Asthma in HIV-Infected Population: A Review of Respiratory Symptoms, Pulmonary Function Abnormalities and Pathophysiology

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Abstract

Asthma is prevalent around the world, requiring frequent hospital admissions and resulting in significant morbidity. National surveillance for asthma in the United States estimated the prevalence of asthma from 2006-2008 to be approximately 7.3% in adults, with the prevalence being higher in females (8.9%) than males (5.5%) [1]. The pathophysiology of asthma is characterized by inflammation and hyper-responsiveness of lung bronchioles. There is emerging evidence indicating an association between asthma and human immunodeficiency virus (HIV) infection, but much remains to be learned. The article will review the prevalence of respiratory symptoms, pulmonary function abnormalities and asthma in the HIV-infected population and summarize recent research focusing on potential mechanisms linking the two disease processes. In addition, we review important asthma treatment considerations in HIV-infected individuals.

Keywords: Asthma; lung bronchioles; human immunodeficiency virus

Respiratory Symptoms and Pulmonary Function in HIV-Infected Individuals

Several studies have investigated prevalence of respiratory symptoms in the HIV-infected population (Table 1). Before anti-retroviral therapy (ART), there was a high prevalence of dyspnea and cough in this population [2]. These studies showed low CD4 cell counts, history of smoking and intravenous drug use, and previous history of pneumonia were associated with increased risk of dyspnea and cough symptoms. More recent studies in the post-ART era show that respiratory symptoms continue to be common in HIV-infected individuals, with the prevalence of cough ranging from 23-37% and prevalence of dyspnea ranging from 16-44% [3,4]. In these studies, significant predictors of respiratory symptoms include age, history of intravenous drug use, smoking history, higher HIV RNA levels and history of pneumonia. In addition George et al.found that forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) was significantly lower in participants with respiratory symptoms [3]. In conclusion, respiratory symptoms are common in the HIV-infected population, and individuals with intravenous drug use, history of

Cui et al. [39]	Cohort of 120 HIV-infected participants with mean age of 43.4. Majority of participants were male, Caucasian and on ART. Participants answered a questionnaire about respiratory symptoms, including cough, sputum production or breathlessness.	53% of patients had at least one respiratory symptom. Smokers had a higher likelihood of having at least one respiratory symptom (OR=4.9, 95% CI 2.0 to 11.8, p<0.0001) after controlling for ART. Smoking was a significant risk factor for each symptom.
Leung et al. [40]	Cohort of 199 HIV-infected males with mean age 49.3±10.1 years. 52% smokers and majority on ART. All participants were administered the SGRQ.	

	316 were HIV-infected. Pre-bronchodilator spirometry obtained over the course of follow up, median follow up of 2.75 years	Compared to HIV-uninfected participants, HIV-infected participants with a viral load >75,000 copies/ml had a greater adjusted annual FEV1 decline (-99.1 vs. -23.5 ml/ year, p=0.004) and a greater adjusted annual FVC decline (-74.0 vs. 8.24 ml/year, p=0.008) Individuals with lowest CD4 counts < 100 cells/mm3 experienced the most rapid decline in FEV1 and FVC compared to HIV-uninfected participants.
ATS = American Thoracic Society, FEV1 = Forced expiratory volume in one second, FVC = Forced vital capacity, OLD = Obstructive lung disease, SGRQ = St. George Respiratory Questionnaire		

Table 2: Studies of pulmonary function testing in HIV-infected cohorts during the post-ART era

