Factors associated with reduced lung function in adolescents living with HIV in Nairobi, Kenya

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Abstract

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Background: Over 5 million children and adolescents are living with HIV (ALWH) worldwide as a result of perinatally-acquired disease. Recent data support high prevalence of chronic respiratory symptoms in this population and a predominant phenotype of irreversible airflow obstruction. The objective of this study was to better understand factors associated with chronic lung disease in ALWH in Nairobi, Kenya.

Methods: We conducted a cross-sectional study of adolescents aged 10-19 years with and without HIV in Nairobi, Kenya. We enrolled ALWH from a single HIV center and HIV-uninfected adolescents with similar sociodemographic characteristics. We administered standardized questionnaires and performed a focused respiratory exam and spirometry. Our primary outcome was post-bronchodilator FEV1 z-score (post zFEV1). We performed linear regression models evaluating the association between HIV infection and post zFEV1. We then restricted the analysis to ALWH and evaluated associations between a number of sociodemographic, clinical, and immune function factors and post zFEV1.

Results: Among the 332 participants, 165 were ALWH (median age 15 years [IQR 13-18], 56% male) and 167 were HIV-uninfected (median age 14 years [IQR 12-17], 38% male). Compared to HIV-uninfected adolescents, ALWH of similar age, sex, smoke and biofuel exposure had 0.29 (95% CI -0.53, -0.05) lower post zFEV1 (p=0.019). Airflow obstruction was present in 10 (6%) ALWH and 10 (6%) HIV-uninfected adolescents (OR= 1.01 [95% CI 0.36, 2.79], p=1.0), while a restrictive pattern was present in 7% ALWH and 2% HIV-uninfected adolescents (OR= 3.90 [95% CI 1.00, 22.1], p=0.031). Among ALWH, factors associated with impaired post zFEV1 included lower BMI z-scores (p<0.001), clubbing (p=0.019), and abnormal lung sounds (p=0.006) in adjusted analysis. Markers of T cell imbalance were not associated with lung function in our analyses.

Conclusion: HIV was an independent risk factor for reduced lung function. Airflow obstruction and restrictive patterns were present in a minority of our study population. Clinically available factors are associated with reduced lung function and may be useful for identifying individuals with reduced lung function in settings where diagnostic testing is not readily available.

Introduction

Over 5 million children and adolescents are living with HIV worldwide as a result of perinatally-acquired disease, with the vast majority living in sub-Saharan Africa (1, 2). Through early diagnosis and management, children with HIV in low- and middle-income countries are surviving to adolescence, shifting the burden of respiratory disease from acute complications during infancy and childhood to chronic respiratory complications in adolescence (3).

The pathogenesis of respiratory complications in HIV is heterogeneous across ages. In children less than 10 years old, acute pulmonary infections and lymphoid interstitial pneumonitis are well described as predominant subtypes, but these complications have declined with improved, widespread prophylaxis and antiretroviral therapy (4-6). Conversely, adults with HIV have higher prevalence of chronic obstructive pulmonary disease (COPD) and emphysema, even after controlling for cigarette smoke exposure (7). More recently, respiratory symptoms have been described in adolescents living with HIV (ALWH). In fact, over half of ALWH reported at least one chronic respiratory symptom in recent studies from Zimbabwe, Malawi, Kenya, and South Africa (4, 8-11), but the pathogenesis of these conditions is unclear; both obstructive and restrictive patterns have been described on lung function testing (4, 8-11), and chest imaging has demonstrated evidence of small airways disease (4).

Data on pulmonary disease in ALWH are largely limited to small cross-sectional observational studies. Early observational studies suggest irreversible airflow obstruction as a predominant phenotype (4, 5, 8, 11). Theories for pathogenesis include chronic or acute immune dysregulation, recurrent or severe respiratory infections, and environmental exposures contributing to high respiratory morbidity. The objective of this study is to better understand the pathophysiology of chronic lung disease in adolescents living with HIV in Nairobi, Kenya. We hypothesized that lung function would be reduced in ALWH compared to uninfected adolescents and explored whether irreversible airflow obstruction would represent a predominant phenotype. Secondly, we hypothesized that biomarkers of immune dysregulation, specifically T cell imbalance, would be associated with reduced lung function in ALWH.

