EDITORIAL COMMENTARY

Visceral Leishmaniasis and HIV Coinfection in Bihar, India: A Wake-up Call?

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(See the Brief Report by Burza et al on pages 552–5.)

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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 200 000–400 000 cases [2]. VL caused by *Leishmania infantum* (*chagasi*) is 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 northeast India, with a population of more than 100 million [3]. Afflicted by poverty, this region also is home to large numbers of migrant workers who travel to and from the major cities in the region.

Human immunodeficiency virus (HIV) coinfection of VL has been identified as an emerging challenge for VL control [4]. HIV infection dramatically increases the risk of VL and, conversely, VL accelerates HIV disease progression. Historically, VL–HIV coinfection prominently emerged in Europe in the early 1990s, where up to 60% of VL cases were coinfected [4]. With the introduction of antiretroviral therapy (ART) in the late 1990s, the incidence of new VL–HIV cases gradually declined [4]. The problem is now severe in some parts of eastern Africa, particularly Ethiopia, where up to 40% of VL patients are HIV coinfected [4]. In Brazil, coinfection was documented in 6% of VL cases in 2011 [5].

In this issue of *Clinical Infectious Diseases*, Burza and colleagues report on a large group of adult VL patients (aged ≥14 years) who 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, the data come from a single nongovernmental program that provides free VL care and can obviously not be considered a representative sample. The authors acknowledge that the estimate could be inflated by the fact that the MSF program has an interest in VL–HIV coinfection and might attract referrals of coinfected 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. However, the use of 1 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 limited number of studies on the topic have generally included very few patients. On the other

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hand, the VL–HIV coinfection rate reportedly increased from 0.88% (339 cases, presumably adults and children combined) in 2000 to 2.18% (776 cases) in 2006 at a major VL clinical trial center in the region [4]. Although further studies and enhanced surveillance are required to more accurately define the extent of coinfection in Bihar and its evolution over time, the message from Burza et al is clear and cannot be ignored. VL–HIV coinfection 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% coinfection 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. In general, VL–HIV coinfection 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 >10-fold increased mortality for coinfected patients [8]. The evidence base for the optimal treatment of VL in HIV patients remains poor, especially the role of combination therapy and how to treat and prevent VL relapse cases [9, 10]. Initiatives such as AfriCoLeish (www.africoleish.org), an international consortium dedicated to VL in Africa, should be extended to India. Within AfriCoLeish, 2 clinical trials (1 relating to VL combination therapy and 1 on secondary prophylaxis) will be conducted in coinfected patients in Ethiopia [11].

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 that requires ART irrespective of CD4 counts. However, the World Health Organization (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 that, since 1995, clearly indicates VL as an AIDS-defining condition [12–14]. As for tuberculosis–HIV coinfection, WHO has taken important steps for program integration [15]. Similar endeavors should be undertaken for VL–HIV coinfection. Integrating VL and HIV guidelines might also engender greater awareness of VL in HIV programs in both VL endemic and nonendemic regions. This is especially important since many coinfected individuals are male migrant workers who travel to and from VL nonendemic regions.

Increasing numbers of VL–HIV coinfected individuals might also have substantial public health consequences, both short term and long term. In Europe, where transmission is zoonotic and humans are not thought to substantially contribute to transmission, coinfected VL cases were found to be highly infectious [16]. More importantly, parasites could easily be cultured from the peripheral blood over a period of up to 10 years, even during asymptomatic periods [17, 18]. This condition has been labeled active chronic VL [18]. Over a longer period of time, these cases might play a relatively important role in ongoing transmission and could contribute to introduction of VL in nonendemic areas, especially given the high mobility of migrant populations. 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, coinfected patients could serve as a source of the emergence and spread of drug-resistant parasites. In Europe, VL–HIV coinfection has been associated with increased parasite strain diversity [19], a trend that, as documented in Italy, was reversed after the scaling up of ART [20]. 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 [21], VL–HIV coinfection 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 in order to avoid rapid disease reemergence once elimination efforts are scaled down. It will be essential that VL–HIV coinfection, which occurs within a difficult-to-reach and mobile population that could possibly act as reservoir, be emphasized in order to eliminate VL.

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

The Brazilian experience can serve as an inspiring contemporary example for national programs. The problem of VL–HIV coinfection was recognized relatively early on by the Brazilian scientific community and, most importantly, taken up by the national program [22]. A surveillance program network was established to build on the preexisting network for monitoring and controlling HIV–AIDS [22]. HIV coinfection was identified as 1 of the factors driving high case fatality rates [23]; as a result, routine HIV testing for VL was implemented. VL and HIV ART guidelines were streamlined and a guideline dedicated to VL–HIV coinfection was written, approaching the problem from within both the HIV and VL programs [24]. Research findings that feed into policy and guidelines have been generated. 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 [25]. 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 coinfection [26].

India has taken significant steps to combat VL, committing to move toward elimination in the region [21]. The country has a strong research community, and many of the pivotal VL clinical trials have been conducted in India [27, 28]. While the findings reported by Burza et al do not provide an estimate of the actual burden of VL–HIV coinfection in India at large, they clearly suggest a wake-up call. It is now time to tackle VL–HIV coinfection.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

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