Published in final edited form as:

J Allergy Clin Immunol. 2012 March ; 129(3): 708–714.e8. doi:10.1016/j.jaci.2011.11.015.

Asthma Diagnosis and Airway Bronchodilator Response in HIV-infected Individuals

Matthew R. Gingo, MD¹, Sally E. Wenzel, MD¹, Chad Steele, PhD², Cathy J. Kessinger, RN¹, Lorrie Lucht¹, Tammi Lawther¹, Michelle Busch, MLT¹, Maria E. Hillenbrand, MS¹, Renee Weinman¹, William A. Slivka, RPFT¹, Deborah K. McMahon, MD¹, Yingze Zhang, PhD¹, Frank C. Sciurba, MD¹, and Alison Morris, MD, MS^{1,3}

¹Department of Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, PA, USA

²Department of Medicine, University of Alabama - Birmingham, Birmingham, AL, USA

³Department of Immunology, University of Pittsburgh, School of Medicine, Pittsburgh, PA, USA

Abstract

Background—Despite the high prevalence of respiratory symptoms and obstructive lung disease in HIV-infected persons, the prevalence of bronchodilator reversibility (BDR) and asthma has not been systematically studied during the era of combination antiretroviral therapy (ART).

Objective—To determine the prevalence of asthma diagnosis and related pulmonary function abnormalities in an HIV-infected cohort and to identify potential mechanisms.

Methods—A cross-sectional analysis of 223 HIV-infected individuals with data on respiratory symptoms and diagnoses, pulmonary function, sputum cell counts, and asthma-related cytokines and chemokines in serum/sputum.

Results—Doctor-diagnosed asthma was present in 46 (20.6%) and BDR (≥ 200 ml and $\geq 12\%$ increase in FEV₁ or FVC) in 20 participants (9.0%). Pulmonary symptoms and function were worse in those with doctor-diagnosed asthma. Doctor-diagnosed asthma was independently associated with female sex ($p=0.04$), body mass index $>29.6\text{kg/m}^2$ (vs. $<29.6\text{kg/m}^2$) ($p=0.03$), history of bacterial or *Pneumocystis* pneumonia ($p=0.01$), and with not currently taking ART ($p=0.04$), and in univariate analysis with parental history of asthma ($n=180$; $p=0.004$). High sputum eosinophil percentages ($>2.3\%$ based on the highest decile) were more likely in those with doctor-diagnosed asthma ($p=0.02$) or BDR ($p=0.02$). Doctor-diagnosed asthma tended to be more common with high sputum IL-4 ($p=0.02$) and RANTES ($p=0.02$), while BDR was associated with high plasma macrophage inflammatory protein (MIP)-1 α ($p=0.002$), and sputum MIP-1 β levels ($p=0.001$).

Conclusion—Asthma diagnosis and BDR are prevalent in an HIV-infected outpatient cohort, and associations with family history, obesity, allergic inflammation, prior infection, the absence of ART, and elevated HIV-stimulated cytokines suggest possible mechanisms of HIV-associated asthma.

© 2011 American Academy of Allergy, Asthma and Immunology. Published by Mosby, Inc. All rights reserved.

Correspondence: Alison Morris, 3459 Fifth Avenue, 628 NW, Pittsburgh, PA 15213, morrisa@upmc.edu, Fax: (412) 692-2260, Phone: (412) 624-8209.

This manuscript contains an Online Repository.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

HIV; asthma; airway obstruction; allergy

INTRODUCTION

While HIV-infected individuals are living longer with fewer infectious pulmonary complications, respiratory symptoms and chronic lung disease remain common.(1, 2) Obstructive lung diseases such as asthma and chronic obstructive lung disease (COPD) may actually be increasing in this population as rates of hospitalization and deaths from obstructive disease have been growing.(3) Recent studies in HIV-infected individuals demonstrate that 31–64% have respiratory symptoms and 8–21% have airway obstruction by spirometry.(1, 2) Although asthma is a common disease in the non-HIV-infected population, relatively little is known about its prevalence or risk factors in those with HIV. Prior to effective combination antiretroviral therapy (ART), HIV-infected persons had a high prevalence of small airway disease and airway hyperresponsiveness.(4–7) Since the introduction of ART, there has been little work examining asthma in this population, and data are lacking regarding the epidemiology, mechanisms, and effects of antiretroviral treatment in HIV-associated asthma. One study found that HIV-infected children receiving ART had greater use of inhaler medications, but asthma diagnoses were not quantified.(8) A recent study of pre-and post-bronchodilator spirometry in an HIV-infected outpatient cohort found that nearly 10% of HIV-infected individuals had reversible airway obstruction, suggesting that asthma or airway hyperresponsiveness may be a notable cause of obstructive lung disease in this population during the current era of effective ART(2); however, specific features of asthma in this population were not examined.

Determining the pathogenesis and impact of asthma and airway hyperresponsiveness in the HIV population is important. For example, certain inflammatory pathways related to T-helper (TH)-2 inflammation, driven by cytokines such as interleukin (IL)-4, IL-5, and IL-13, are important mediators of asthma, but inflammatory pathways related to asthma in the setting of HIV infection have not been assessed. In addition, protease inhibitors, an important part of ART, have interactions with the inhaled corticosteroid fluticasone, one of the mainstays of asthma therapy and may lead to elevated peripheral corticosteroid levels.(9–11) Inhaled corticosteroids have other adverse effects such as increased risk of pneumonia or tuberculosis which in theory might be worse in HIV-infected individuals.(12, 13) Given the limitations of current therapy in this population, improved understanding of the relationship between HIV infection, ART, and the development of asthma and airway hyperreactivity is important in guiding investigations into unique mechanisms and potential therapies for asthma in HIV infection.