Methods

Study design and setting

We conducted a cross-sectional analysis of baseline data collected in 2017-2018 from an ongoing prospective cohort study of adolescents with and without HIV in Nairobi, Kenya. Data collection took place in Nairobi, Kenya in an outpatient clinic setting. The main study site was the Coptic Hope Center for Infectious Diseases, a comprehensive and free antiretroviral treatment (ART) facility caring for children, adolescents and adults with HIV, where all study procedures were performed. Participants were also recruited from the surrounding geographic catchment area, including from the Kenyatta National Hospital, a neighboring medical center located less than 15 minutes walking distance from the Hope Center.

Study subjects

We recruited adolescents aged 10 to 19 years living with HIV from the Coptic Hope Center for Infectious Diseases. For the comparison group, we recruited HIV-uninfected adolescents with similar sociodemographic characteristics and without acute illness from: 1) siblings of ALWH, 2) the neighboring Kenyatta Hospital and 3) children enrolled in other University of Washington studies from the surrounding catchment area. The comparison group consists of adolescents who were both perinatally HIV-exposed/uninfected and HIV-unexposed/uninfected. Exclusion criteria included acute respiratory tract infection within the preceding 4 weeks, as defined by at least 2 of the following by self-report: 1) cough/purulent phlegm production above what they would consider “normal”, 2) fever, 3) treatment with antibiotics; illness requiring urgent hospitalization; smear-positive tuberculosis within 8 weeks; pregnancy; or participating in a recent pilot study in which chest CT scans were already performed.

Data collection

Standardized questionnaires were administered via interview format in English or Kiswahili to all participants at the enrollment visit. Self-reported respiratory symptoms included cough, shortness of breath, wheezing, chest tightness and sputum production that were present as part of the participant's usual state of health; subjective functional capacity was assessed using validated questionnaires (12-15). Respiratory-focused examinations ascertained respiratory rate, height, weight, abnormal lung sounds, digital clubbing, oxygen saturation at rest and after sub-maximal exercise. Spirometry with a minimum of three maneuvers was performed before and after bronchodilator administration in all participants using NDD EasyOne portable spirometers (Andover, MA) to produce measures of lung function. We used American Thoracic Society standards to determine reproducibility and acceptability. We used the online training and feedback program Spirometry360 for spirometry quality control (www.spirometry360.org). HIV status was confirmed by ELISA HIV test at the Coptic Hope Center for Infectious Diseases.

Outcomes

Outcomes included several measures of lung function. The primary outcome measure of lung function was post-bronchodilator forced expiratory volume in 1 second z-score (post zFEV1). Post zFEV1 is a measure of irreversible airflow limitation compared to pre-bronchodilator zFEV1 (pre zFEV1) and would, therefore, be more consistent with obliterative/constrictive bronchiolitis. Lower FEV1 is also considered an independent predictor of mortality (16). To further characterize lung function in study participants, we evaluated additional continuous spirometry parameters: forced vital capacity z-scores (zFVC) as a marker for restrictive physiology and zFEV1/FVC as a measure of airflow obstruction. We defined different phenotypes of abnormal lung function: airflow obstruction (based on zFEV1/FVC pre-bronchodilator and severity based on zFEV1), fixed airflow obstruction (based on zFEV1/FVC post-bronchodilator), restrictive pattern (based on zFVC pre-bronchodilator), and mixed restrictive/obstructive pattern pre-bronchodilator using existing guidelines (17, 18) (Table 1). We defined bronchodilator reversibility as improvement in FEV1 by 12% following bronchodilator administration.

