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Management of Rheumatic Heart Disease in Uganda: The Emerging Epidemic of Non-AIDS Co-morbidity in Resource-Limited Settings

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The expansion of antiretroviral therapy (ART) in resource-limited settings (RLS) has dramatically changed the face of the AIDS epidemic in Sub-Saharan Africa over the past decade ¹. The progress in HIV/AIDS care is in large part due to successful bilateral and multilateral collaborations of governments and non-governmental AIDS organizations. In Uganda, for example, with funding support from the National Institutes of Health (NIH) and the President's Emergency Plan for AIDS Relief, Case Western Reserve University (CWRU) and others have partnered with Ugandan institutions to develop a comprehensive HIV/AIDS infrastructure. Because of this concerted effort, the country has seen a fall in HIV prevalence from a peak of 25-30% in major urban areas to now less than 7% nationally, and nearly half of those who qualify for treatment are currently receiving it ².

These successes, however, bring new challenges. As HIV has now become a manageable chronic disease, the infected population has aged, and the higher prevalence of co-morbidities such as cardiovascular disease is increasingly recognized. The specter of a dual epidemic of HIV/AIDS and non-communicable disease threatens to place significant demands on these fragile healthcare systems ³. In addition to the higher risk of ischemic heart disease observed in the developed and developing world, the burden of endemic cardiovascular disease such as tuberculous pericarditis and rheumatic heart disease among persons living with HIV in RLS is unknown. Recognizing this emerging need, Makerere University School of Medicine, Mulago Hospital, and the Uganda Heart Institute have partnered with CWRU to extend collaboration beyond HIV/AIDS to cardiovascular disease (CVD), neurology, and oncology. Funded in part by the NIH/Fogarty International Medical Education Partnership Initiative (MEPI), the cardiology collaboration aims to provide contextually appropriate training of cardiovascular specialists and conduct research on CVD risk factors, including the impact of HIV/AIDS.

As part of the MEPI collaboration, a team of cardiologists from CWRU traveled to Kampala, Uganda in August 2012 to perform procedures in the newly opened cardiac catheterization laboratory at the Uganda Heart Institute (UHI), Mulago Hospital, including the country's first percutaneous mitral balloon valvuloplasties (PMBV) for rheumatic mitral stenosis (Figure 1A and B). Although rarely seen in the developed world, rheumatic heart disease (RHD) remains a leading cause of cardiovascular morbidity and mortality in RLS, affecting over 1 million children in Sub-Saharan Africa alone ⁴. RHD is a chronic complication of rheumatic fever, an auto-immune reaction to antecedent Group A streptococcus pharyngitis that causes varying degrees of carditis ⁵. Significant valvular regurgitation or stenosis may occur during the initial insult or after repeated damage to the valve from recurrent bouts of acute rheumatic fever ⁵. Congestive heart failure then develops insidiously and may lead to death in the 2nd to 5th decades of life if the valve is not repaired. The current treatment of choice in developed countries for rheumatic mitral valve stenosis without significant regurgitation is percutaneous balloon valvuloplasty⁶.

The first patient to benefit from this minimally-invasive procedure in Uganda was HIV-infected. In a country with a high prevalence of HIV/AIDS, it may be coincidence that this patient happened to be HIV-infected. Nonetheless, several questions arise regarding the impact of HIV on RHD (and other endemic non-communicable disease) in the country. Are perinatally HIV-infected children more or less likely than their uninfected peers to acquire acute rheumatic fever? What is the role of chronic inflammation and immune activation associated with HIV on outcomes among children with RHD? In patients with AIDS, does the CD4+ lymphopenia associated with acute rheumatic fever lead to further immunosuppression and increased susceptibility to opportunistic infections? Is someone with subclinical RHD acquired in childhood more or less likely to develop progressive disease if they become HIV-infected as an adult? Among patients colonized with Group A streptococci who are started on ART therapy, can subclinical rheumatic carditis develop within the spectrum of immune reconstitution inflammatory syndromes (IRIS)?

Although RHD is rare in the developed world, other rheumatic/immunologic complications of HIV/AIDS are not uncommon. The spectrum of disease has changed since the introduction of combination ART in the mid-1990's ^{8,9}. Autoimmunity appears to be increased in chronic HIV-infection, and molecular mimicry may be an important mechanism ¹⁰. For example, in a recent study from South Africa, anti-cyclic citrullinated peptide (anti-CCP) antibody titers were increased in advanced HIV-infection compared to controls and decreased after initiation of antiretroviral therapy ¹¹. In this context, the anti-CCP antibodies lacked the typically high specificity for rheumatoid arthritis. In some cases, inflammatory arthritis such as psoriatic arthritis ¹² or rheumatoid arthritis ¹³ may be the initial presentation of HIV/AIDS. On the other hand, advanced immunosuppression may suppress the clinical manifestations of pre-existing auto-immune conditions such as inflammatory bowel disease, systemic lupus erythematosus and rheumatoid arthritis ¹⁴. Despite this literature, little is known about the interaction of HIV with rheumatic fever and RHD. Some studies have demonstrated an increased risk for group A streptococcal infection with underlying HIV infection¹⁵; however, to our knowledge, only one case of acute rheumatic fever in an AIDS patient has been reported previously ¹⁶.

The CWRU team continues to return quarterly to Uganda as part of a comprehensive skills transfer program that also includes training for Ugandan physicians in Cleveland, Ohio. In addition, CWRU has partnered with the UHI and the Joint Clinical Research Centre (a center in existence in Uganda for care and research in HIV/AIDS) to focus specifically on RHD through an innovative foundation-funded project. This program will utilize an existing network of HIV/AIDS infrastructure to create community-based RHD treatment centers of excellence. If successful, this program may serve as a model for leveraging HIV/AIDS resources for the treatment of non-communicable diseases among both HIV-infected and uninfected patients in RLS.

We are now at a crossroads. An opportunity exists to build upon the dramatic improvements in healthcare infrastructure that HIV/AIDS investment has brought over the past decade. To extend the benefits of the ART rollout to the treatment of non-AIDS co-morbidities such as RHD will require a coordinated research effort and capital investment in health systems, particularly in human resources. Multilateral collaborations in medical specialties beyond infectious diseases that share the tripartite mission of research, education, and clinical care such as the one described in this report will be needed to move to the next level of HIV/AIDS treatment in Sub-Saharan Africa and other RLS.

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Figure 1.

A) Members of the Case Western Reserve University team with the Uganda Heart Institute physicians and cardiac catheterization lab staff. The new facility at the Uganda Heart Institute was completed in February of 2012. B) Dr. Marco Costa and Dr. Dan Simon prepare an Inoue balloon for a valvuloplasty procedure.