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HIV and asthma, is there an association?

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Summary

Objective—To evaluate whether asthma and airway hyper-responsiveness are associated with HIV infection.

Methods—We reviewed the literature on HIV-associated pulmonary diseases, pulmonary symptoms, and immune changes which may play a role in asthma. The information was analyzed comparing the pre-HAART era to the post-HAART era data.

Results—HIV-seropositive individuals commonly experience respiratory complaints yet it is unclear if the frequency of these complaints have changed with the initiation of HAART. Changes in pulmonary function testing and serum IgE are seen with HIV infection even in the post-HAART era. An increased prevalence of asthma among HIV-seropositive children treated with HAART has been reported.

Conclusion—The spectrum of HIV-associated pulmonary disease has changed with the introduction of HAART. Current data is limited to determine if asthma and airway hyper-responsiveness are more common among HIV-seropositive individuals treated with HAART.

Keywords

Asthma; Airway hyper-responsiveness; HIV; Antiretroviral

Introduction

HIV-related pulmonary diseases have been recognized from the onset of the AIDS epidemic.[1,2] Initially, pulmonary-related HIV diseases were predominantly infectious and associated with a high morbidity and mortality.[3] The introduction of highly active antiretroviral therapy (HAART) changed both HIV treatment and the spectrum of HIV-

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associated diseases. Progression to acquired immune deficiency (AIDS) and HIV-related mortality have declined since HAART became the standard of care.[4,5] A shift in the epidemiology of HIV-associated infections has also occurred in the era of HAART with decreased incidences in pulmonary opportunistic infections[6,7] and bacterial pneumonia[8–10] in developed countries. However, emerging data suggests an increase in the incidence of HIV-related non-infectious pulmonary conditions.

Recently, several studies have suggested an increased incidence of asthma among HIV-seropositive individuals receiving treatment with HAART.[11–13] However, our current understanding of the underlying mechanisms accounting for this association and the role of anti-retrovirals in HIV-associated pulmonary complications is incomplete and we are unable to answer key questions such as: What are the effects of HAART on the pulmonary system? Does HAART modify the Th1/Th2 balance and thus increase the risk of asthma? Why do persons with HIV, even those treated with HAART, suffer a high burden of pulmonary complaints? Are pulmonary symptoms among HIV infected persons a clinical clue to underlying pathologic changes which are increasing their risk for non-infectious pulmonary diseases? The purpose of this paper is to review the current literature on HIV and its potential relationship to asthma. Since asthma itself is a complex disease with varying phenotypes this paper will be divided into sections where both the clinical aspects and the science of HIV and asthma overlap.

HIV and respiratory symptoms

Asthma is a heterogeneous pulmonary disease characterized by episodic symptoms with several clinical phenotypes now recognized.[14] Respiratory symptoms such as wheezing, chest tightness, dyspnea and cough are nonspecific but are commonly associated with and can be clinical clues to the diagnosis of asthma. This section will review the literature to determine whether HIV-seropositive individuals suffer from respiratory symptoms consistent with asthma and if these symptoms changed after HAART.

During the pre-HAART era an increased prevalence of respiratory symptoms commonly associated with asthma, notably cough and dyspnea was described among HIV-seropositive individuals.[15,16] Risk factors for these symptoms in the pre-HAART era included smoking, intravenous drug use, low CD4 cell count, and previous pneumonia.[15] Respiratory symptoms were also noted in persons without a history of AIDS-related pulmonary infections. The exact etiology of these symptoms remains unclear, but several theories have been put forth to explain these data.

HIV infection alone appears to be related to dyspnea and a few small studies have tried to explain this association. These studies focused on functional mechanisms of dyspnea with limited data on potential inflammatory mechanisms of dyspnea similar to those postulated for asthma. In a study by Schulz L et al.[17] twenty-three HIV-seropositive males without evidence of AIDS were compared to age- and weight-matched HIV-seronegative males. HIV-infected males were found to have a significantly lower maximal inspiratory pressure, maximal expiratory pressure, and respiratory muscle endurance as measured by incremental threshold loading compared to their HIV-seronegative counterparts. Additionally, a

significant association between dyspnea and respiratory muscle dysfunction regardless of CD4 cell count was demonstrated.[17]

A more recent study from Nigeria evaluated the burden of respiratory symptoms among HIV-seropositive individuals who were not on HAART. They excluded smokers and those exposed to biomass fumes which would limit those with possible tobacco related lung disease. Among HIV-infected subjects cough was the most common complaint, 48%, with 35% having cough with sputum production.[18] Wheezing was also found to be more prevalent among HIV-seropositive individuals, 7% vs. 0% in HIV-seronegative individuals, however there no statistically significant difference.[18] While this study again demonstrates that HIV infection is associated with a high prevalence of respiratory symptoms it was limited by the lack of evaluation for opportunistic infections.

