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Filarial/Human Immunodeficiency Virus Coinfection in Urban Southern India

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Abstract. The disease course of human immunodeficiency virus (HIV) is often altered by existing or newly acquired coinfections. Treatment or prevention of these concomitant infections often improves the quality and duration of life of HIV-infected persons. The impact of helminth infections on infections with HIV is less clear. However, HIV is frequently most problematic in areas where helminth infections are common. In advance of the widespread distribution of drugs for elimination of lymphatic filariasis, we assessed the prevalence of active *Wuchereria bancrofti* infection among HIV-positive patients in Chennai, India at two time points separated by four years. We found that the overall prevalence of *W. bancrofti* infections among HIV-positive persons was 5–9.5%, and there were no quantitative differences in circulating filarial antigen levels between HIV-positive and HIV-negative filarial-infected patients.

INTRODUCTION

The disease course of human immunodeficiency virus (HIV) is dependent on many factors, including host, virus, treatment, and environment. Mechanisms delaying disease progression are of primary importance. One such strategy is to address concomitant infections: from the beginning of the HIV epidemic, HIV was recognized by a constellation of opportunistic infections that accompany advanced disease. Through treatment and prevention of these non-HIV diseases, life expectancies of HIV-infected persons are greatly prolonged, even without specific antiretroviral treatments.

Coinfection with systemic helminths, in addition to causing morbidity on their own, may contribute to an increased morbidity from HIV. An *in vitro* study demonstrated that peripheral blood mononuclear cells from persons with actively filarial infections were more susceptible to HIV infection than were the cells from the same persons after definitive treatment of their filarial infections.[1] Moreover, a cross-sectional prevalence study in Tanzania showed that people positive for circulating antigen of *Wuchereria bancrofti* were more likely to be HIV positive than persons without filarial infections.[2] Although intriguing and with potential significance for HIV control programs in filarial-endemic areas, the implications of these findings have yet to be determined.

Few studies have examined the burden of parasitic infections in HIV-infected persons, yet it is likely to be as high or higher than that in the general population. The latest figures from the World Health Organization estimate that 129 million persons worldwide are infected with *W. bancrofti*, *Brugia malayi*, or *B. timori*, the major causative agents of lymphatic filariasis, that 3.5 billion persons are infected with intestinal helminths, and that there are 300–500 million new cases of malaria per year. Most of this burden of disease is concentrated in countries where HIV incidence and prevalence are greatest. In India, parasitic infections are endemic throughout the country with the prevalence of hookworm infection ranging between 30% and 62% (in regions around Chennai); the prevalence of *Strongyloides* and *Ascaris* is lower.[3] The prevalence of lymphatic filariasis, a disease caused by the nematode *W. bancrofti* in southern India, is estimated to be 6–20% on the basis of circulating filarial antigenemia.[3]

According to figures from the National AIDS Control Organization and the United Nations Joint Program on HIV/AIDS,[4] the estimated number of adults in India living with HIV/acquired immunodeficiency syndrome in 2007 was 0.36% of the general population (approximately 2.5 million people); the distribution is not uniform, with a higher prevalence in the southern Indian states than in northern states. Prevalence rates among select groups, such as commercial sex workers, persons who come to sexually transmitted disease clinics, and intravenous drug users, are much higher and approach 10–30%.[5] Use of antiretroviral drugs in the public health system is expanding gradually in this population, with an estimated 100,000 persons (6–15% of the population qualifying for antiretroviral drugs) receiving the medications at the end of 2006.[6,7]

In advance of mass drug administration for lymphatic filariasis and to ultimately assess the impact of antifilarial treatment on HIV/filaria coinfection in India, we conducted two surveys four years apart in serum samples of HIV-positive patients, looking for evidence of active filarial infection. Our question was whether HIV-infected persons had a higher or lower prevalence of filarial infection than HIV-negative patients in Chennai, Tamil Nadu, India.

