Visceral leishmaniasis and HIV co-infection in Bihar, India: a wake-up call?

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Visceral leishmaniasis (VL) is a vector-borne protozoan infection caused by the *Leishmania donovani* spp. complex. Typical disease manifestations include persistent fever, hepatosplenomegaly and pancytopenia [1]. Without treatment, overt VL is universally fatal. The disease is a global health problem, with an estimated annual incidence of 200-400,000 cases [2]. VL caused by *Leishmania infantum* (*chagasi*) is mainly prevalent in Latin-America and the Mediterranean region, whereas *L. donovani* causes VL in East-Africa and the Indian subcontinent. Around 90% of VL in India, and almost half of the global burden occur in Bihar, a state in the North-East of India with a population of over 100 million inhabitants [3]. Afflicted by poverty, this region also is home to large numbers of migrant workers, traveling to and from the major cities in the region.

HIV co-infection of VL has been identified as one of the emerging challenges for VL control [4]. HIV infection dramatically increases the risk of VL and conversely, VL accelerates HIV disease progression. Historically, VL-HIV co-infection most prominently emerged in Europe in the early nineties, where up to 60% of VL cases were co-infected [4]. With the introduction of antiretroviral therapy (ART) in the late nineties, the incidence of new VL-HIV cases gradually declined [4]. The problem is now severe in some areas of Eastern Africa, particularly in Ethiopia, where up to 40% of VL patients are HIV co-infected [4]. In Brazil, co-infection was documented in six percent of VL cases in 2011 [5].

In this issue of the journal, Burza and colleagues report on a large group of adult VL patients (age ≥14 years) that were systematically offered HIV testing within a VL program run by Médecins Sans Frontières (MSF) in Bihar, India [6]. Of the 2130 individuals diagnosed with VL over an 18 month period, 2077 (97.5%) agreed to HIV testing, of whom 117 (5.6%) were found to be HIV positive. This included 49 (2.4%) newly diagnosed HIV cases and 68 (3.3%) cases that had been diagnosed previously at other health facilities and were retested in the MSF program. Males aged 35-44 years were most markedly affected, with a total HIV prevalence of 12.8% and a prevalence of previously undiagnosed HIV of 5.4%.

While the strengths of the report include the large sample size and the high uptake of HIV testing, these data come from a single non-governmental program providing free VL care and can obviously not be considered a representative sample. The authors acknowledge that the estimate could somehow be inflated by the fact that the MSF program has an interest in VL-HIV co-infection and might attract referrals of co-infected patients from other centers. Nevertheless, newly diagnosed HIV infection in 2.4% of VL cases, which would have been missed without routine HIV testing, is still high. Assuming quality-assured testing, the applied HIV diagnostic algorithm should be appropriate, with very rare false positive results although the use of one of the HIV rapid diagnostic tests in the MSF program could theoretically have led to a few missed diagnoses of HIV. The increased likelihood of atypical presentation of VL and the reportedly lower sensitivity of serological tests for VL in HIV infected patients could possibly further contribute to underdiagnosis [7].

There are also few data to triangulate these findings. The scarce previous reports have generally included very few patients. On the other hand, the VL-HIV co-infection rate also reportedly increased from 0.88% (a total of 339 cases – adults and children presumably combined) in 2000 to 2.18% (a total of 776 cases) in 2006 in one of the major VL clinical trial centers in the region [4]. Although further studies and enhanced surveillance are required to more accurately define the extent of co-infection in Bihar and it's evolution over time, the message the paper by Burza *et al* carries is clear and cannot be ignored. VL-HIV co-infection should be taken seriously, and taken up by the Indian national program.

Given the large burden of (adult) VL cases in Bihar, a mere 2% co-infection rate would translate into several thousand VL-HIV cases, the largest national burden in absolute numbers at the global level. To reduce case fatality rates – one of the objectives for national programs – knowledge of HIV status is key. Generally speaking, VL-HIV co-infection is associated with increased drug toxicity (particularly with antimonials), high case fatality (up to 24% in some studies) and lower cure rates [4]. Previous data from the same MSF program indirectly suggested a more than ten-fold increased mortality for co-infected patients [8]. The evidence base for the optimal treatment of VL in HIV patients remains poor, especially on the role of combination therapy and how to treat and prevent VL relapse cases [9,10]. Initiatives such as AfriCoLeish [11], an international consortium dedicated to VL in Africa, should be extended to India. Within AfriCoLeish, two clinical trials (one relating to VL combination therapy, and one on secondary prophylaxis) will be conducted in co-infected patients in Ethiopia [12].