In this study, we determine the prevalence and associated demographic, social, and clinical factors of asthma diagnoses, asthma-related respiratory symptoms, and asthma-related pulmonary function abnormalities in an HIV-infected cohort. We also explore biomarkers associated with asthma diagnosis and asthma-related pulmonary function abnormalities.

METHODS

Study population

Persons with documented HIV infection were recruited between July 1, 2007 and September 30, 2010. A description of study procedures and a subset of the cohort has been published previously.(2) Details can be found in the online repository. Recruitment was performed using posted advertisements, word of mouth, and by contacting patients in a research

registry. All participants signed written informed consent, and the University of Pittsburgh IRB approved the protocol.

Data collection

Demographic and clinical data were collected by participant interview and medical record review. Self-report of a diagnosis of asthma was ascertained by asking the participant: "Has a doctor or health care provider EVER told you that you had asthma?" Age of asthma diagnosis was determined by asking: "How old were you when your doctor FIRST told you that you had asthma?" Although all participants were currently attending a single clinic, the diagnosis of asthma could have been made at the clinic or elsewhere. Participants determined to have asthma during the study visit did not count as providing a self-report of ever having asthma. Respiratory symptoms were assessed using a modified version of the St. George's Respiratory Questionnaire(14, 15) and were considered significant if occurring at least monthly over the past year and were not related to colds. Sputum eosinophil counts and percents were determined from induced sputum as previously described.(16)(17) Adequate induced sputum samples (squamous cell percent<30) were available from 161 participants. Serum IgE levels were measured using an Elecsys® 2010 Immunoassay System (Roche Diagnostics, Indianapolis, IN). In participants with an available sample (n=123 for plasma, n=116 for sputum), selected asthma-related cytokines (IL-4 and IL-13) and chemokines (eotaxin-1, macrophage inflammatory protein [MIP]-1 α , MIP-1 β , and Regulated on Activation Normal T Cell Expressed and Secreted [RANTES]) were measured using Luminex (Luminex Corporation, Austin, TX, USA).

Pulmonary function testing

All participants performed pre- and post-bronchodilator (480 μ g of albuterol administered through a spacer from a metered-dose inhaler) spirometry in accordance with American Thoracic Society (ATS) standards(18, 19) as previously described(2) and further detailed in the online repository. Bronchodilator reversibility (BDR) between pre- and post-bronchodilator spirometry was used as a surrogate for airway hyperresponsiveness. Participants were determined to have BDR if they had an improvement in either the FEV₁ or FVC of at least 200ml and 12%.(20)

Statistical analysis

Statistical analyses were performed using Stata version 10 (StataCorp, College Station, Texas, USA). For further details of statistical analysis see the online repository. BMI data were normalized using 1/BMI and categorized as the highest quartile vs. the lower three quartiles. IgE level was log-normalized. Sputum eosinophil percent was also not normally distributed, and the highest decile (>2.3%) was classified as high, a cut-off similar to the upper limit of normal eosinophil percentages from induced sputum of healthy subjects.(21, 22) Demographic and clinical criteria were compared between participants with and without a diagnosis of asthma and participants with and without BDR using t-tests, Wilcoxon rank sum test, Fisher's exact test, and chi-square test where appropriate. Serum and sputum cytokines and chemokines were not normally distributed, and values were dichotomized to low ($\leq$ median) or high ($>$ median). To determine associations with cytokines and chemokines data, we used t-tests for continuous outcomes (FEV₁ % predicted, FEF_{25%-75%} % predicted, and change in FEV₁ with bronchodilator) and chi-square test for categorical dependent variables (doctor-diagnosed asthma and BDR). A $p \leq 0.01$ was considered significant for associations of the cytokine data to account for multiple testing. Multivariable logistic regression was used to determine independent associations between potential demographic or clinical predictors and presence of doctor-diagnosed asthma or BDR. Sputum cell counts, and plasma and serum cytokine and chemokine levels were available for only a subset of participants and were therefore not considered in the

multivariable modeling. Clinically relevant variables significant at a $p \leq 0.10$ were entered into the model in order of increasing univariable logistic regression p -values. The likelihood ratio test was used to compare hierarchical models, and those variables reaching a significance level of $p \leq 0.10$ were retained in the model. Step-down regression was then performed by removing variables in order of decreasing p -value. Variables were retained in the model if the likelihood ratio test was significant at a level of $p \leq 0.05$. We tested for interactions between smoking and other significant predictors, and the models were assessed for collinearity. To assess for confounding by parental history of asthma, race, and smoking status, we included these variables with the model as a sensitivity analysis and found no significant impact on the results of the final model except that including parental history in the model decreases the association of sex and doctor-diagnosed asthma; however, a greater proportion of women with doctor-diagnosed asthma had missing information on parental history. Hosmer-Lemeshow test was used to assess models for goodness of fit.(23)

RESULTS

Participant characteristics

Of 239 participants recruited, ten failed screening, three did not attend their study visit, and three had pulmonary function testing that did not meet ATS criteria. There were 223 HIV-infected participants who completed the study. Forty-six participants (20.6%) reported doctor-diagnosed asthma. This prevalence was nearly twice as high as that of doctor-diagnosed COPD in the cohort (11.4%). Using inhaler medication or oral steroids for breathing was common with 30% using inhaler medication within the last year. An albuterol inhaler was used by 25.6% of the cohort, while an inhaled steroid was used by 7.2%, and an oral steroid was used specifically for breathing problems within the past year by 9.0%.

