 Matlashewski G, Arana B, Kroeger A *et al.* Visceral leishmaniasis: elimination with existing interventions. *Lancet Infect. Dis.* 11(4), 322–325 (2011).

20 Sinha PK, Roddy P, Palma PP *et al.* Effectiveness and safety of liposomal amphotericin B for visceral leishmaniasis under routine program conditions in Bihar, India. *Am. J. Trop. Med. Hyg.* 83(2), 357–364 (2010).

21 Sundar S, Singh A, Rai M *et al.* Efficacy of miltefosine in the treatment of visceral leishmaniasis after a decade of use in India. *Clin. Infect. Dis.* doi:10.1093/cid/cis474 (2012) (Epub ahead of print).

22 Hasker E, Singh SP, Malaviya P *et al.* Factors Associated with Visceral Leishmaniasis in Rural Bihar, India. *Emerg. Infect. Dis.* (2012) (In Press).

23 John TJ, Dandona L, Sharma VP, Kakkar M. Continuing challenge of infectious diseases in India. *Lancet* 377(9761), 252–269 (2011).

24 Singh SP, Hasker E, Picado A *et al.* Risk factors for visceral leishmaniasis in India: further evidence on the role of domestic animals. *Trop. Med. Int. Health* 15(Suppl. 2), 29–35 (2010).

25 Killick-Kendrick R. Education is key to controlling visceral leishmaniasis. *Bull. World Health Organ.* 88(1), 11–12 (2010).

Website

101 WHO. Elimination of kala-azar from endemic countries in the southeast Asia region: health ministers sign memorandum of understanding (2005). www.searo.who.int/en/Section316/Section503/Section1861_9726.htm