

## New Perspectives from China on HIV Rheumatic Manifestations



Over the past 3 decades, we have witnessed astounding changes in the course of the HIV and AIDS epidemic, with dramatically improved survival rates among those with access to medications that suppress the disease. The most significant change began in 1995, with the increase of antiretroviral drugs and the aggressive use of combinations of these drugs to curb replication of the virus. These combinations are now referred to as “highly active antiretroviral therapy” (HAART) and generally include the use of 3 or more drugs from the array of agents effective against HIV. With HIV now managed as a chronic illness in areas of the world with access to medications, and increased survival rates in a growing number of patients, we are witnessing a shift in complications arising from both HAART drug therapy and patients living longer with their disease.

Despite these remarkable advances, many questions still remain about rheumatic manifestations of HIV. Since the 1980s, early on in the HIV epidemic, rheumatic manifestations of HIV have been recognized and have often proved to be intriguing and clinically challenging. The first known report of AIDS with reactive arthritis was published in 1987<sup>1</sup>. Many subsequent cases have linked HIV infection to arthralgias, oligo and polyarthritis, psoriatic arthritis, seronegative spondyloarthropathies, infectious arthritis, pyomyositis, inflammatory myopathies, Sjögren’s syndrome, vasculitis, and fibromyalgia. Since the introduction of HAART therapy in 1995, there is emerging evidence of significant shifts in the frequency and nature of rheumatic complications seen in HIV.

An inflammatory reaction following institution of HAART known as “immune reconstitution syndrome” has been described in numerous reports. It is believed to result from an augmented immune response to pathogens that are prevalent in the host but had been clinically masked<sup>2,3</sup>. A similar syndrome occurring about 9 months after initiating HAART as either *de novo* appearance or an exacerbation of

previously occult autoimmune syndrome was described by Calabrese and colleagues in 31 patients with HIV through a review of medical literature in 2005<sup>4</sup>.

In the post-HAART era of HIV, researchers have observed a remarkable drop in the rate of new rheumatic complications, such as inflammatory arthritis and connective tissue disease<sup>4,5</sup>, while also noting increased rates of avascular necrosis (AVN) and osteoporosis in the HIV population<sup>6,7</sup>. We still have much to learn, however, about the rheumatic manifestations of HIV; researchers have concluded that in the future, further new manifestations of rheumatic disease likely will be described.

In this issue of *The Journal*, Zhang and coworkers present their unique findings of the spectrum of rheumatic manifestations in a cohort of 98 consecutive inpatients infected with HIV admitted from 1999 to 2006 to a large referral center in China. Researchers initially collected demographic data, routes of transmission, clinical features, and laboratory findings [including antinuclear antibody and hepatitis C virus (HCV) screening] and established a database. HIV infection was diagnosed by the enzyme-linked immunosorbent assay and confirmed by Western blotting. A structured interview as well as a systematic rheumatological examination was conducted for each patient by one of 2 rheumatologists. Interestingly, the majority of patients in the study acquired HIV from blood transfusion (74/98), while only 6 cases were from sexual transmission and just 2 from intravenous drug abuse. Most of the patients received contaminated blood products from Henan Province prior to mandatory testing of donated blood for HIV-1, which began in 1990. Only 7/98 patients had started HAART therapy before they were admitted to the hospital in this study. In all, 27/98 patients were coinfectd with HCV. All HCV-positive patients were started on treatment with interferon-alpha unless contraindicated.

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The main findings were:

- Rheumatic disorders such as vasculitis (20 cases, 15 of which were Behçet's disease), Sjögren-like syndrome/diffuse infiltrative lymphocytosis syndrome (11 cases), lupus-like syndrome (10 cases), and myositis (8 cases) were common in Chinese patients with HIV
- Articular disorders in these patients were rare (1/98 patients), and no cases of spondyloarthropathy were observed
- CD4+ T cell depletion and HCV coinfection predisposed HIV patients to develop rheumatic manifestations

The study is not without limitations. One reason for the high incidence of vasculitis (20 cases) in this cohort of 98 patients, compared with previous studies of rheumatic manifestations of HIV, could be that all study patients were inpatients at a tertiary referral center. Thus there was a selection bias for more severe cases of rheumatic manifestations, while less severe articular manifestations that would likely be managed in an outpatient setting were likely excluded. Also, the incidence and prevalence of Behçet's disease (accounting for 15/20 of the vasculitis cases) are high along the old Silk Road, which extends from the Middle East to China. HCV coinfection was more commonly seen in Chinese HIV patients with rheumatic complications (20/53, 38%) than in those without complications (7/45, 16%), which helps explain why Sjögren's syndrome/diffuse infiltrative lymphocytosis syndrome was commonly seen in this Chinese cohort.

Another interesting observation of the cohort is that 75% of the patients were infected with HIV by blood transfusion; in all of China, however, 60% to 70% of reported HIV infections are actually from drug users<sup>8</sup>. Could the route of transmission have implications as to the unique manifestation of associated rheumatic disease? Previous studies have noted that in HIV patients who were addicted to IV drugs or who were hemophiliacs, there was an absence of reactive arthritis, a low frequency of symptoms of articular swelling, and a marked history of septic arthritis<sup>9,10</sup>. The practices that lead to HIV infection may play a decisive role in the type of rheumatic manifestations observed in a population.

About 650,000 people in China (with a population greater than 1.3 billion) were living with HIV in 2005. The Joint United Nations Programme on HIV/AIDS says that China could have 10 million people infected with HIV or AIDS by 2010<sup>8</sup>. Although China has an increasing prevalence of HIV infection, this study is the first of its kind to report on the spectrum and characteristics of rheumatic complications in Chinese HIV patients.

What are the take-to-the-clinic messages of this study and how should we integrate these intriguing findings for HIV patients with rheumatic manifestations in our clinics? Despite tremendous advances in treatment, HIV and its rheumatic manifestations remain a significant cause of morbidity and mortality. Zhang and colleagues' study provides further evidence of the remarkable shifts in the frequency and nature of HIV associated rheumatic complications. Thus, vigilance and careful attention by physicians to these emerging patterns of rheumatic disease in the HIV population are essential to provide the best possible diagnosis and treatment for this population.

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