While there is an overall paucity of data on the prevalence of respiratory symptoms consistent with asthma in HIV-seropositive individuals in the HAART era, the studies to date support an increased frequency of respiratory complaints among HIV-seropositive individuals on HAART versus those not on HAART.[19,20] The first study to evaluate respiratory symptoms in HIV-infected individuals during the HAART era evaluated 234 subjects from a single, outpatient HIV clinic.[19] The majority of the subjects, 83.3%, were receiving HAART at the time of the study. All subjects underwent spirometry in addition to evaluation for respiratory symptoms. Thirty-one percent reported chronic respiratory symptoms consistent with asthma: cough, shortness of breath, and/or dyspnea on exertion. Cough was the most common symptom, occurring in 23% of subjects. Respiratory symptoms were more likely to occur among current smokers, former smokers, history of intravenous (IV) drug use, advanced age, higher HIV viral loads, history of bacterial pneumonia, and individuals with a lower FEV_1/FVC ratio.[19] Despite the significant burden of respiratory symptoms 93.2% of the subjects had normal spirometry, which would be more consistent with possible asthma then primarily tobacco related lung disease. This study was limited by the large male predominance, 82.5%, high prevalence of current and/or former smokers, 59.8%, and a large percentage of its subjects with a history of an AIDS defining illness, 64.1%.[19]

Similar results were reported by Gingo et al.,[20] who evaluated 167 HIV-seropositive individuals at a single outpatient HIV clinic. This cohort had a high prevalence of HAART use, 80.7%, and 63.5% of the subjects complained of at least one respiratory symptom with dyspnea and cough being the most frequent, 43.7% and 37.1% respectively.[20] HIV-associated risk factors of IV drug use and personal smoking histories were again associated with a greater likelihood of respiratory symptoms. Men who have sex with men were less likely to have respiratory complaints. Several others have also reported an increase in respiratory symptoms consistent with asthma among HIV-seropositive persons in the post-HAART era however these studies specifically looked at intravenous drug users (IVDU) in urban populations[21–23] and thus are limited due to the potential for IV drug abuse to result in pulmonary disease.[24,25]

While these data suggest that respiratory symptoms consistent with asthma are common in HIV-seropositive individuals the true prevalence of these symptoms in the HAART era is

limited by the small number of individuals studied. Additionally, it is not apparent if HAART increases or decreases these symptoms (see Table 1). Furthermore, no clear etiology for these symptoms has been determined, but there have been attempts to evaluate lung function in these individuals and correlate abnormalities with symptoms. Research evaluating the cellular and physiological changes occurring after HIV infection and initiation of antiretroviral therapy is needed to advance our understanding of HIV-associated respiratory symptoms and its potential link to obstructive airway diseases such as asthma and COPD.

HIV, IgE, and cytokine profiles

An association between asthma and IgE has long been recognized.[14,26,27] More recent focus has been on defining various asthma phenotypes and allergic asthma in association with atopy and elevated serum IgE levels is one well accepted asthma phenotype.[28–32] Interestingly, an elevation of serum IgE levels in HIV-seropositive individuals was first recognized during the AIDS epidemic[33,34] but it is not yet know if there is an association between IgE levels and the presence of symptoms or formal diagnosis of asthma. In addition, the impact of HAART on IgE levels is unclear.

The etiology for elevated serum IgE in patients with HIV is not completely understood. Serum IgE synthesis occurs in B-cells with significant influence from T-regulatory cells. T-helper cells are critical to the induction of IgE production and alterations in T-helper cells secondary to HIV is believed to contribute to abnormal IgE levels. Research has shown a change in serum cytokine profiles in HIV-seropositive individuals[35–39] with an increase in IL-4 and IL-10 and a decrease in IFN-g and IL-2 when compared to HIV-seronegative control.[37,40] This increase in Th2 cyto-kines and decrease in Th1 cytokines leads to increased synthesis of IgE from B-cells and is a cytokine profile described in association with an allergic asthma phenotype[41,42] and thus may be important in the apparent association of HIV infection and allergic asthma.

