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High prevalence of asthma in HIV-infected adults—new insights

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Over the past decade, many new insights into asthma pathophysiology have been reported in *JACI* and elsewhere, complemented by reports of increasingly sophisticated therapeutic approaches. Disturbingly, however, the Centers for Disease Control and Prevention continues to report rising rates of asthma prevalence and incidence (http://www.cdc.gov/vitalsigns/Asthma/). Consequently, asthma is now the most common chronic disease of children in the United States and many other nations and is one of the most common chronic disorders of adulthood. The ineffable reality of asthma is that despite such progress on the research side, it remains a disease without a clear immune pathogenesis, prognostic tools, and certainly not even the remote possibility of a cure. Only by viewing asthma from as many different research perspectives as possible do we stand the greatest possibility of making the key unique insight(s) that are genuinely needed to improve clinical management and alter short- and long-term outcomes.

Gingo, et. al.,[1] have potentially made such a timely and unique contribution to the asthma literature because of their systematic and illuminating study of the prevalence of asthma and bronchodilator reversibility (BDR) in adult patients with HIV infection in the era of combination antiretroviral therapy (ART). Their findings are that 20.6% of such patients have asthma and BDR, more than double the 8.2% estimate in the general population. Although their study did not have a control cohort and did not study patients in the pre-ART era and contained certain patient types that might be expected to have a higher prevalence of asthma, nevertheless their findings are compelling enough to warrant a future controlled study of sufficient magnitude and rigor to confirm or modify their present observations. Associations the authors linked to family history, obesity, allergic inflammation, prior infection, absence of ART, and increased HIV-stimulated cytokines are commendable and will serve as models for future investigation. Several studies in vertically acquired HIV infection in pediatrics have witnessed a similar increased presence of asthma assessed by asthma mediation use, physician diagnosis or both.[2–4] These studies were controlled for HIV by inclusion of pediatric subjects who were born to HIV-infected mothers and thus were exposed to but not infected with HIV. Because of timing in the pre-ART era, one such study

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was controlled for ART and a mechanism of sudden immunoreconstitution with increasing $CD4^+$ T cell counts was made plausible as a factor precipitating airway hyperresponsiveness,[5] possibly by sensitized and dysregulated T cells attacking HIV antigens of target $CD4^+$ T cells or fungal antigens in commensal or infected relationships.[6] Allergy was also identified as a possible mechanism by physician-documented increased incidence of atopic dermatitis in HIV-infected patients with increased incidence of asthma.[4] Also, genetic predisposition is another mechanism for pediatric patients with increased asthma with inheritance of certain HLA Class I antigens, e.g. HLA.A68 (highest risk) and HLA-Cw6 (lower risk).[7] Although not established yet, the inheritance of filaggrin gene mutations, which are known to have increased prevalence in patients with atopic dermatitis and asthma,[8] would be worthy of future study in HIV-infected patients with asthma.

In addition to gene mutations that are unquestionably at play, the high prevalence of asthma across diverse genetic backgrounds strongly hints at an environmental influence, but sorting through the many allergens and other agents linked to asthma for a dominant factor has proved elusive. The surprising link between asthma and HIV potentially sheds light in this regard as well. Most complications of HIV infection and AIDS encountered prior to the ART era were ultimately linked to infections, including HIV-related malignancies such as Kaposi's sarcoma[9]. Perhaps most noteworthy, the most common AIDS-related infections were pulmonary in origin. Pneumonias due to all organism classes are increased in prevalence in AIDS patients, but a single organism class-the fungi-dominates in the United States, producing a diverse group of airway-related syndromes ranging from thrush, to frank pneumonias due to a variety of yeast-like and filamentous fungi including *Pneumocystis jirovecii* (née *carinii*), *Cryptococcus neoformans*, *Aspergillus spp*., and many others[10]. Thus, a key lesson learned from the AIDS era is that T cells are exceptionally important to the control of airway fungal infections of all kinds. The implication of the study of Gingo et. al., is therefore that the asthma seen after the initiation of ART in HIV might be due to increased inflammation directed against one or more airway fungi, the prevalence of which, while alone not sufficient to produce an outright opportunistic infection, might nonetheless be sufficient to trigger inflammation upon immune reconstitution. Abundant data from mice now clearly demonstrate the ability of diverse filamentous fungi to infect even the normal airway and produce asthma-like disease through the secretion of allergenic proteinases[11, 12]. Further support for this concept comes from the salutary effect of anti-fungal antibiotics such as itraconazole when given to asthma patients with fungal sensitization[13].

However, no studies have documented true fungal airway infection in the setting of asthma, with or without concomitant HIV infection. A major reason for this is probably the inhibitory effect of respiratory secretions on fungal growth. For example, our preliminary analysis of sinus and lower respiratory tract specimens from patients with allergic respiratory tract disease suggests that careful removal of respiratory mucus from these specimens markedly enhances recovery of both yeast and filamentous fungi (D. Corry, unpublished). Nonetheless, a formal analysis of the prevalence of airway fungi in asthma has yet to be performed. Distinguishing the commensal from true infectious presence of recovered fungi represents an additional daunting challenge to any such study. Thus, essential studies remain to be done, but these diverse published findings suggest the possibility that fungal airway infection may in part underlie the increased prevalence of asthma in HIV infection treated with ART.

HIV-infection has been a great instructor in the numerous ways the human immune response protects and paradoxically harms us. The sudden return of unregulated immunity with ART in patients undoubtedly has proven itself beneficial, but the excesses identified in both adult and pediatric lung complications of that process are worthy of special study considering the number of humans world-wide (estimated 7 million) who may develop HIV-related asthma

and BRD. Of particular interest moving forward will be to analyze the importance of airway fungal infection in both conventional and HIV-related asthma and potentially other forms of allergic disease.

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