METHODS

The Institutional Review Boards of the National Institute of Allergy and Infectious Diseases (Bethesda, MD), the Y. R. Gaitonde Centre for AIDS Research and Education, and the Tuberculosis Research Center (both in Chennai, India) reviewed and approved this study. In 2000, 432 HIV-positive serum samples (and for comparison a group of HIV-negative sera from voluntarily screened patients) from the HIV clinic at Y. R. Gaitonde Centre for AIDS Research and Education were assessed for active filarial infection by detection of circulating filarial antigen (CFA). In 2004, 200 HIV-positive sera from patients from the HIV clinic at the Tuberculosis Research Center were tested. Samples from both clinics were well-characterized stored sera from persons referred for HIV testing. The HIV-positive and HIV-negative samples were from persons of the same socioeconomic status. Because samples were de-identified, no information was available on age, sex, or other demographic information.

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We used the *W. bancrofti* NOW® immunochromographic (ICT) antigen card test (Binax, Portland, ME) to determine prevalence of filarial infection.[8] To quantify antigen levels, ICT-positive sera were analyzed using the *W. bancrofti* Og4C3 antigen-capture enzyme-linked immunosorbent assay (TropBio, James Cook University, Townsville, Queensland, Australia) according to the manufacturer's instructions.[9] No duplication of patients occurred between 2000 and 2004. Statistical analysis was done using the Mann-Whitney U test and StatView™ software (Abacus, London, United Kingdom).

RESULTS

Of 432 HIV-positive patients screened in 2000, 21 (4.9%) were positive for filarial antigen by the ICT card test. In 2004, 200 patient serum samples were screened, 19 of which were positive by the ICT card test, resulting in an HIV/*W. bancrofti* coinfection prevalence of 9.5% (Figure 1A). Prevalence of *W. bancrofti* infection in HIV-positive persons did not differ statistically from that of HIV-persons (7%, n = 99).

Because infection with *W. bancrofti* likely preceded the acquisition of HIV, we assessed whether HIV infection influenced the level or burden of filarial infection. Thus, levels of *W. bancrofti* circulating antigen were quantitated in both HIV-positive and HIV-negative persons. When filarial-infected persons with or without HIV infections were assessed by quantitative enzyme-linked immunosorbent assay for CAg of *W. bancrofti*, there was no statistically significant ($P = 0.07$) difference in the level of filaria antigenemia in the two groups (Figure 1B). The geometric mean (range) CAg levels were 2,700 (217–21,080) units/mL in HIV-positive persons and 3,211 (501–7,799) units/mL in HIV-negative persons.