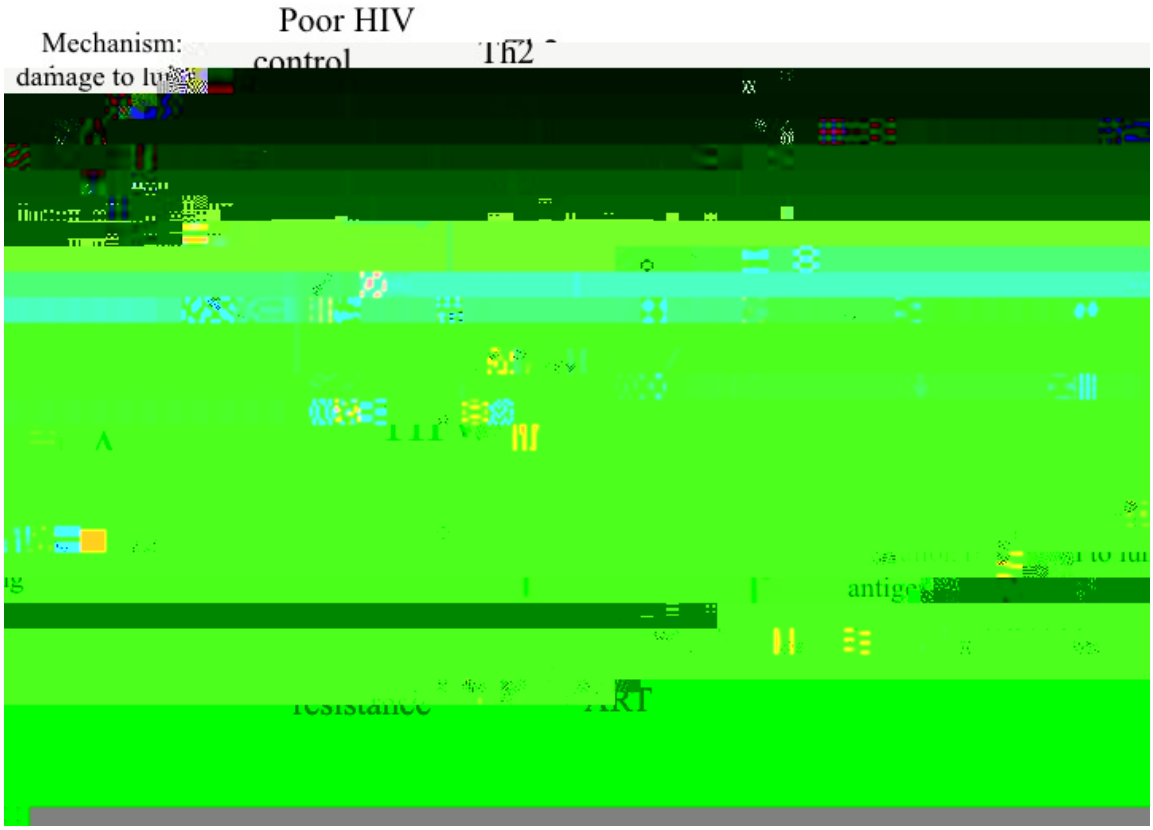

Figure 1: Proposed mechanisms involved in the pathogenesis of asthma in HIV-infected population;

One factor to consider in the pathogenesis of asthma in HIV-infected individuals is the role of HIV virus. As noted above, some studies indicate that higher viral loads and poor HIV control are associated with worse lung function [5,6]. In addition, some studies have shown that higher HIV RNA levels are predictors of respiratory symptoms [3]. These studies would indicate that the virus itself may be important in pathways that can lead to asthma. Unfortunately, research studying the mechanisms involving the virus itself leading to asthma is lacking.

Interestingly, ART itself has been associated with the pathogenesis of asthma in HIV-infected individuals, but data are conflicting. Evidence suggesting a detrimental relationship with ART comes from pediatric literature. A large study compared asthma medication use in HIV-infected children on ART to medication use in HIV-infected children not on ART [14]. Based on a time dependent Cox model, researchers found that HIV-infected participants on ART were more likely to be on asthma medication compared to HIV-infected participants not on ART (hazard ratio=3.34, p=0.01). In addition, the study analyzed asthma medication use at follow up in participants born in pre-ART era. The prevalence of asthma medication use at 11 years of age in this group was higher in HIV-infected participants on ART compared to those not on ART (OR 3.38, p=0.02). The researchers hypothesized that loss of CD4 T cells in untreated HIV-infected children is protective against asthma, and ART acts as a potential risk factor for asthma due to immune-reconstitution of CD4 T cells. Similar results were seen in an earlier smaller study of 136 HIV-infected adult participants in a community clinic showed that a recent CD4 count of ≥ 200 cells/dL was positively associated with current asthma (p=0.01) [15]. In addition, the mean CD4 count in participants with asthma was significantly higher than other participants (log CD4 cells/μ l5.63±0.73 vs. 4.92±1.38, p=0.01). Potential mechanisms involving ART in the pathogenesis of asthma include auto-immune reaction or an immune reconstitution-like reaction to antigens in lungs and direct effects of ART. Overall, the role of ART in asthma pathogenesis in the HIV-infected population is unclear and may differ in children and adults, possibly due to varying underlying causes of asthma.

Certain inflammatory pathways and cytokines may be important in the pathogenesis of asthma in the HIV-infected population. Immunoglobulin E (IgE) is a well-known mediator of allergy and asthma. Early studies showed significantly higher IgE levels in the HIV-infected population with CD4 cell count ≤ 200 cells/mm3, and there was an inverse relationship between IgE level and both helper T cell and suppressor/cytotoxic T cell numbers [16]. Another study showed IgE levels were elevated in HIV-infected vs. HIV-uninfected participants (log IgE IU/ml 4.40±0.48 vs. 3.60±0.18, p<0.05), with the difference being especially strong when comparing participants with AIDS (log IgE IU/ml 4.96±0.23 vs. 3.60±0.18, p<0.005) [17]. The study also showed that IgE levels were important markers of disease progression and survival. The exact etiology of elevated IgE levels is not well-understood, but T helper cells may play a role. HIV leads to decreases and alterations in T helper cells, which are critical in IgE

synthesis [2]. More recently, IgE levels have been shown to be positively associated with sputum eosinophil count in a cohort of 223 HIV-infected participants [11]. An older study found elevated IgE levels to be independent predictors of bronchial hyper-responsiveness based on methacholine challenge ($p=0.0035$) [9]. Thus, the clinical significance of elevated IgE levels in HIV-infected individuals needs to be further investigated, along with the relationship between elevated IgE levels and asthma in HIV. Future research focusing on correlation between elevated IgE levels and pulmonary function, and interventions to decrease the IgE levels in HIV-infected individuals could provide further insight into the role of IgE in this population.