Covariates

We examined a number of factors in relation to lung function. Sociodemographic factors included age, sex, indoor biofuel exposure (hours/day), tobacco smoke exposure, and household income. Anthropometric factors included body mass index (BMI)-for-age Z-scores and height-for-age Z-scores. HIV-related factors included route of HIV acquisition (perinatal vs behavioral, based on self-report), recent prophylaxis for *pneumocystis jiroveci* pneumonia with co-trimazole, recent CD4 cell count (cells/µL), recent CD8 cell count (cells/µL), recent CD4/CD8, ART regimen, and proportion of life on ART. Available historical data for ALWH from the Coptic Hope Center included WHO HIV stage, nadir and initial CD4 count, nadir and initial CD8, and nadir CD4/CD8. Clinical signs/symptoms included self-reported respiratory symptoms of cough, chest tightness, breathlessness, or wheezing; resting respiratory rate; oxygen saturation before and after sub-maximal exercise; presence of digital clubbing; and abnormal lung exam on auscultation (i.e., wheezing, crackles, rhonchi).

Data management

All data were entered into an electronic data collection form using Open Data Kit for all participants and merged with existing Hope Center data for ALWH.

Statistical analysis

Baseline characteristics and lung function testing were summarized using counts and proportions for categorical variables or median and interquartile range for continuous variables. We used linear regression models to test the hypothesis that HIV infection was associated with reduced lung function, adjusting for age, sex, tobacco smoke exposure, and indoor biofuel exposure as potential confounders, specified *a priori*. We focused on post zFEV1 as the primary outcome indicator of lung function. Because we did not find significant confounding in our linear regression models and due to small numbers, we calculated unadjusted odds ratios to evaluate associations between HIV infection and clinical phenotypes of lung function with p-values based on Fisher’s exact test. To better understand potential risk factors associated with lung function in ALWH, we used linear regression models to identify sociodemographic, clinical, and HIV-related factors associated with post zFEV1 in ALWH, adjusting for age and sex. Given the lack of confounding in the relationship between HIV infection and lung function, we chose a more parsimonious model and did not adjust for tobacco smoke exposure or indoor biofuel exposure.

We performed several sensitivity analyses. First, because adolescents who are HIV-exposed/uninfected may have immune dysregulation that differs from HIV-unexposed/uninfected adolescents (19, 20), we evaluated whether adolescents who were HIV-exposed/uninfected differed from those who were HIV-unexposed/uninfected by participant characteristics and lung function measures, using summary statistics and linear regression models, respectively. Secondly, because perinatal and behavioral acquisition of HIV may affect the development of pulmonary disease differently, we repeated the primary analyses excluding individuals with behaviorally-acquired HIV. Finally, we excluded values of FEV1/FVC and zFVC when FEV1/FVC was >0.95, as an FEV1/FVC ratio that nears 1 may represent submaximal expiration and a falsely low FVC.

Missingness in the dataset were as follows: primary outcome post zFEV1 3/332 (1%) and secondary outcomes pre zFEV1 5/332 (1.5%), pre zFVC 23/332 (7%), pre zFEV1/FVC 23/332 (7%), post zFVC 36/332 (11%), post zFEV1/FVC 36/332 (11%) (Figure 1). Missingness of clinical phenotypes was reflective of continuous lung function values: airway obstruction 23/332 (7%), fixed airway obstruction 36/332 (11%), restrictive pattern 23/332 (7%), and mixed pattern 23/332 (7%). Missingness of additional exposures included income 77/332 (23%), percentage of life on ART 8/165 (4%), WHO HIV class 1/165 (1%), recent CD4 6/332 (2%), recent CD8 7/332 (2%), nadir CD4 20/165 (12%), nadir CD4/CD8 21/165 (13%), prior pneumonia 1/332 (0.3%), hospitalized for pneumonia 2/332 (1%), and exam (RR, SpO2, clubbing, lung auscultation) 7/332 (2%). Ninety-nine percent of observations had complete data for primary analysis with HIV exposure, primary outcome, and confounding variables; <1% were missing outcome only. Eighty-six percent of observations had complete secondary outcome data; 7% were missing post zFVC and post zFEV1/FVC only; 2% were missing pre zFVC and pre zFEV1/FVC. We assumed data were missing at random. We performed a complete case analysis to test our hypotheses.

All results were considered significant at a two-sided $p < 0.05$. Analyses were performed using Stata version 14.2 (StataCorp LP, College Station, Texas).

Ethics

All participants provided written informed consent/assent. Ethical approval was obtained from both the Kenyatta National Hospital/University of Nairobi and the University of Washington.