Doctor-diagnosed asthma

Participants with doctor-diagnosed asthma were different in certain demographic and clinical characteristics (Table 1). Participants who had doctor-diagnosed asthma were younger than those who did not (mean [standard deviation] age in years, 42.6 [9.7] vs. 45.9 [9.6]; $p=0.04$) and were more likely to be female (41.3% vs. 22%; $p=0.008$). In 180 participants with information on family history, those with doctor-diagnosed asthma were more likely to have a parent with asthma (37.5% vs. 16.4%, $p=0.004$). Participants with asthma were also more likely to be current smokers (73.9% vs. 52.5%; $p=0.03$). A history of having either bacterial pneumonia or *Pneumocystis* pneumonia was also more likely in participants with asthma (60.9% vs. 39.9%; $p=0.01$). Participants with asthma were less likely to be taking ART (67.4% vs. 81.9%; $p=0.03$), but not less likely to have ever been on ART (82.6% vs. 88.1%; $p=0.3$). In addition, there were no significant differences in average CD4+ T-cell counts or HIV RNA levels between the two groups. Those diagnosed with asthma compared to those not diagnosed with asthma were more likely to have had significant recurrent respiratory symptoms over the past year (91.3% vs. 59.9%; $p<0.001$), wheezing at times other than respiratory infection (56.5% vs. 18.6%; $p<0.001$), and recurrent phlegm production (50.0% vs. 30.5%, $p=0.01$)(Figure 1). The use of any inhaled respiratory medication was also more common in those diagnosed with asthma (82.6% vs. 16.4%; $p<0.001$)(See Table E1 in the Online Repository). Participants with doctor-diagnosed asthma had worse spirometry than those without: pre-bronchodilator FEV₁/FVC (mean [SD] 0.69 [0.11] vs. 0.76 [0.09]; $p<0.001$), FVC percent predicted (94.9% [17.3] vs. 101.1% [14.9]; $p=0.02$), FEV₁ percent predicted (80.7% [18.9] vs. 95.8% [16.9]; $p<0.001$), and FEV_{25%-75%} percent predicted (56.2% [32.5] vs. 88.1 [34.8]; $p<0.001$). Despite worse spirometry, participants with doctor-diagnosed asthma were no more likely to have BDR than those who had not been diagnosed with asthma (13.0% vs. 7.9%; $p=0.28$). The DL_{CO}

% predicted in each group were low on average, but not significantly different (62.4% [16.4] vs. 67.1% [15.2]; $p=0.07$).

Bronchodilator reversibility

BDR was present in 9.0% of the cohort. Participants with BDR were similar to those without BDR in age, gender, HIV risk factor, drug use, infection history, antiretroviral medication use, CD4 counts, and HIV RNA levels. Those with BDR were more likely to wheeze (45.0% vs. 24.6%; $p=0.05$) (See Figure E1 in the Online Repository) and to have used an oral steroid for their breathing in the past year (25.0% vs. 7.4%; $p=0.009$) (See Table E2 in the Online Repository). Spirometry was also significantly lower in participants with BDR compared to those without: pre-bronchodilator FEV₁/FVC (0.63 [0.12] vs. 0.76 [0.09]; $p<0.001$), FVC percent predicted (91.1% [19.3] vs. 100.6% [15.0]; $p=0.01$), FEV₁ percent predicted (70.5% [18.1] vs. 94.9% [16.9]; $p<0.001$), and FEF_{25%-75%} percent predicted (41.5% [27.7] vs. 84.4% [35.0]; $p<0.001$). The DL_{CO} percent predicted was also lower in those with BDR compared to those without (57.0% [19.2] vs. 67.1% [14.9]; $p=0.01$).

Body mass index and asthma

There was an association between doctor-diagnosed asthma and obesity. Median (quartile [Q1-Q3]) BMI for the cohort was 25.6 (22.7–29.7), and those with doctor-diagnosed asthma had a higher BMI than those without doctor-diagnosed asthma (median [Q1-Q3] BMI, 28.4 [23.9–33.5] vs. 25.4 [22.5–28.8]; $p=0.003$). There was no difference in respiratory symptoms or wheezing among the BMI quartiles. Prevalence of doctor-diagnosed asthma increased with each BMI quartile and was significantly greater in the highest BMI quartile, and this association persisted when controlling for gender and ART use (odds ratio [OR] of highest vs. other quartiles 2.28; 95% CI, 1.09–4.76; $p=0.03$) (Table 2). There was no difference in BMI between those with and without BDR, and there was no association between FEV₁ % predicted or FEF_{25%-75%} % predicted and BMI.