Timely introduction of ART is required to increase survival and reduce subsequent VL relapse rates [4]. In that respect, guidelines should clearly identify VL as an AIDS-defining condition, requiring ART irrespective of CD4 count levels. However, the international WHO HIV/ART guideline - used by many national programs as the basis of their own recommendations - only mentions "atypical disseminated leishmaniasis", which is not even a well-established and clearly defined clinical entity. This is in striking contrast to the WHO VL treatment guideline, which - since 1995 - clearly indicates VL as an AIDS defining condition [13-15]. As for TB/HIV co-infection, WHO has taken important initiatives for program integration [16]. Similar endeavors should be undertaken for VL/HIV co-infection. Integrating VL and HIV guidelines might also engender greater awareness about VL in HIV programs in both endemic and non-VL endemic regions. This is especially important since many co-infected cases are male migrant workers, traveling to and from VL non-endemic regions.

Increasing numbers of VL-HIV co-infected individuals might also have substantial public health consequences, both short and long-term. In Europe, where transmission is zoonotic and humans are not thought to substantially contribute to transmission, co-infected VL cases were found to be highly infectious [17]. More importantly, parasites could easily be cultured from the peripheral blood over a period of up to ten years, even during asymptomatic periods [18,19]. This condition has been labelled active chronic visceral leishmaniasis [19]. Over a longer time frame, these cases might play a relatively important role in ongoing transmission and could, especially given the high mobility of migrant

populations, even contribute to introduction of VL in non-endemic areas. Studies on the infectivity of HIV patients in India during asymptomatic and symptomatic *Leishmania* infection would be worthwhile.

Combined with their often repeated exposure to VL drugs, co-infected patients could even serve as source of the emergence and spread of drug-resistant parasites. In Europe, VL-HIV co-infection has been associated with increased parasite strain diversity [20], a trend that - as documented in Italy - was reversed after the scaling-up of ART [21]. Such information is not available from India, but it would be worthwhile to collect and monitor for it.

In addition, for the VL elimination initiative [22], VL-HIV co-infection might bring additional challenges. One of the most difficult but crucial aspects of successful disease elimination is to reach the final pockets of infected and/or diseased individuals, to avoid rapid disease re-emergence once elimination efforts are scaled down. Giving due emphasis to VL-HIV co-infection, occurring within a difficult to reach and mobile population that could possibly act as reservoir, will be essential to achieve VL elimination.

Without doubt, both for individual treatment success and public health safety, VL-HIV co-infection has to be taken seriously. The authors refer to the website of the National Vector Borne Disease Control Program to underscore their statement that VL-HIV co-infection is not considered a major public health issue in India. As websites are not always regularly updated, it would be useful to have the current official take of the national program on this issue. Nevertheless, the available guidelines do not reflect due attention for VL-HIV co-infection.

The Brazilian experience can serve as an inspiring contemporary example for national programs. The problem of VL-HIV co-infection was recognized relatively early on by the Brazilian scientific community and, most importantly, taken up by the national program [23]. A surveillance program network was established, building on the pre-existing network for the monitoring and control of HIV/AIDS [23]. HIV co-infection was identified as one of the factors driving high case fatality rates [24]; as a result, routine HIV testing for VL cases was implemented. VL and HIV/ART guidelines were streamlined and a guideline dedicated to VL-HIV co-infection was written, approaching the problem both from within the HIV and the VL program [25]. Research findings have been generated, feeding into policy and guidelines. The country now appears prepared to tackle the problem and mitigate its impact. India has a long way to go.

It might be wise to also look beyond HIV to non-HIV patients with immunosuppressive conditions such as organ transplants and cancer, or those on immunosuppressive drugs for various reasons [26]. At the global level, the prevalence of these conditions is expected to rise and might even overtake HIV as the main immunosuppressive conditions associated with VL. For instance, in a recent outbreak of leishmaniasis in Madrid, non-HIV related immunosuppression outnumbered the cases of VL-HIV co-infection [27].

India has taken significant steps combatting VL, committing to move towards elimination in the region [22]. The country has a strong research community, and many of the pivotal VL clinical trials have been conducted in India [28,29]. While the findings reported by Burza *et al* do not provide an estimate of the actual burden of VL-HIV co-infection in India at large, they clearly suggest a wake-up call. It is now time to tackle VL-HIV co-infection.

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