A further correlation between asthma and reconstitution of CD4+ T-cells after antiretroviral therapy initiation has been reported in HIV-seropositive children.[12,13] Immune reconstitution usually occurs within weeks to months after starting HAART and represents an inflammatory response.[43,44] Typically, the inflammatory response is to a pre-existing opportunistic infection however recent research has also identified certain human leukocyte antigen (HLA) and cytokine profiles associated with an increased susceptibility to immune reconstitution disease.[43–46] Furthermore, HIV infection itself can yield immune reconstitution disease.[47,48] Another interesting observation is the report of 3 cases of successful treatment of immune reconstitution disease with montelukast[49] which is also an effective medication for the treatment of asthma.[14,50] The underlying mechanism(s) for the immune reconstitution syndrome and cytokine switching has yet to be defined.

Thus, while elevations in serum IgE are common in HIV both pre- and post-HAART, the exact prevalence and clinical significance of this finding, particularly as it relates to the potential development of asthma, is unknown.

HIV and bronchial hyperresponsiveness

A classic feature of asthma is bronchial hyperresponsiveness (BHR) which is commonly measured via bronchoprovocation testing such as a methacholine challenge test. The details of methacholine challenge testing are beyond the scope of this review, however while it has good sensitivity for the diagnosis of asthma in patients with a high clinical probability of having asthma, there are some limitations to the testing notably that some people with no evidence of a pulmonary disease have a positive test.[51–55] While exact prevalence is difficult to determine, current data suggests 10%–16% of adults without pulmonary disease will have a positive methacholine challenge test, with increased rates noted in people with allergic rhinitis and smokers.[54] Despite these limitations, BHR determined by methacholine testing remains a hallmark of asthma and is often part of the evaluation of a patient with respiratory symptoms consistent with asthma.[42] Therefore, given the previously noted increase in respiratory symptoms consistent with asthma in HIV-seropositive people several studies attempted to quantify the prevalence of BHR in HIV-seropositive people, with additional attempts to correlate BHR and respiratory symptoms, i.e. consistent with a diagnosis of asthma.

In the pre-HAART era, O'Donnell et al.[56] analyzed pulmonary function testing on 105 AIDS patients in the Boston area from 1983 through 1986. Abnormally decreased forced expiratory flow rates or significant response to bronchodilators consistent with obstructive lung disease was observed in 44% of their subjects.[56] However, further analysis of their data demonstrates a temporal relationship between obstructive pattern on spirometry and acute Pneumocystis pneumonia. Subsequently a study was done comparing bronchial hyperresponsiveness to methacholine challenge tests amongst HIV-seropositive individuals with a mean CD4 cell count of 398 cells/mm^3 and no evidence of a respiratory infection versus HIV-seronegative individuals of similar baseline demographics. The incidence of BHR was greater in the HIV-seronegative cohort, 16% compared to 8% in the HIV-seropositive subjects despite a greater prevalence of respiratory symptoms in the HIV-seropositive individuals suggesting the previous findings of obstruction were likely due to acute PCP infection.[57] In addition, this study was limited by the fact that all the participants were former intravenous drug users and thus had significant risk factors for lung disease which might confound the PFT pattern.[24,25]

Wallace et al.[58] performed methacholine challenge testing during the pre-HAART era on 66 HIV-seropositive predominantly male individuals. Their study found no statistically significant difference in bronchial hyperresponsiveness between the HIV-seropositive, and the HIV-seronegative cohort matched for age, gender, race and smoking history, 19.7% and 12.5% respectively. The most recent study evaluating HIV infection and its potential link to BHR occurred just prior to the introduction of HAART. This study compared 248 HIV-seropositive males to 236 HIV-seronegative males between the ages of 20 and 44 years living in Montreal, Canada.[59] They found a statistically significant greater prevalence of wheezing (54.4% vs. 21.2%) within the last year and BHR via methacholine challenge testing (26.2% vs. 14.4%), in the HIV-seropositive cohort. Further review of their results demonstrates a statistically significant increase in positive skin testing and elevated serum IgE among HIV-seropositive subjects with BHR compared to HIV-seropositive subjects

without BHR. This study was limited by its focus on males and the higher prevalence of smoking and previous diagnosis of asthma in the HIV-seropositive cohort. Nonetheless, it does suggest that amongst people with HIV infection there may be a correlation between respiratory symptoms, serum IgE levels and bronchial hyperresponsiveness. This constellation of clinical symptoms, IgE, and bronchial hyperresponsiveness would be consistent with a diagnosis of asthma.

There is no data on the prevalence of BHR among HIV-seropositive individuals on HAART and future research is needed to evaluate this question and determine if any correlations exist between BHR, respiratory symptoms, atopy and serum IgE levels consistent with an allergic asthma phenotype.