Sputum eosinophils, serum IgE levels, and inflammatory cytokines and chemokines

Several biomarkers were associated with asthma. Median (Q1–Q3) eosinophil percentage was 0.36% (0–0.9%). A high eosinophil count (>2.3%) was found in 16 (9.9%) participants, and a high eosinophil count was more common in those with doctor-diagnosed asthma (OR, 3.6; 95% CI, 1.2–10.4; $p=0.02$) and BDR (OR, 5.0; 95% CI, 1.3–18.8; $p=0.02$) (Figure 2). When controlling for age, gender, race, smoking status, and ART use, the association remained significant between sputum eosinophils and doctor-diagnosed asthma (OR, 3.3; 95% CI, 1.1–10.3; $p=0.04$) and was stronger for BDR (OR, 5.3; 95% CI, 1.4–20.8; $p=0.02$). In the cohort, median (Q1–Q3) IgE level was 42.3 international units (IU)/mL (11.0–175.7 IU/mL), and while IgE level correlated with sputum eosinophil percent (Spearman $r=0.24$; $p=0.002$), IgE level was not associated with respiratory symptoms, doctor-diagnosed asthma, BDR, or airway obstruction.

Specific sputum and plasma cytokines were associated with doctor-diagnosed asthma and BDR. Doctor-diagnosed asthma tended to be more common with high sputum IL-4 (27% vs. 10.5%; $p=0.02$) and RANTES (26.6% vs. 9.8%; $p=0.02$), though not statistically significant at a level of <0.01 to account for multiple comparisons (See Tables E3 in the Online Repository). BDR was more common in those with high plasma MIP-1 α (26.3% vs. 4.8%; $p=0.002$), and high sputum MIP-1 β (26.1% vs. 4.3%; $p=0.001$) (See Figure E2 in the Online Repository). A greater % change in FEV₁ with bronchodilator was seen in those with high plasma MIP-1 β (4.6% [6.2] vs. 1.0% [5.1]; $p<0.001$) (See Table E4 in the Online Repository). High sputum % eosinophils was associated with high sputum MIP-1 β (OR, 8.57; 95% CI 2.14–34.30; $p=0.001$) (See Figure E3 in the Online Repository), but not with other cytokines or chemokines. There were no associations of doctor-diagnosed asthma,

BDR, FEV₁ % predicted, or FEF_{25%–75%} % predicted with plasma or induced sputum IL-13 or eotaxin-1.

Multivariable analysis

In multivariable models, doctor diagnosis of asthma was more common in females (OR, 2.21; 95% CI, 1.05–5.07; $p=0.04$), those in the 4th quartile of BMI compared to those in the other 3 quartiles (OR 2.28; 95% CI 1.18–9.02; $p=0.03$), and those with a history of bacterial or *Pneumocystis* pneumonia (OR, 2.65; 95% CI, 1.21–5.40; $p=0.01$), but less common in those on ART (OR, 0.43; 95% CI, 0.19–0.95; $p=0.04$) (Table 2). BDR was not independently associated with any factors other than sputum eosinophils.

DISCUSSION

In a cohort of HIV-infected outpatients, we found that asthma was the most commonly diagnosed chronic pulmonary disease. Asthma-related symptoms such as wheezing, medication use, and BDR were also common. Doctor-diagnosed asthma was associated with parental history of asthma, female sex, obesity, prior pneumonia, and not being on ART. Higher sputum eosinophils were associated with doctor-diagnosed asthma and BDR, and inflammatory cytokines and chemokines were associated with BDR and sputum eosinophilia.

The prevalence in our cohort of doctor-diagnosed asthma was 20.6%, more than double the most recent estimate in the general adult population of 8.2%.⁽²⁴⁾ However, it should be noted that the HIV population has a higher prevalence of smokers and African-Americans than the general population which may affect the estimate for prevalence of doctor-diagnosed asthma, and making a determination of whether asthma is more prevalent in the HIV population is difficult without a well-matched control population.⁽²⁵⁾

We found several risk factors associated with doctor-diagnosed asthma in the cohort. ART use was associated with a lower risk of doctor-diagnosed asthma and was not associated with BDR, in contrast to prior studies that suggest that ART is associated with airflow obstruction in adults and asthma in children.^(1, 2) The variance between these studies and the current findings may be explained by differences in asthma between children and adults or by differences in the outcomes examined. In adults, the association of ART use with airway obstruction likely represents a phenotype of COPD, not asthma, as the majority of these individuals had irreversible obstruction and decreased DL_{CO}. In asthma, ART use may be protective by decreasing pneumonia which we found associated with asthma diagnosis. In addition, participants with asthma were less likely to be using ART currently, but were no less likely to have ever taken ART, indicating that those with asthma were more likely to have discontinued ART. We do not know if this finding could be due to the onset or worsening of asthma associated with ART. Studies have found that children on ART are more likely to use inhaler medications than those not on ART⁽⁸⁾, and 28% of children during the ART era were treated for persistent asthma compared to none prior to ART.⁽²⁶⁾

