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COMMENTARY

The Leishmaniasis East Africa Platform (LEAP): strengthening clinical trial capacity in resource-limited countries to deliver new treatments for visceral leishmaniasis

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Visceral leishmaniasis is a neglected tropical disease endemic in East Africa where improved patient-adapted treatments are needed. The Leishmaniasis East Africa Platform (LEAP) was created in 2003 to strengthen clinical research capacity, serve as a base for training, and evaluate and facilitate implementation of new treatments. Major infrastructure upgrades and personnel training have been carried out. A short course of Sodium Stibogluconate and Paramomycin (SSG&PM) was evaluated and is now first-line treatment in the region; alternative treatments have also been assessed. LEAP can serve as a successful model of collaboration between different partners and countries when conducting clinical research in endemic countries to international standards.

Keywords: Capacity building, Clinical trial, East Africa, Kala-azar, LEAP, Leishmaniasis

Visceral leishmaniasis (VL), or 'kala-azar', is a parasitic disease highly endemic in the Indian subcontinent and East Africa.[1] Caused by the protozoan parasites *Leishmania donovani* and *Leishmania infantum*, VL is potentially fatal and responsible for the deaths of up to 40 000 people per year. It is spread by the bite of an infected female sand fly; symptoms include fever, hepatosplenomegaly, lymphadenopathy, anemia, weight loss and weakness.

The Leishmaniasis East Africa Platform (LEAP) was founded in 2003 in Khartoum, Sudan, by the Drugs for Neglected Diseases *initiative* (DNDi), bringing together stakeholders from Kenya, Ethiopia and Sudan, and was joined by those from Uganda in 2006. New, improved, treatment options were needed to address the specific needs of the eastern African region, such as drug combinations, less toxic and more affordable shorter course treatments and, ideally, an effective, safe, oral treatment. Existing therapies have serious drawbacks: pentavalent antimonials, such as Sodium Stibogluconate (SSG), require 30 d of injections and there are concerns about resistance and cardiotoxicity; miltefosine is expensive and teratogenic; paromomycin (PM) shows geographical differences in efficacy and there are concerns about developing resistance when used as a monotherapy; and liposomal amphotericin B, AmBisome (Gilead Sciences Inc., Foster City, CA, USA), needs to be administered intravenously and is expensive.

One of the original aims of the platform was to evaluate a short course of SSG and PM in combination. A multi-center trial (LEAP 0104) was conducted between 2004 and 2010 to evaluate the safety and efficacy of PM alone or in combination with SSG administered over 17 d. The combination was found to have a very good safety profile with similar efficacy to the standard 30 d SSG treatment,[2–4] confirmed in a subsequent pharmacovigilance study.[5] In March 2010, the WHO Expert Committee on the Control of Leishmaniases recommended SSG&PM as first-line treatment for VL in eastern Africa. It has been included in the national guidelines of Sudan, South Sudan, Ethiopia and Kenya. PM is registered in Uganda (2011) and Kenya (2013), and is in the process of being registered in Sudan and Ethiopia.

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Significant capacity-building was needed in the region when trials started in 2004. LEAP built two 24-bed Leishmaniasis research and treatment centers in Ethiopia and rehabilitated facilities at three sites in Uganda, Kenya and Sudan. Patient treatment has been vastly improved; previously in Kenya VL patients were brought to Nairobi from endemic areas to receive treatment, and Ethiopian patients were treated in tents. Other projects and institutes have made use of these new/improved facilities. The data centre was established in Nairobi, Kenya, in 2004 to provide centralized clinical data management for LEAP trials, and has become a specialized unit within the region for processing data in a way that conforms to international Good Clinical Practice (GCP) standards. An open source system has been adapted in order to capture clinical data offline in remote areas where internet infrastructure is unreliable.[6]

Following on from this original trial, LEAP members have been evaluating alternative treatments for VL. Liposomal amphotericin B (AmBisome) has been used mostly as second-line therapy in Africa; the LEAP 0106 trial in Ethiopia and Sudan attempted to determine the minimum efficacious single dose compared to multiple administration, but none of the doses tested were found to have sufficient efficacy in African patients,[7] despite having been previously shown to be efficacious in Indian patients.[8] Miltefosine alone or in combination with SSG was evaluated (LEAP 0208) and although efficacy in all arms was below that for SSG&PM, the trial collected important safety, efficacy and pharmacokinetic data, particularly with regard to underexposure of miltefosine in children (M Wasunna, S Njenga, M Balasegaram et al., results in preparation). An allometric dosing study of miltefosine (LEAP 0714) was undertaken in pediatric VL patients (4 to 12-years-old), to ascertain whether drug exposure in children can be safely increased to equivalent adult drug exposure, and to assess tolerability; results from the study are awaited.