Results

Participant Characteristics

We enrolled 170 ALWH and 175 HIV-uninfected adolescents in the comparison group. Data from 5 ALWH and 8 HIV-uninfected adolescents were excluded, because they either withdrew at the initial study visit, had missing questionnaires or had no acceptable spirometry elements (Figure 1). Among the ALWH, 160 (97%) had acquired HIV perinatally. A larger proportion of ALWH were male (56% vs 38%); they reported slightly higher household income (57% vs 43% >15,000 Ksh) although more ALWH had missing data for this variable, and environmental (secondhand) tobacco smoke exposure (24% vs 18%) (Table 2). Median age was 15 years (interquartile range [IQR] 13 – 18 years) among ALWH and 14 years (IQR 12 – 17 years) among the uninfected adolescents. ALWH had lower median recent CD4 cell counts (576 [IQR 359 – 787] cells/µL vs. 920 [707 – 1118] cells/µL), higher CD8 cell counts (788 [IQR 585 – 1115] cells/µL vs. 638 [478– 797] cells/µL) and lower CD4/CD8 ratio (0.7 [IQR 0.4 – 1.0] cells/µL vs. 1.5 [1.1 – 1.8] cells/µL) compared to the uninfected group. Median nadir CD4 count among the ALWH was 408 (IQR 167 – 532) cells/µL, and 30% had nadir CD4 <200 cells/µL; median nadir CD4/CD8 was 0.3 (IQR 0.1 – 0.5). A larger proportion of ALWH who reported prior pneumonia also reported being hospitalized for pneumonia (50 vs. 28%). Thirteen percent of ALWH and 1% of uninfected adolescents reported pulmonary tuberculosis. While both groups reported relatively high prevalence of respiratory symptoms, ALWH had a higher prevalence of cough (34 vs. 20%). Physical exam findings were notable for a relatively high proportion of both groups with oxygen saturations less than 92% after sub-maximal exercise (20% in ALWH vs. 18% in uninfected group) and abnormal lung sounds on auscultation (16% in ALWH vs. 11% in uninfected group) (Table 2).

HIV and lung function

ALWH had lower zFEV1 and zFVC before and after bronchodilator administration. In individuals of similar age, sex, tobacco smoke exposure, and biofuel exposure, ALWH had a post zFEV1 0.29 (95% CI -0.53, -0.05) lower than uninfected adolescents (p=0.039) (Table 3). ALWH also had a pre zFVC 0.31 (95% CI -0.54, -0.07) lower than adolescents without HIV after adjusting for these potential confounders (p=0.013). The groups had similar zFEV1/FVC before and after bronchodilator, and zFEV1/FVC improved following bronchodilator administration to a similar degree in both groups. Few of the adolescents in either group met criteria for bronchodilator reversibility (8% in ALWH vs. 6% in uninfected group; OR=1.34 [95% CI 0.52, 3.51] p=0.525. Prevalence of pre-bronchodilator airflow obstruction was 6% in both groups (OR=1.01 [95% CI 0.36, 2.79], p=1.0). Fixed airflow obstruction was also similar between groups (4% in ALWH vs. 3% in the uninfected group; OR=1.5 [95% CI 0.35, 7.37], p=0.750). Compared to HIV-uninfected adolescents, ALWH had higher prevalence of a restrictive pattern of lung function abnormality (7% vs. 2%; OR= 3.90 [95% CI 1.00, 22.1], p=0.031) but similar prevalence of a mixed pattern (1% vs. 0; OR not possible due to zero cells, p=0.248) (Table 3).

Sociodemographic and clinical factors related to lung function in ALWH

There was a trend that ALWH who reported secondhand tobacco smoke exposure had a post zFEV1 score that was 0.39 lower (95%CI -0.85, 0.07; p=0.096) compared to those unexposed to tobacco smoke (Table 4). We did not detect associations between post zFEV1 and income, age, or sex. Among the ALWH, clinical factors related to post zFEV1 included BMI (0.38 higher zFEV1 per 1-unit change in BMI-for-age Z-score; 95%CI 0.20, 0.55, p<0.001), clubbing (-1.42 lower zFEV1 ; 95%CI -2.61, -0.23, p=0.019), and abnormal lung sounds on auscultation (-0.63 lower zFEV1; 95%CI -1.08, -0.18, p=0.006). There was a trend that a history of asthma in ALWH of similar age and sex was associated with 0.50 (95%CI –1.10 – 0.10) lower post zFEV1 (p=0.103). T cell counts were not significantly associated with post zFEV1 (Table 4).

