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Editorial

Chagas Disease in HIV-Infected Patients: It's Time to Consider the Diagnosis

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Chagas disease, caused by the parasite *Trypanosoma cruzi*, is a leading cause of heart failure in Latin America, with a significantly worse prognosis than other causes of cardiomyopathy.[1] Unfortunately, less than 1% of infected persons in the United States and endemic countries receive antiparasitic treatment.[2,3] The lack of standardized surveillance and prompt treatment leaves infected individuals vulnerable to life-long chronic infection, which in 20% to 30% of infected individuals can manifest as gastrointestinal tract organomegaly or cardiac system abnormalities. In those who develop cardiac disease, illness manifests as dilated cardiomyopathy, thromboembolism, or sudden cardiac death.[4] Immunocompromised patients can develop severe disease during the acute phase or reactivation at any point during their lifetime. Reactivation typically manifests as myocarditis or central nervous system (CNS) disease, and should be considered in those diagnosed with HIV infection, or those undergoing cancer chemotherapy or receiving organ or bone marrow transplantation.[5]

This neglected tropical disease has increasingly become globalized as immigrant populations from endemic areas of Central and South America establish themselves in the United States, Europe, Japan, and elsewhere.[6] More than 300,000 infected immigrants live in the United States, and more live in Spain and other non-endemic countries,[7] highlighting the need for expansive awareness among the medical community. Mounting evidence supports Chagas disease surveillance in Latinx immigrants in the United States, where up to 20% of cases presenting with classic Chagas disease clinical signs and symptoms or epidemiological risk factors are misdiagnosed.[8,9] As the recent coronavirus disease 2019 pandemic has taught us, these vulnerable groups are particularly susceptible to poor health-care access, and the imperative to diagnose this chronic, silent killer has never been greater.

HIV-infected patients are particularly susceptible to *T. cruzi* reactivation, manifesting as meningoencephalitis, CNS chagomas, acute myocarditis, and other sequelae.[10] Although patients with reactivation disease can be treated with standard therapy (e.g., benznidazole),[11] delayed diagnosis can prove fatal. An article in this issue of the *American Journal of Tropical Medicine and Hygiene* highlights the importance of heightened Chagas disease surveillance among HIV-infected patients. Reimer-McAtee et al.[12] conducted a cross-sectional study of *T. cruzi* prevalence among a Bolivian cohort of ambulatory and hospitalized HIV-infected individuals, identifying 28% *T. cruzi* seropositivity, and reactivation disease in 12.5% of *T. cruzi* seropositive individuals. They present compelling evidence that, regardless of specific signs or symptoms, HIV-infected patients from endemic countries should be tested for Chagas disease.

A challenge in treating HIV-infected patients with *T. cruzi* infection is understanding the parasite burden and whether CNS reactivation is imminent. Reimer-McAtee et al. used quantitative polymerase chain reaction (qPCR) to detect high levels of parasitemia, and demonstrated that these correlated with lower CD4 T-cell counts. These results suggest that qPCR may be used in conjunction with direct microscopy to suggest imminent reactivation disease. The current HIV treatment guidelines from the U.S. CDC, NIH, and the HIV Medicine Association of the Infectious Diseases Society of America suggest that qPCR assays can be performed on serial blood specimens in individuals infected with HIV and *T. cruzi*, and that an increasing parasite burden over time suggests reactivation.[13] Furthermore, Reimer-McAtee et al. demonstrated that lower CD4 T-cell counts were associated with increased risk of reactivation disease. Notably, one of the outstanding questions in clinical care for HIV-infected individuals with Chagas disease is when to start combination antiretroviral therapy vis-à-vis anti-trypanosomal therapy. Current recommendations suggest no contraindication to concurrent treatment, but these patients should be monitored closely for possible immune reconstitution inflammatory syndrome. Furthermore, as a result of the elevated risk of treatment failure in HIV-infected patients, qPCR monitoring after treatment completion is recommended to offer an earlier indicator of treatment failure compared with serological conversion.[14]

Reimer-McAtee et al. highlight the burden of Chagas disease in Bolivians. Bolivia has a long history of active *T. cruzi* transmission, and its emigrant population has demonstrated high seropositivity years after migration.[15] The lack of readily available treatment of Chagas disease in Bolivia[3] renders HIV-infected individuals still living in Bolivia particularly vulnerable to *T. cruzi* reactivation. Furthermore, most Central and South American countries have high HIV-Chagas disease burdens,[16] and the results of Reimer-McAtee et al. have important implications for these populations.

Despite their uniquely high seropositivity, Chagas disease surveillance in the United States should not be limited to Bolivian immigrants. Studies in the United States suggest overall seroprevalence rates of 1% to 3.8%,[17,18] higher rates in family members of those with Chagas disease (7.4%),[19] and up to 19% rates in Latinx immigrants with evidence of cardiomyopathy.[8,9] Importantly, diagnosis and treatment of women in child-bearing years prevent congenital transmission[20]; lack of testing and treating infected women globally will result in new pediatric cases in endemic countries and among immigrants. Furthermore, a new wave of vector-acquired infections is potentially occurring in Latin America following the eradication of *Rhodnius prolixus*.[21] Vector-borne disease transmission was believed to have been greatly interrupted as a result of the eradication of this key vector; however, new evidence

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suggests that transmission from non-eradicated secondary vectors (e.g., *Triatoma dimidiata*) is occurring and will result in new pediatric cases.[16,22] Collectively, these two aforementioned factors highlight the need to consider children, not just adults, for Chagas disease diagnosis.

Reimer-McAtee et al. bring new attention to Chagas disease, an underdiagnosed problem, especially outside endemic regions. Clinicians in endemic countries and those working with Latinx patients more widely, particularly HIV-infected patients, should consider Chagas disease routinely in their differential diagnosis and clinical practice. Perhaps by raising awareness about Chagas disease among HIV providers, this neglected tropical disease can emerge from obscurity. Development of diagnostic and treatment guidelines by professional organizations such as the Infectious Diseases Society of America and the American Society of Tropical Medicine and Hygiene would help promote this goal.

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