Coinfection with HIV is an increasing concern, with up to 35 countries reporting cases; both diseases are mutually reinforcing. The efficacy of liposomal amphotericin B (AmBisome) in combination with miltefosine and as a higher dose monotherapy in HIV-coinfected Ethiopian patients (LEAP 0511) is ongoing. Monthly infusions of pentamidine as secondary prophylaxis, in addition to antiretroviral therapy, was found to decrease the VL relapse rate in HIV-coinfected patients.[9]

Diagnostic tests have also been assessed, as a result of which the Kenyan Ministry of Health revised their national guidelines and now recommends rk39 rapid diagnostic test to be used for diagnosis of VL in remote areas.[10]

The research platform has facilitated training sessions for over 800 personnel between 2004 and 2014, encompassing all aspects of conducting trials to international standards, VL diagnosis, and treatment and country-specific guidelines, resulting in increased capacity for conducting clinical trials and improvements in the quality of care for all patients: 30 people have undertaken graduate studies or higher degrees. DND*i* has also trained LEAP partners in good financial practice. However, high staff turnover at partner institutions is a challenge.

LEAP is currently composed of 60 individual members representing over 20 institutions, covering the spectrum of clinical research and disease control organizations working in leishmaniasis-endemic countries in Sudan, Uganda, Kenya and Ethiopia. The secretariat is coordinated by DND*i*'s African regional office in Nairobi. The platform meets biannually, publishes a newsletter and held its first scientific conference in 2014. The total direct cost for the LEAP platform for the period 2003–2015 is US$3.8 million (€3.4 million).

The platform has faced a number of challenges, especially during the early years whilst trust was being built up. Although initially members, perhaps understandably, sought to maximize infrastructure upgrades for their own countries, with time there has been a move towards using the external funding available for capacity building across the whole platform, to the benefit of all. Biannual meetings and regular consultations help overcome challenges, and collaboration between countries and staff has been key to the success of the trials, in particular with regards to monitoring, cross-validation of samples and sharing of safety data. All stakeholders are involved from the beginning in the LEAP platform activities, including priority-setting, clinical trials, capacity strengthening and dissemination of results. Including investigators and clinicians in decision-making has ensured a strong ownership of the platform and empowered them to initiate additional collaborations. Throughout the process, DND*i* and LEAP have worked with regulatory authorities and Ministries of Health. This has helped their understanding of the issues and patient needs, ensuring LEAP efforts are aligned with programmatic (rather than academic) needs and, if successful, resulting in an easier uptake of results into policy. Although the SSG&PM combination has been incorporated into the revised guidelines of some of the LEAP countries, issues with patient access to treatment persist; the platform must continue to work with Ministries of Health and affected communities to ensure SSG&PM is purchased for all VL patients. In order to avoid the lengthy regulatory approvals processes seen in some countries, further capacity building is important for ethics and drug regulatory authorities and regulatory harmonization within the LEAP countries to become possible. By joining efforts and engaging the scientific community and regulatory authorities regionally, LEAP has overcome political and cultural differences to define a regional strategy for alleviating the burden of VL in eastern Africa. The platform has enabled efficient translation of research into policy by giving ownership to its members and promoting communication and exchanges of information and skills across borders.

Looking to the future, LEAP will continue to provide a solid clinical research environment, fostering ongoing collaborations and encouraging and mentoring young scientists. In addition, it would like to offer improved infrastructure to ensure capacity at a regional level, such as for Phase I studies, pharmacovigilance studies and data collection, and to have an impact in other VL endemic areas in the region. Moreover LEAP would like to join forces with other regional platforms, ultimately aiming at creating a virtual global network for infectious diseases research in the region, which could encompass basic science research, new treatments, vaccines, epidemiology, vector and disease control, diagnostics, access to treatments and the sharing of expertise. This pan-African network of excellence should be sustainable and able to mobilize resources effectively.

Authors' contributions: AH, AM and MW are the current and previous LEAP chairs respectively; JA and MB are the current and previous Heads of the leishmaniasis programme at DND*i*; AM, AH, EGK, JO, RJ and MW are Country Principal Investigators; SW and MW drafted the initial manuscript. All authors read and approved the final manuscript. Drugs for Neglected Diseases initiative is the guarantor for the manuscript.

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