Sensitivity analyses

Adolescents who were HIV-exposed/uninfected and HIV-unexposed/uninfected had similar baseline characteristics and measures of lung function (Supplemental Tables 1 and 2). We identified similar associations between lung function and HIV infection after excluding adolescents with behaviorally-acquired HIV (Supplemental Table 3). Similar associations were also detected after excluding zFVC and zFEV1/FVC values where FEV1/FVC was >0.95 (Supplemental Table 4).

Discussion

In this study, we found that HIV infection was independently associated with reduced lung function in adolescents in Nairobi, Kenya. Until recently, chronic lung disease in general and lung function abnormalities in particular have been underrecognized in older children and young adults with HIV (3). Regardless of the etiology, reduced FEV1 is independently associated with mortality, cardiovascular disease, and respiratory hospitalization in an international cohort of adults (16). This may be of additional importance if present during adolescence because we expect lung function to decline with age after peaking in the mid-20s (22). Reduced lung function in adolescence may hasten further decline in adulthood, thereby increasing the risk for COPD and emphysema later in life (23). Identifying adolescents at risk early offers an opportunity to intervene through anticipatory guidance, medication, and counseling to avoid smoke exposure and other high risk activities. Clinical factors most significantly associated with reduced lung function included lower BMI z-score, clubbing, and abnormal lung sounds on auscultation. Additionally, while not statistically significant, there was a trend towards reduced lung function in ALWH who reported secondhand tobacco smoke exposure and history of asthma. These simple clinical features, if present, may signal higher risk for reduced lung function in ALWH in resource-constrained settings where lung function testing is not readily available.

We also explored associations between HIV infection and different lung disease phenotypes, including obstructive, restrictive, and mixed phenotypes. We found different phenotypes of lung disease in our study population, but the predominant phenotype that emerged from this study population was a restrictive phenotype (reduced zFVC with normal zFEV/FVC). Prior studies report differing results, including both features of airflow obstruction (4-6, 11) and restrictive pattern, (8) supporting the hypothesis that heterogeneous lung disease exists in this population. However, we anticipated airflow obstruction predominance in our study population based on pilot data from our group that demonstrated fixed airflow obstruction (post zFEV1 < -1.64) to be present in 13/47 (28%) of a now older and potentially less healthy cohort of ALWH in Nairobi compared to 4% in our study population (24). Regardless, our results suggest an important phenotype of reduced lung function in ALWH that may reflect different underlying pathophysiology than fixed airflow obstruction. For example, restrictive lung disease may be closely linked with factors related to lung growth in early childhood, and nutritional status has been linked to vital capacity in a number of chronic diseases in pediatrics (25, 26). In fact, we found that ALWH who had lower BMI-for-age Z-scores have significantly lower lung function based on post-bronchodilator FEV1. While we did not have historical BMI data, recent BMI likely reflects longstanding nutritional status and therefore underscores the importance of early childhood nutrition for lung growth, especially in individuals with HIV. Restrictive lung disease may also reflect lung scarring or interstitial lung disease from previous pulmonary infections or other pathophysiologic mechanism and will be investigated further through CT chest imaging.

Importantly, our lung function data describing obstructive and restrictive phenotypes were limited by the lack of high quality FVC in 309/332 (93%) of participants pre-bronchodilator and 296/332 (89%) of participants post-bronchodilator. FVC is challenging to perform, especially for individuals who have not previously performed spirometry, and is prone to early truncation, leading to falsely lower FVC. This may lead to higher zFEV1/FVC scores, thereby underestimating airflow obstruction and failing to characterize phenotypes for all study participants due to poor quality FVC data. We plan to mitigate these challenges in the future through prospective monitoring of lung function in the same study population. We were also limited in our lung function data by inability to perform plethysmography, which would provide valuable information on total lung volume, the gold standard for diagnosing restrictive lung disease. Finally, spirometry testing does not adequately reflect focal lung disease. Therefore, future directions include evaluating chest CT imaging of this cohort for features of obstructive disease (i.e. bronchiectasis and mosaic attenuation) as previously described and restrictive disease (i.e. scarring, pleural thickening, interstitial markings).