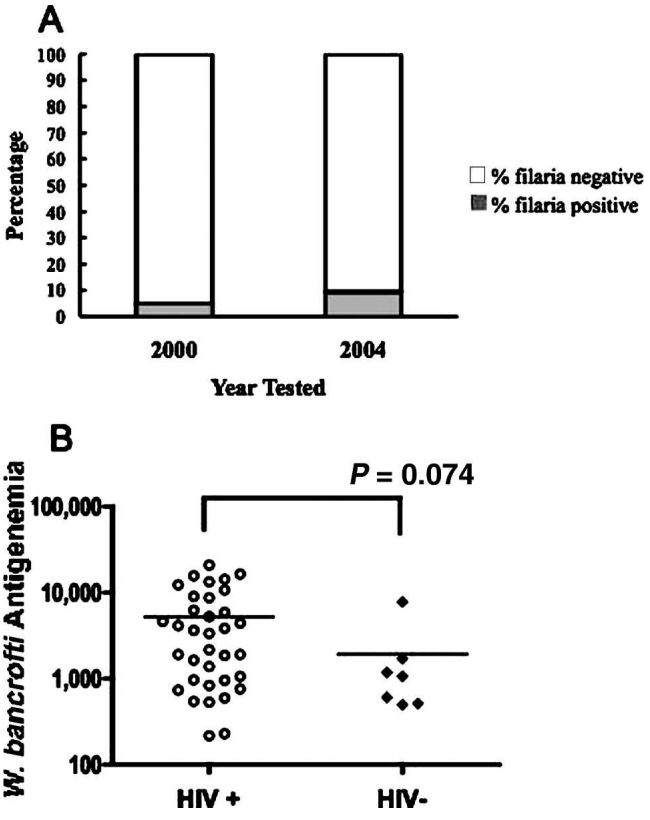

FIGURE 1. **A**, Filarial antigen-positive sera in total number of sera positive for human immunodeficiency virus (HIV) tested, by year. The gray bars represent percentages that were filarial antigen positive within the total number of sera tested. **B**, Filarial antigen levels by detected by enzyme-linked immunosorbent assay in HIV-negative and HIV-positive persons. The bar in the center represents the median and each circle represents an individual patient.

DISCUSSION

Controlling concomitant infections that may have a detrimental effect on infection with HIV is imperative. Although infection with HIV will progress and definitive antiretroviral treatment will be necessary, the precedence for postponing illness and death in HIV patients by controlling concomitant infections has been well established in other coinfections. The impact of parasitic infection, other than that with *Toxoplasma gondii*, on HIV has only recently been examined. Many countries now considered epicenters of HIV transmission and disease are in tropical and subtropical areas of the world where the burden of parasitic diseases remains highly significant.

The interaction of helminth infections with HIV has not been completely clarified. The dominance of type 2 cytokines present in persons with helminth infections has been postulated to encourage HIV replication because immune control of HIV requires Th1-mediated mechanisms. Some studies have shown that patients infected with HIV and concomitant intestinal helminth infections have decreased viral loads upon treatment.[10] Other studies have shown that patients infected with HIV and helminths had higher CD4 cell counts, lower viral loads, and higher CD4:CD8 ratios than did HIV-positive, helminth-negative patients. This finding was also observed in those with concomitant hookworm infections.[11] Coinfection with hookworm was associated with a lower mortality rate in HIV-positive patients.[12] Another study demonstrated that hookworm-infected patients were less likely to become infected with HIV than hookworm-negative patients.[2]

Few studies have examined the interaction of filarial infection with HIV. In two small studies of coinfection with *Onchocerca volvulus* and HIV, those infected with HIV had more significant onchocercal skin disease[13] and were less likely to have antibodies in response to onchocercal antigens.[14] *In vitro* studies showed that peripheral blood mononuclear cells from filarial-infected persons were more susceptible to HIV infection, and this susceptibility decreased once the patients were treated for their filarial infection.[1] One recent study that examined the prevalence of HIV and parasitic coinfections in Tanzania found that filarial antigen positivity was a positive predictor of HIV infection.[2] When persons HIV positive and CFA positive were compared with persons who were HIV-negative and CFA positive, there was no difference in levels of CFA. Presence of filarial antigen did not affect HIV viral load, CD4 cell count, or CD4%.[15] When a small subset of HIV-positive persons was treated with diethylcarbamazine, 12 weeks after treatment there was a statistical difference in HIV viral load between CFA-positive and CFA-negative volunteers.[16] Both *in vitro* and *in vivo* findings, if they can be shown to have wider applications, may have an impact on the Global Program to Eliminate Lymphatic Filariasis, as well as the National HIV control programs.

We attempted to determine the coprevalence of HIV and filarial infection in an area where filaria are endemic, and HIV is a growing problem. We found that the rate of filarial infection is similar to that reported in the general population (6–10%). Moreover, at a quantitative level, filarial antigenemia did not differ between HIV-positive and HIV-negative filarial infected groups. Because of the mass drug administration programs to interrupt transmission of filarial infections, it is important to know the effect of antifilarial treatment on HIV viral loads and disease progression. This question is being addressed in a prospective, case-controlled study of HIV/filarial coinfection.