Higher BMI was also associated with doctor-diagnosed asthma. We did not find that greater BMI was associated with more respiratory symptoms, suggesting that the association between obesity and asthma was not due to an increased tendency of doctors to diagnose asthma in a more symptomatic population.⁽²⁷⁾ Obesity and asthma have been linked in the general population^(28–31), and HIV-infected individuals are at risk for similar types of metabolic disturbances with development of lipodystrophy and metabolic syndrome with certain antiretroviral agents.^(32–34) Potential mechanisms linking obesity to asthma in HIV include changes in adipocytokine levels (such as increases in leptin or decreases in

adiponectin) that are common to obesity and HIV-related lipodystrophy and occur secondary to certain antiretroviral medications linked to HIV-related lipodystrophy.(33, 35, 36)

Allergic inflammation is another important component of asthma in HIV-uninfected populations and is manifested by increased eosinophils and IgE levels.(37) Sputum eosinophils, but not IgE levels, were associated with asthma in our HIV-infected cohort. The high sputum eosinophils found in those diagnosed with asthma suggest the importance of TH-2 immunity in HIV-associated asthma. Prior work has not examined eosinophils in respiratory disease and HIV, but one previous study found elevated IgE levels in HIV-infected individuals and a correlation with response to methacholine challenge.(6) In contrast, we did not find that IgE levels correlated with BDR, but we used a less sensitive test for airway hyperresponsiveness (pre- and post-bronchodilator spirometry) than methacholine challenge.

Increased atopy and allergy characterized by a TH-2 inflammation may be a particular problem in HIV-infected persons due to abnormal T-regulatory cell function(38, 39), but relationships of specific cytokines and chemokines to HIV-associated asthma have not been explored. While there were trends for associations of traditional TH-2 cytokines such as IL-4 with doctor-diagnosed asthma, the strongest associations were between MIP-1 α and MIP-1 β with airflow obstruction and BDR. These chemokines (along with RANTES) are released by CD8+ T-cells as HIV suppressive factors in chronic HIV infection(40) and have been implicated in airway inflammation related to asthma in HIV-uninfected populations(41–44), suggesting that HIV infection may increase risk for asthma via stimulation of chronic inflammation.

Although diffusing capacity abnormalities are not typically associated with asthma, the average DL_{CO} was decreased in our cohort, including in participants with asthma. Diffusion impairment and emphysema are widespread in the HIV-infected population.(45, 46) With as many as 64% of HIV-infected adults having an abnormal DL_{CO}(2), it is likely that there is overlap between asthma and abnormal DL_{CO}. The decreases in DL_{CO} seen in those with HIV may represent emphysema, pulmonary vascular disease, or other factors associated with HIV that could overlap with an asthma diagnosis.(47, 48) In addition, in the non-HIV population, overlap between COPD and airway hyperresponsiveness is not uncommon, and 17–19% of the population with obstructive lung disease report both a COPD and asthma diagnosis.(49, 50) Additionally, although BDR is greater in asthmatics, it may not be necessarily sensitive or specific to differentiate asthma and COPD.(51)

There are several limitations of our study. It is a single center cross-sectional assessment, and it is possible that participation was biased. Applicability to all HIV populations may be limited as this cohort had a higher prevalence of smoking and intravenous drug use compared to prior studies.(1) Smoking and intravenous drug use, however, are much more common among HIV-infected individuals than the general population(25, 52); therefore, the results of the study are likely applicable to many HIV-infected individuals. Asthma history was based on patient report of a doctor diagnosis of asthma, and we could not accurately determine time of asthma onset in relation to HIV infection. Our cohort is young and has a high prevalence of smoking, and it is possible that some participants were misdiagnosed with asthma as opposed to COPD, which would account for the finding that the prevalence of BDR and IgE levels did not differ between those with and without doctor-diagnosed asthma. Even though BDR did not correlate exclusively with doctor-diagnosed asthma, pre- and post-bronchodilator spirometry may fail to detect airway hyperresponsiveness, and prevalence of airway hyperresponsiveness is likely higher if tested by methacholine challenge. Finally, BMI may not capture subtleties of body composition, and more specific

measures for visceral versus peripheral adiposity could provide more detailed insight into the relationship between obesity and asthma.(53)

In conclusion, our study is the first to systematically assess asthma in HIV-infected individuals during the current era of ART. We found that asthma diagnosis and BDR are quite prevalent and an important cause of chronic respiratory disease in the HIV population. The relationship in HIV between parental history of asthma, allergic inflammation, HIV-stimulated cytokines, and obesity with asthma/BDR suggest possible mechanisms of HIV-associated asthma including TH-2 related immune responses, inflammation related to chronic HIV infection, and inflammation related to metabolic syndrome/disease. Appropriate diagnostic evaluation is important as HIV-infected persons are at risk for a wide range of acute and chronic respiratory diseases and have a high prevalence of frequent respiratory symptoms, particularly in those already diagnosed with asthma. Our findings indicate that asthma should be considered in HIV-infected patients with respiratory symptoms fitting the clinical syndrome.