Unlike previously published pilot data from our group, we did not find significant associations between markers of T cell imbalance (CD4, CD8, and CD4/CD8) and lung function (24). There are many potential reasons for this. First, as previously mentioned, this study population may reflect a healthier cohort. For example, ALWH in our study overall had higher median nadir CD4 count (408 [167 – 532] vs. 269 [153 – 471] cells/µL) and lower recent CD8 count (788 [585 – 1,115] vs. 1,005 [838 – 1,341] cells/µL) compared to previously published work (24). Another possibility is that other markers of immune dysregulation through endothelial activation or innate immune activation and inflammation may better explain the mechanism by which lung function is affected in ALWH and will be evaluated in this cohort. Third, timing of CD4/CD8 imbalance may be more important in its effect on lung function in early childhood during critical stages in lung development. Our historical data in this cohort are limited. Therefore, future studies should include early childhood biomarkers and other clinical markers of lung health where possible.

Our study has substantial strengths. We used regression modeling to adjust for potential confounders identified *a priori*. Interestingly, our unadjusted and adjusted models were quite similar, suggesting that confounding by age, sex, indoor biofuel exposure and tobacco smoke exposure may not play a major role in the relationship between HIV infection and lung function. We used strong quality control measures when obtaining and interpreting lung function parameters (27). We compared a number of readily available clinical signs and symptoms with reduced lung function to better understand potentially modifiable risk factors for and markers of impaired lung function in ALWH. We also demonstrated high prevalence of respiratory morbidity in the comparison population, highlighting the importance of a comparison group where respiratory symptoms are highly prevalent.

Our study has a few additional limitations. First, our sample size was relatively small, and therefore the lack of statistically significant associations present may reflect lack of power in our study. We were limited to performing unadjusted odds ratios to measure effect size between HIV infection and clinical phenotypes of lung function due to small numbers. However, we believe that these relationships are close to the truth given lack of confounding in our models. Secondly, this was a cross-sectional analysis.

Because the exposures and outcome were assessed simultaneously, causation cannot be directly inferred. However, the exposure HIV infection in most cases was acquired perinatally and therefore present during early stages of lung development, thereby increasing plausibility for causality. Thirdly, our observational study likely has residual confounding and may have unmeasured confounding. For example, we did not directly adjust for measures of socioeconomic status as they were limited to self-reported family income with a high proportion (>20%) of missingness. We used self-reported indoor biofuel exposure, which may be an indirect measure of socioeconomic status and may be underreported if the adolescent does not spend significant time at home. We also used a crude measure of ambient air pollution exposure through the adolescent's reported distance living from a major road that may not accurately reflect the amount of particulate matter to which the individual is exposed. Future directions will explore additional measures of socioeconomic status and objective measures of environmental pollutants, including individual air quality sensors and satellite air pollution mapping. Self-reported data is also at risk for recall bias.

In conclusion, we found that HIV was an independent risk factor for reduced lung function in adolescents in Nairobi, Kenya. These data support that ALWH have heterogeneous lung disease including both obstructive and restrictive phenotypes. By identifying factors associated with disease, including abnormal lung sounds and clubbing, we may be able to better counsel healthcare workers in settings where lung function testing is not readily available to identify high risk patients. We also may be able to identify modifiable factors, most notably nutrition, in early childhood to improve lung function later in life.