Recent studies also provide evidence for involvement of other inflammatory mediators in the development of asthma in HIV. In the cohort of 223 HIV-infected participants discussed above, doctor-diagnosed asthma appeared to be more common in participants with high sputum interleukin (IL-4) (27% with asthma if high IL-4 vs. 10.5% with asthma if low IL-4, $p=0.02$), and high regulated on activation, normal T cell expressed and secreted (RANTES) (26% vs. 9.8%, $p=0.02$) [11]. The association between IL-4 and RANTES with

of assessment of insulin resistance (HOMA-IR). After adjustment for age, HOMA-IR was a statistically significant risk factor for AHR, but became non-significant after adjustment for age and BMI. Similarly, in women, the HOMA-IR and BMI were statistically significant risk factors for AHR after adjustment for age. The relationship between HOMA-IR and AHR again became insignificant after adjustment for age and BMI. Insulin resistance is important in the HIV-infected population because of the high prevalence of metabolic changes in this population. Recent estimates of diabetes mellitus is ~3% in ART-naïve HIV-infected individuals and ~10% in individuals on highly active ART [31]. In addition, metabolic changes that occur in HIV infection have been known to cause lipohypertrophy likely secondary to chronic inflammation [32]. Biron et al.found a prevalence of metabolic syndrome of 18.2% in cross-sectional study of 269 HIV-infected individuals started on ART with a median duration of 30 months of treatment [33]. The researchers concluded that HIV-infected individuals on ART are at high risk of complications like cardiovascular disease. Thus, HIV-infected individuals with obesity and insulin resistance may be at risk for asthma. Future studies in this area need to explore the relationship between insulin resistance, and asthma in HIV-infected individuals, including investigating prevalence of AHR in HIV-infected population with insulin response and their response to treatment.

Treatment of Asthma in HIV Infection

Current asthma treatments used in the general population have not been tested in the HIV-infected population. If HIV-infected individuals have different mechanisms of asthma than the general population, then current therapies may be less effective, particularly if HIV or ART are involved in pathogenesis. In addition, there are several interactions of concern in the HIV-infected population including increased complications of inhaled corticosteroids (ICS) such as candidiasis, tuberculosis, and bacterial pneumonia [34]. The TORCH (towards a revolution in COPD health) study in COPD treatment studied adverse effects of combination therapy with salmeterol and fluticasone compared to the placebo group [35]. The study found that probability of developing bacterial pneumonia during the 3 year follow-up was greater in combination therapy group than the placebo group (19.6% vs. 12.3%, $p<0.001$). Tuberculosis risk may also be increased. In a study of 853,439 participants with inhaled respiratory medicine use, the use of ICS was associated with an increased rate of TB diagnosis (adjusted OR 1.20. 95% CI 1.08-1.34, $p<0.001$) [36]. The HIV-infected population is likely at increased risk of such complications with ICS therapy. Furthermore, ART can lead to systemic side effects of ICS. Pharmacologic studies and case reports provide evidence that combination of ritonavir and fluticasone can lead to symptoms of Cushing's syndrome and adrenal insufficiency, and the combination treatment is contraindicated in HIV-infected individuals [37]. The interaction between these medications is likely secondary to the CYP3A4 system, and other inhaled corticosteroids also are substrates of CYP3A4, which is inhibited by ritonavir. It is possible that there are interactions between ritonavir and other inhaled corticosteroids at higher doses. These important treatment considerations should be remembered in the HIV-infected population and further research needs to determine efficacy and safety of current asthma treatments in this population.

Conclusion

In summary, pulmonary diseases including asthma appear to be highly prevalent in the HIV population, and they are increasingly becoming an important cause of morbidity and mortality. Asthma is one of the most common pulmonary diseases in the HIV-infected population, and recent evidence suggests a higher rate of bronchial hyper-responsiveness in HIV-infected individuals. Smoking, in particular, appears to be a strong risk factor in development of respiratory symptoms and obstructive pathophysiology. Newer research points to several inflammatory cytokines, metabolic diseases such as obesity, and ART in the pathogenesis of asthma in HIV patients. Future research needs to focus on understanding the mechanisms that lead to development of asthma in HIV to improve prevention and treatment.

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