HIV and asthma

One of the first published studies exploring a potential association between HIV and asthma in the post-HAART era comes from the pediatric literature. A cross-sectional chart review of 83 HIV-seropositive people ages 1–24 years undergoing medical care at Texas Children's Hospital in 2005 was performed.[12] Individuals were assessed for a diagnosis of asthma by ICD-9 codes. The authors found a significant increase in the prevalence of asthma among HIV-seropositive individuals, 34%, compared to both the prevalence of asthma via a chart review of demographically matched HIV-seronegative children receiving care at their hospital, 2.9% and the reported prevalence of asthma in the Houston area, 5%. They found no difference in CD4 cell count or HIV viral load between HIV-seropositive asthmatics and non-asthmatics, and only 6 of the 83 seropositive subjects study met AIDS criteria by CD4 cell count. Interestingly, 75% of their HIV-seropositive subjects were receiving HAART therapy at the time of their asthma diagnosis. Subgroup analysis of 25 patients revealed a potential association between asthma and immune reconstitution. Immune reconstitution was defined as an increase in CD4+ T-cells of greater than or equal to 5% while on HAART therapy. They found 6 of 25 patients had documented immune reconstitution within 2 years prior to their diagnosis of asthma. The mean time to asthma medications after HAART initiation was 1.8 years (±3.3 years) among this subset.[12] These data would thus suggest that inflammatory changes (immune reconstitution) induced by HAART may result in the development of asthma in a subset of HIV-seropositive patients.

Another larger retrospective study was performed on prospectively collected data of children born to HIV-seropositive individuals, the Women and Infants Transmission Study (WITS). Children were enrolled in this multicenter study in the United States and Puerto Rico at the time of birth from 1988 to 2006, thus capturing both the pre- and post-HAART eras. In this study asthma was defined by the use of asthma medications which the authors listed as: short-acting bronchodilators, long-acting bronchodilators, inhaled corticosteroids, and leukotriene antagonists. Foster et al.[11] compared 2471 HIV-seronegative controls to 193 HIV-seropositive children and found a greater prevalence of asthma in HIV-seropositive children treated with HAART (n = 113) compared to HIV-seropositive children who had never received HAART (n = 80), 10.4% compared to 3.8%. Further analysis of their cohorts did not demonstrate any differences in sex, race/ethnicity, or socioeconomic status. They also report a cumulative incidence of asthma in HIV-seropositive children on HAART of

33.5% compared to 11.5% in HIV-seropositive children who were never treated with HAART. They did not demonstrate a significant difference in asthma prevalence between HIV-seronegative children and HIV-seropositive children receiving HAART. This may be due to the relatively high prevalence of asthma reported in the HIV-seronegative cohort, 10.5%.[11]

Similar prevalence rates of asthma were more recently reported in a pediatric HIV-seropositive population from Detroit, Michigan. In a retrospective chart review of 85 HIV infected children ages 3–16 years, 24 of 85 children (28%) met the criteria for the diagnosis of asthma based on recorded clinical history, PFTs and medication use.[13] The authors do not report if any of the children were receiving HAART therapy.

The current data on the prevalence of asthma in HIV-seropositive adults on HAART is limited. Crothers et al.[60] retrospectively reviewed data from veterans in the Veterans Aging Cohort Study Virtual Cohort. Two large cohorts, 3707 HIV-seropositive and 9980 HIV-seronegative, were evaluated for the non-infectious pulmonary diseases defined by ICD-9 codes. The cohorts were matched for age, race and gender however, alcohol abuse, drug use and hepatitis C were more common among the HIV-seropositive cohort. Use of HAART in the HIV-seropositive group was 65% and the median CD4 cell count in this cohort was 264 cells/mm^3. COPD and asthma were the most common non-infectious pulmonary diseases among the HIV-seropositive persons, 4.6% and 2% respectively. While COPD was noted to have a higher prevalence among those infected with HIV this was not true for asthma, as the prevalence of asthma in the HIV-seronegative cohort was 2.4%. This study was limited by the fact that the cohorts were predominately male, 98% in both HIV-seropositive and HIV-seronegative, with a greater percentage of smokers in the HIV infected group, 80% vs. 76% ($p < 0.001$).

Overall, these retrospective studies suggest an increase in a diagnosis of asthma in HIV-seropositive children. They also suggest a further increase in asthma in those children on HAART, with some data supporting a positive correlation with immune reconstitution further suggesting alterations in the host inflammatory response with HAART may increase the incidence of asthma. There is a clear need for prospective studies to determine if these findings are valid and there is little data at present regarding the incidence of asthma in HIV-seropositive adults on HAART.