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Table 1. Clinical phenotypes of lung function abnormalities

Lung function abnormality	Definition
Airflow obstruction	zFEV/FVC <-1.64 SD before bronchodilator administration
Mild	zFEV1 ≥ -1.64 SD
Moderate	zFEV1 < -1.64 SD
Severe	zFEV1 < -3 SD
Fixed obstruction	zFEV/FVC <-1.64 SD after bronchodilator administration
Restrictive pattern	zFVC < -1.64 SD before bronchodilator administration and zFEV/FVC ≥ -1.64 SD
Mixed pattern	Meets criteria for both zFEV/FVC <-1.64 SD and zFVC <-1.64 SD before bronchodilator administration
Bronchodilator responsiveness	Improvement in FEV1 by 12% after bronchodilator administration

Table 2. Characteristics of the study population

	HIV+ N=165	HIV- N=167
	n (%) or median (IQR)	
Sociodemographic factors		
Male	93 (56)	64 (38)
Age	15 (13 – 18)	14 (12 – 17)
Household income[#]		
<10,000 Ksh	26 (22)	53 (38)
10,001-15,000 Ksh	24 (21)	25 (18)
>15,000 Ksh	67 (57)	60 (43)
Aggregate indoor biofuel exposure (hours/week)	10 (3 – 23)	14 (4 – 28)
Charcoal burning	3 (0 – 10)	3 (0 – 14)
Kerosene burning	0 (0 – 6)	2 (0 – 14)
Secondhand tobacco smoke exposure	40 (24)	30 (18)
Distance of residence from major road		
<100m	96 (58)	107 (64)
100-500m	51 (31)	40 (44)
>500m	18 (11)	20 (12)
HIV-related factors		
Perinatally-acquired HIV	160 (97)	–
Currently taking ART	157 (100)	–
Percentage of life on ART	58 (24 – 79)	–
WHO HIV class 3/4 at diagnosis	56 (34)	–
Current co-trimoxazole use	159 (96)	–
Recent CD4 count*	576 (359 – 787)	920 (707 – 1118)
Recent CD4 <200 cells/µL	14 (9)	0 (0)
Recent CD8 count*	788 (585 – 1115)	638 (478– 797)
Recent CD4/CD8	0.7 (0.4 – 1.0)	1.5 (1.1 – 1.8)
Nadir CD4 count*	408 (167 – 532)	–
Nadir CD4 <200 cells/µL	43 (30)	–
Nadir CD4/CD8	0.3 (0.1 – 0.5)	–
Clinical factors		
BMI-for-age Z-score	-0.4 (-1.2 – -0.2)	-0.1 (-0.8 – 0.6)
Height-for-age Z-score	-1.2 (-1.8 – -0.5)	-0.5 (-1.2 – 0.1)
Prior pneumonia	52 (32)	40 (24)
Hospitalized for pneumonia	25 (15)	11 (7)
Prior pulmonary TB	21 (13)	1 (1)
History of asthma	10 (6)	10 (6)
Chronic respiratory symptoms		
Any respiratory symptom	101 (61)	83 (50)
Cough	57 (34)	33 (20)
Phlegm	37 (22)	30 (18)
Chest tightness	43 (26)	44 (26)
Breathlessness	15 (9)	20 (12)
Wheezing	39 (24)	28 (17)
Resting respiratory rate	22 (20 – 22)	20 (18 – 22)
Oxygen saturation %, resting	97 (96 – 98)	97 (96 – 98)
Oxygen saturation %, after sub-maximal exertion	94 (92 – 96)	95 (93 – 97)
Oxygen saturation <92% after sub-maximal exertion	33 (20)	28 (18)
Clubbing	3 (2)	0
Abnormal lung exam (crackles, wheeze, rhonchi)	26 (16)	18 (11)

[#]Household income in 1 month. 5000 Ksh ≈ $47 USD
*measured in cells/µL

Missing data: Income: HIV+ 48; HIV- 29. Recently taking ART & Proportion of life on ART = 8. WHO HIV class = 1. Recent CD4: HIV+ 2, HIV- 4. Recent CD8: HIV+ 2, HIV- 5. Nadir CD4: 20. Nadir CD4/CD8: 21. Prior pneumonia: HIV+ 1. Hospitalized for pneumonia HIV+ 2. Exam (RR, SpO2, clubbing, lung auscultation) HIV- = 7.

Table 3. Measures of lung function among HIV-infected and uninfected adolescents.