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REFERENCES

1. Gopinath R, Ostrowski M, Justement SJ, Fauci AS, Nutman TB, 2000. Filarial infections increase susceptibility to human immunodeficiency virus infection in peripheral blood mononuclear cells *in vitro. J Infect Dis 182:* 1804–1808.
2. Nielsen NO, Simonsen PE, Magnussen P, Magesa S, Friis H, 2006. Cross-sectional relationship between HIV, lymphatic filariasis and other parasitic infections in adults in coastal northeastern Tanzania. *Trans R Soc Trop Med Hyg 100:* 543–550.
3. Lipner EM, Gopi PG, Subramani R, Kolappan C, Sadacharam K, Prevots DR, Narayanan PR, Nutman TB, Kumaraswami V, 2006. Coincident filarial, intestinal helminth, and mycobacterial infection: helminths fail to influence tuberculin reactivity, but BCG influences hookworm prevalence. *Am J Trop Med Hyg 74:* 841–847.
4. UNAIDS. *Press Release: 2.5 Million People Living with HIV in India*. Available at: http://www.unaids.org/en/MediaCentre/PressMaterials/FeatureStory/20070704_India_new_data.asp. Accessed August 20, 2007.
5. Steinbrook R, 2007. HIV in India—A complex epidemic. *N Engl J Med 356:* 1089–1093.
6. WHO, UNAIDS, UNICEF, 2007. *Towards Universal Access: Scaling up Priority HIV/AIDS Interventions in the Health Sector*. Progress Report. Geneva: World Health Organization, 53.
7. NACO, 2007. Number of Patients on ART Cross 1 Lakh Mark. *NACO News 3(3):* 3. Available at: http://www.nacoonline.org/Quick_Links/Publication/NewsLetter/. Accessed on December 5, 2007.
8. Weil GJ, Lammie PJ, Weiss N, 2007. The ICT filariasis test: a rapid format antigen test for diagnosis of *Bancroftian filariasis. Parasitol Today 13:* 401–404.
9. More SJ, Copeman DB, 1990. A highly specific and sensitive monoclonal antibody-based ELISA for the detection of circulating antigen in *Bancroftian filariasis. Trop Med Parasitol 41:* 403–406.
10. Wolday D, Mayaan S, Mariam ZG, Berhee N, Seboxa T, Britton S, Galai N, Landay A, Bentwich Z, 2002. Treatment of intestinal worms is associated with decreased HIV plasma viral load. *J Acquir Immune Defic Syndr 31:* 56–62.
11. Modjarrad K, Zulu I, Redden DT, Njobvu L, Lane HC, Bentwich Z, Vermund SH, 2005. Treatment of intestinal helminths does not reduce plasma concentrations of HIV-1 RNA in coinfected Zambian adults. *J Infect Dis 192:* 1277–1283.
12. Brown M, Kizza M, Watera C, Quigley MA, Rowland S, Hughes P, Whitworth JA, Elliott AM, 2004. Helminth infection is not associated with faster progression of HIV disease in coinfected adults in Uganda. *J Infect Dis 190:* 1869–1879.
13. Kipp W, Bamuhiiga J, Rubaale T, 2003. *Simulium neavei*-transmitted onchocerciasis: HIV infection increases severity of onchocercal skin disease in a small sample of patients. *Trans R Soc Trop Med Hyg 97:* 310–311.
14. Tawill SA, Gallin M, Erttmann KD, Kipp W, Bamuhiiga J, Buttner DW, 1996. Impaired antibody responses and loss of reactivity to *Onchocerca volvulus* antigens by HIV-seropositive onchocerciasis patients. *Trans R Soc Trop Med Hyg 90:* 85–89.
15. Nielsen NO, Friis H, Magnussen P, Krarup H, Magesa S, Simponsen PE, 2007. Co-infection with subclinical HIV and *Wuchereria bancrofti*, and the role of malaria and hookworms, in adult Tanzaniains: infection intensities, CD4/CD8 counts and cytokine responses. *Trans R Soc Trop Med Hyg 101:* 602–612.
16. Nielsen NO, Simonsen PE, Dalgaard P, Krarup H, Magnussen P, Magesa S, Friis H, 2007. Effect of diethylcarbamazine on HIV load, CD4%, and CD4/CD8 ratio in HIV-infected adult Tanzanians with or without lymphatic filariasis: randomized double-blind and placebo-controlled cross-over trial. *Am J Trop Med Hyg 77:* 507–513.