Acknowledgments

Sources of support: NIH T32 HL007563, K23 HL108697 (MG); P50 HL084948, N01 HR46163R01 (FS); R01 HL083461 and HL083461S (AM); and the University of Pittsburgh CTSI (UL1 RR024153)

Abbreviations

AIDS	acquired immune deficiency syndrome
ART	combination antiretroviral therapy
ATS	American Thoracic Society
BD	bronchodilator
BDR	bronchodilator reversibility
BMI	body mass index
CD4	CD4+ T-lymphocyte
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DLCO	diffusion capacity for carbon monoxide
FEF25%-75%	forced expiratory flow between 25% and 75% of vital capacity
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
HIV	human immunodeficiency virus
IgE	immunoglobulin E
IL	interleukin
IU	international units
MIP	macrophage inflammatory protein
OR	odds ratio
RANTES	Regulated on Activation Normal T Cell Expressed and Secreted
RNA	ribonucleic acid

SD	standard deviation
TH	T-helper

References

1. George MP, Kannass M, Huang L, Sciurba FC, Morris A. Respiratory symptoms and airway obstruction in HIV-infected subjects in the HAART era. *PLoS One*. 2009; 4(7):e6328. [PubMed: 19621086]
2. Gingo MR, George MP, Kessinger CJ, Lucht L, Rissler B, Weinman R, et al. Pulmonary function abnormalities in HIV-infected patients during the current antiretroviral therapy era. *Am J Respir Crit Care Med*. 2010 Sep 15; 182(6):790–6. [PubMed: 20522793]
3. Louie JK, Hsu LC, Osmond DH, Katz MH, Schwarcz SK. Trends in causes of death among persons with Acquired Immunodeficiency Syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994–1998. *J Infect Dis*. 2002 Oct 1; 186(7):1023–7. [PubMed: 12232845]
4. Moscato G, Maserati R, Marraccini P, Caccamo F, Dellabianca A. Bronchial reactivity to methacholine in HIV-infected individuals without AIDS. *Chest*. 1993 Mar; 103(3):796–9. [PubMed: 8449071]
5. O'Donnell CR, Bader MB, Zibrak JD, Jensen WA, Rose RM. Abnormal airway function in individuals with the Acquired Immunodeficiency Syndrome. *Chest*. 1988 Nov; 94(5):945–8. [PubMed: 3263260]
6. Poirier CD, Inhaber N, Lalonde RG, Ernst P. Prevalence of bronchial hyperresponsiveness among HIV-infected men. *Am J Respir Crit Care Med*. 2001 Aug 15; 164(4):542–5. [PubMed: 11520712]
7. Wallace JM, Stone GS, Browdy BL, Tashkin DP, Hopewell PC, Glassroth J, et al. Nonspecific airway hyperresponsiveness in HIV disease. Pulmonary Complications of HIV Infection Study Group. *Chest*. 1997 Jan; 111(1):121–7. [PubMed: 8996005]
8. Foster SB, McIntosh K, Thompson B, Lu M, Yin W, Rich KC, et al. Increased incidence of asthma in HIV-infected children treated with highly active antiretroviral therapy in the National Institutes of Health Women and Infants Transmission Study. *J Allergy Clin Immunol*. 2008 Jul; 122(1):159–65. [PubMed: 18547627]
9. Foisy MM, Yakiwchuk EM, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. *HIV Med*. 2008 Jul; 9(6):389–96. [PubMed: 18459946]
10. Kaviani N, Bukberg P, Manassis A, Yen V, Young I. Iatrogenic osteoporosis, bilateral hip osteonecrosis, and secondary adrenal suppression in an HIV-infected patient receiving inhaled corticosteroids and ritonavir-boosted HAART. *Endocr Pract*. 2011 Jan-Feb; 17(1):74–8. [PubMed: 20713349]
11. Kedem E, Shahar E, Hassoun G, Pollack S. Iatrogenic Cushing's syndrome due to coadministration of ritonavir and inhaled budesonide in an asthmatic human immunodeficiency virus infected patient. *J Asthma*. 2010 Sep; 47(7):830–1. [PubMed: 20653496]
12. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007 Feb 22; 356(8):775–89. [PubMed: 17314337]
13. Hirschtick RE, Glassroth J, Jordan MC, Wilcosky TC, Wallace JM, Kvale PA, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med*. 1995 Sep 28; 333(13):845–51. [PubMed: 7651475]
14. Barr JT, Schumacher GE, Freeman S, LeMoine M, Bakst AW, Jones PW. American translation, modification, and validation of the St. George's Respiratory Questionnaire. *Clin Ther*. 2000 Sep; 22(9):1121–45. [PubMed: 11048909]
15. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis*. 1992 Jun; 145(6):1321–7. [PubMed: 1595997]