HIV and COPD

While there is limited data on HIV and asthma prevalence in adults there is a large body of literature noting an association between HIV and COPD, which shares many clinical and physiologic parameters with asthma. The association between HIV and airway obstruction and emphysema was reported by several groups prior to the introduction of antiretroviral therapy.[61–64] A recent study again reported an association between obstruction on spirometry and HIV. Spirometry was performed on 100 HIV-seropositive Nigerians presenting to a teaching hospital afflicted with the University of Nigeria.[18] This cross-sectional study attempted to limit co-founding factors which could result in abnormal spirometry by excluding those with a prior diagnosis of COPD, asthma, bronchiectasis,

pulmonary tuberculosis, congestive heart failure, spinal deformities, work exposure to coal mines, quarries or wood workers, those exposed to biomass fuels, and current or former smokers. Obstruction on spirometry was found in 3% of the HIV-seropositive cohort compare to 0% of the HIV-seronegative cohort. None of the subjects were receiving HAART.

Despite these data there is still not a clear understanding of the underlying mechanism(s) accounting for the development of COPD after HIV infection. Studies have established an association between tobacco use, history of pneumonia, advanced HIV disease or AIDS, and IV drug use with airway obstruction and pneumonias specifically due to *Pneumocystis jiroveci* were also associated with reversible airway obstruction and bronchial hyperreactivity.[59,65] Evaluation of this known association in the post-HAART era has been sparse.

Antiretroviral therapy was associated with a decreased FEV_1/FVC in the study by George et al.[19] This study evaluated 234 HIV-seropositive adults. The majority were male, 83% and Hispanic 53%. The major risk factor for HIV in this cohort was men who have sex with men, 48%. While the mean CD4 cell count was 371cells/μl, 64% of the participants had a history of AIDS including 16% with a history of Pneumocystis pneumonia. Spirometry was normal in 93% of the subjects. The prevalence of obstruction, defined as $FEV_1/FVC < 0.70$, was 6.8%. Although no statistically significant association was discovered between airway obstruction and subject characteristics there was a trend toward HAART use and decreased FEV_1/FVC ratio. In addition, HAART use was associated with obstruction independent of age, smoking history, IV drug use, and previous pneumonia.

Gingo et al., 2010 reported a similar association between airway obstruction and antiretroviral therapy. One hundred sixty seven HIV infected persons were evaluated for respiratory symptoms, inhaler use and PFTs. Anti-retroviral use was high in this study population with 80% on HAART at the time of study enrollment. Irreversible airway obstruction was noted in 21% of HIV-seropositive persons.[20] Irreversible airway obstruction was associated with advancing age, history of smoking, IV drug use, hepatitis B and/or C, and antiretroviral therapy ($p = 0.04$). No link between CD4 T cell count, HIV viral load or duration of HIV infection was established.

The association between irreversible airway obstruction consistent with COPD and HIV continues to be a consistent finding in the HAART era however the underlying mechanism(s) for this association remain unfounded and an area in need of additional research.

Conclusion

It appears people with HIV have an increased incidence of respiratory symptoms, elevated IgE, more response to bronchoprovocation, and higher incidence of asthma than seronegative controls. This may be increased with HAART, but definite conclusions are difficult based on fewer studies since the advent of HAART therapy. Possible explanations

for these associations may be direct viral effects, changes to the TH1/TH2 balance, medication side effects, or a manifestation of immune reconstitution syndrome.

A greater number of individuals are currently living with HIV for increasingly longer periods since HAART. Physicians need to be aware of and recognize the burden of non-infectious respiratory symptoms namely dyspnea, cough, wheezing, and chest tightness. This knowledge will allow physicians to provide optimal care for these patients. Additionally, awareness of these respiratory symptoms among persons with HIV will aid in increasing our understanding on whether these symptoms are representative of changes leading to certain pulmonary diseases such as asthma and COPD. Advancing our knowledge on pulmonary diseases associated with HIV and HAART use will require further understanding of inflammatory and cellular changes and requires physicians to take bedside observations back to the bench.

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Table 1

Prevalence of respiratory symptoms among HIV-seropositive individuals.

	Pre-HAART[16,60]	Post-HAART[20–22,24]
Cough	40%	23–51%
Dyspnea on exertion	29–42%	16–44%
Shortness of breath	2%	3–7%
Wheezing	19–54%	19–36%
Sputum	42%	32–43%
Any respiratory symptom	36%	32–64%