16. Gershman NH, Wong HH, Liu JT, Mahlmeister MJ, Fahy JV. Comparison of two methods of collecting induced sputum in asthmatic subjects. *Eur Respir J*. 1996 Dec; 9(12):2448–53. [PubMed: 8980952]
17. Fahy JV, Boushey HA, Lazarus SC, Mauger EA, Cherniack RM, Chinchilli VM, et al. Safety and reproducibility of sputum induction in asthmatic subjects in a multicenter study. *Am J Respir Crit Care Med*. 2001 May; 163(6):1470–5. [PubMed: 11371420]
18. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005 Aug; 26(2):319–38. [PubMed: 16055882]
19. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005 Oct; 26(4):720–35. [PubMed: 16204605]
20. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005 Nov; 26(5):948–68. [PubMed: 16264058]
21. Belda J, Leigh R, Parameswaran K, O’Byrne PM, Sears MR, Hargreave FE. Induced sputum cell counts in healthy adults. *Am J Respir Crit Care Med*. 2000 Feb; 161(2 Pt 1):475–8. [PubMed: 10673188]
22. Spanevello A, Confalonieri M, Sulotto F, Romano F, Balzano G, Migliori GB, et al. Induced sputum cellularity. Reference values and distribution in normal volunteers. *Am J Respir Crit Care Med*. 2000 Sep; 162(3 Pt 1):1172–4. [PubMed: 10988149]
23. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. *Stat Med*. 1997 May 15; 16(9):965–80. [PubMed: 9160492]
24. Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001–2009. *MMWR Morb Mortal Wkly Rep*. 2011 May 6; 60(17):547–52. [PubMed: 21544044]
25. Prevalence of risk behaviors for HIV infection among adults—United States, 1997. *MMWR Morb Mortal Wkly Rep*. 2001 Apr 13; 50(14):262–5. [PubMed: 11411830]
26. Gutin F, Butt A, Alame W, Thomas R, Secord E. Asthma in immune-competent children with human immunodeficiency virus. *Ann Allergy Asthma Immunol*. 2009 May; 102(5):438. [PubMed: 19492668]
27. Pakhale S, Doucette S, Vandemheen K, Boulet LP, McIvor RA, Fitzgerald JM, et al. A comparison of obese and nonobese people with asthma: exploring an asthma-obesity interaction. *Chest*. 2010 Jun; 137(6):1316–23. [PubMed: 20154078]
28. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med*. 2007 Apr 1; 175(7):661–6. [PubMed: 17234901]
29. Kronander UN, Falkenberg M, Zetterstrom O. Prevalence and incidence of asthma related to waist circumference and BMI in a Swedish community sample. *Respir Med*. 2004 Nov; 98(11):1108–16. [PubMed: 15526812]
30. Ronmark E, Andersson C, Nystrom L, Forsberg B, Jarvholm B, Lundback B. Obesity increases the risk of incident asthma among adults. *Eur Respir J*. 2005 Feb; 25(2):282–8. [PubMed: 15684292]
31. Shore SA. Obesity, airway hyperresponsiveness, and inflammation. *J Appl Physiol*. 2010 Mar; 108(3):735–43. [PubMed: 19875711]
32. Han SH, Chin BS, Choi HK, Shin SY, Chae YT, Baek JH, et al. Prevalence of and clinical factors associated with lipodystrophy in HIV-infected Koreans receiving highly active antiretroviral therapy. *Tohoku J Exp Med*. 2009 Oct; 219(2):145–53. [PubMed: 19776532]
33. Miller J, Carr A, Emery S, Law M, Mallal S, Baker D, et al. HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. *HIV Med*. 2003 Jul; 4(3):293–301. [PubMed: 12859330]
34. Moreno S, Miralles C, Negredo E, Domingo P, Estrada V, Gutierrez F, et al. Disorders of body fat distribution in HIV-1-infected patients. *AIDS Rev*. 2009 Jul-Sep; 11(3):126–34. [PubMed: 19654854]
35. Gougeon ML, Penicaud L, Fromenty B, Leclercq P, Viard JP, Capeau J. Adipocytes targets and actors in the pathogenesis of HIV-associated lipodystrophy and metabolic alterations. *Antivir Ther*. 2004 Apr; 9(2):161–77. [PubMed: 15134178]

36. Tsiodras S, Perelas A, Wanke C, Mantzoros CS. The HIV-1/HAART associated metabolic syndrome - novel adipokines, molecular associations and therapeutic implications. *J Infect.* 2010 Jul; 61(2):101–13. [PubMed: 20547180]
37. Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol.* 2010 Feb; 125(2 Suppl 2):S73–80. [PubMed: 20176269]
38. Moreno-Fernandez ME, Zapata W, Blackard JT, Franchini G, Chougnet CA. Human regulatory T cells are targets for human immunodeficiency virus (HIV) infection, and their susceptibility differs depending on the HIV type 1 strain. *J Virol.* 2009 Dec; 83(24):12925–33. [PubMed: 19828616]
39. Jesser RD, Li S, Weinberg A. Regulatory T cells generated during cytomegalovirus in vitro stimulation of mononuclear cells from HIV-infected individuals on HAART correlate with decreased lymphocyte proliferation. *Virology.* 2006 Sep 1; 352(2):408–17. [PubMed: 16782163]
40. Cocchi F, DeVico AL, Garzino-Demo A, Arya SK, Gallo RC, Lusso P. Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV-suppressive factors produced by CD8+ T cells. *Science.* 1995 Dec 15; 270(5243):1811–5. [PubMed: 8525373]
41. Bisset LR, Schmid-Grendelmeier P. Chemokines and their receptors in the pathogenesis of allergic asthma: progress and perspective. *Curr Opin Pulm Med.* 2005 Jan; 11(1):35–42. [PubMed: 15591886]
42. Bogaert P, Naessens T, De Koker S, Hennuy B, Hacha J, Smet M, et al. Inflammatory signatures for eosinophilic versus neutrophilic allergic pulmonary inflammation reveal critical regulatory checkpoints. *Am J Physiol Lung Cell Mol Physiol.* 2011 May; 300(5):L679–90. [PubMed: 21335522]
43. Grob M, Schmid-Grendelmeier P, Joller-Jemelka HI, Ludwig E, Dubs RW, Grob PJ, et al. Altered intracellular expression of the chemokines MIP-1alpha, MIP-1beta and IL-8 by peripheral blood CD4+ and CD8+ T cells in mild allergic asthma. *Allergy.* 2003 Mar; 58(3):239–45. [PubMed: 12653799]
44. Maurer M, von Stebut E. Macrophage inflammatory protein-1. *Int J Biochem Cell Biol.* 2004 Oct; 36(10):1882–6. [PubMed: 15203102]
45. Diaz PT, King MA, Pacht ER, Wewers MD, Gadek JE, Nagaraja HN, et al. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann of Intern Med.* 2000 Mar 7; 132(5):369–72. [PubMed: 10691587]
46. Diaz PT, King MA, Pacht ER, Wewers MD, Gadek JE, Neal D, et al. The pathophysiology of pulmonary diffusion impairment in human immunodeficiency virus infection. *Am J Respir Crit Care Med.* 1999 Jul; 160(1):272–7. [PubMed: 10390411]
47. Sitbon O, Lascoux-Combe C, Delfraissy J-F, Yeni PG, Raffi F, De Zuttere D, et al. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. *Am J Respir Crit Care Med.* Jan 1; 2008 177(1):108–13. [PubMed: 17932378]
48. Crothers K, Huang L, Goulet JL, Goetz MB, Brown ST, Rodriguez-Barradas MC, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med.* 2011 Feb 1; 183(3):388–95. [PubMed: 20851926]
49. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest.* 2003 Aug; 124(2):474–81. [PubMed: 12907531]
50. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax.* 2009 Aug; 64(8):728–35. [PubMed: 19638566]
51. Kesten S, Rebuck AS. Is the short-term response to inhaled beta-adrenergic agonist sensitive or specific for distinguishing between asthma and COPD? *Chest.* 1994 Apr; 105(4):1042–5. [PubMed: 8162722]
52. Celli BR, Halbert RJ, Nordyke RJ, Schau B. Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. *Am J Med.* 2005 Dec; 118(12):1364–72. [PubMed: 16378780]
53. Onat A, Avci GS, Barlan MM, Uyarel H, Uzunlar B, Sansoy V. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. *Int J Obes Relat Metab Disord.* 2004 Aug; 28(8):1018–25. [PubMed: 15197408]

Clinical Implications

Asthma diagnosis and reversible airway obstruction are common in HIV-infected persons. Metabolic derangements prior infections, or allergic inflammation may play an important role in asthma in HIV.

Figure 1.

Prevalence of respiratory symptoms (a) and pulmonary function values (b) in participants diagnosed with asthma by their physician in the past and those without an asthma diagnosis. DL_{CO} = diffusion capacity for carbon monoxide, FEV₁ = forced expiratory volume in 1 second, FEF_{25%-75%} = forced expiratory flow between 25% and 75% of vital capacity, FVC = forced vital capacity, % = percent predicted.

Figure 2.
Prevalence of a high (>2.3%) eosinophil count in induced sputum between participants with or without doctor-diagnosed asthma or positive bronchodilator reversibility (BDR).

Table 1

Characteristics of participants with and without doctor diagnosed asthma

	No Asthma (n=177)	Asthma (n=46)	p-value
Age, mean years (range)	45.9 (9.6)	42.6 (9.7)	0.04
Female, n (%)	39 (22.0)	19 (41.3)	0.008
African-American, n (%)	89 (50.3)	26 (56.5)	0.50
Parental history of asthma, n (%)[*]	23 (16.4)	15 (37.5)	0.004
Men who have sex with men, n (%)	94 (53.4)	19 (41.3)	0.14
Current smoker, n (%)	93 (52.5)	34 (73.9)	0.03
Ever smoker, n (%)	135 (76.3)	41 (89.1)	0.057
Intravenous drug use, n (%)	38 (21.5)	7 (15.2)	0.34
Marijuana use, n (%)	141 (79.7)	33 (71.7)	0.20
Cocaine use, n (%)	75 (45.5)	17 (39.5)	0.49
History of PCP or BP, n (%)	69 (39.9)	28 (60.9)	0.01
ART in past 3 months, n (%)	145 (81.9)	31 (67.4)	0.03
Ever on ART, n (%)	156 (88.1)	38 (82.6)	0.32
On PCP prophylaxis currently, n (%)	66 (37.7)	15 (33.3)	0.60
CD4 cells/ml, median (range)	472 (6–1921)	479 (41–1107)	0.50
HIV RNA, median copies/ml (range)	<50 (<50–1.96×10 ⁶)	<50 (<50–1.25×10 ⁶)	0.10

^{*} Data only available or known for 180 participants for parental history of asthma. ART = combination antiretroviral therapy; BP = bacterial pneumonia; PCP = *Pneumocystis* pneumonia; RNA = ribonucleic acid.

Table 2

Multivariable regression results

Outcome	Covariate	OR (95% CI)	p-value
Doctor-diagnosed asthma	Female	2.21 (1.05–5.07)	0.04
	BMI, Q4 vs. Q1–Q3	2.28 (1.18–9.02)	0.03
	ART, current	0.43 (0.19–0.95)	0.04
	History of BP or PCP	2.65 (1.21–5.40)	0.01
BD response	none		

ART, antiretroviral therapy; BMI, body mass index; BP, bacterial pneumonia; PCP, *Pneumocystis pneumonia*; Q, quartile.