	HIV-infected N=163	**HIV-uninfected** N=166	**Unadjusted Difference**		**Adjusted Difference***	
	mean z-score (95% CI)		difference (95% CI)	p	difference (95% CI)	p
Pre-bronchodilator						
zFEV1 pre-bronchodilator	-0.33 (-0.51, -0.15)	-0.06 (-0.21, 0.09)	-0.27 (-0.50, -0.04)	0.020	-0.26 (-0.50, -0.01)	0.040
zFVC pre-bronchodilator	-0.28 (-0.45, -0.12)	0.04 (-0.11, 0.20)	-0.33 (-0.55, -0.10)	0.005	-0.31 (-0.54, -0.07)	0.012
zFEV1/FVC pre-bronchodilator	-0.16 (-0.32, -0.01)	-0.18 (-0.33, 0.03)	0.02 (-0.19, 0.24)	0.850	0.01 (-0.21, 0.23)	0.917
Post-bronchodilator						
zFEV1 post-bronchodilator	-0.15 (-0.32, 0.03)	0.16 (0.01, 0.31)	-0.31 (-0.54, -0.07)	0.010	-0.29 (-0.53, -0.05)	0.019
zFVC post-bronchodilator	-0.27 (-0.44, -0.10)	-0.06 (-0.10, 0.22)	-0.33 (-0.57, -0.10)	0.006	-0.31 (-0.55, -0.07)	0.012
zFEV1/FVC post-bronchodilator	0.13 (-0.01, 0.28)	0.17 (0.03, 0.30)	-0.04 (-0.23, 0.16)	0.701	-0.05 (-0.25, 0.15)	0.643
	n (%)	n (%)	OR (95% CI)	p[a]		
Airflow obstruction			1.01 (0.36, 2.79)[b]	1.0		
None	144 (94)	145 (94)				
Mild	4 (2)	7 (4)				
Moderate/Severe	6 (4)	3 (2)				
Fixed airflow obstruction	6 (4)	4 (3)	1.5 (0.35, 7.37)	0.750		
Restrictive pattern	11 (7)	3 (2)	3.90 (1.00, 22.1)	0.031		
Mixed obstructive/restrictive pattern[#]	2 (1)	0	NP	0.248		
Bronchodilator responsiveness	13 (8)	10 (6)	1.34 (0.52, 3.51)	0.525		

*adjusted for age, sex, tobacco smoke exposure, and biofuel exposure

[#]Subset of individuals with airflow obstruction and restrictive pattern

[a] Based on Fisher's exact test.

[b] Comparing airflow obstruction as a binary variable (yes/no)

NP: not possible with zero count cells

Table 4. Factors associated with post-bronchodilator FEV1 Z-score in ALWH

	Unadjusted Difference		**Adjusted Difference***	
	difference (95% CI)	p	difference (95% CI)	p
Sociodemographic factors				
Age	-0.03 (-0.09, 0.03)	0.336	-0.03 (-0.09, 0.03)	0.312
Male	0.29 (-0.07, 0.65)	0.115	0.29 (-0.06, 0.65)	0.108
Income (n=115)				
10,001-15,000 Ksh	-0.08 (-0.76, 0.59)	0.805	-0.07 (-0.70, 0.56)	0.835
>15,000 Ksh	-0.10 (-0.58, 0.38)	0.680	-0.14 (-0.62, 0.34)	0.558
Kerosene exposure[a]	-0.03 (-0.21, 0.15)	0.750	-0.03 (-0.21, 0.15)	0.741
Wood exposure[a]	-0.03 (-0.28, 0.22)	0.796	-0.06 (-0.32, 0.19)	0.629
Charcoal exposure[a]	0.06 (-0.09, 0.21)	0.421	0.09 (-0.07, 0.25)	0.266
Biofuel exposure[a]	-0.003 (-0.13, 0.12)	0.965	-0.004 (-0.12, 0.11)	0.937
Secondhand tobacco smoke exposure	-0.36 (-0.81, 0.10)	0.122	-0.39 (-0.85, 0.07)	0.096
Distance of residence from major road				
100-500m	-0.36 (-0.74, 0.02)	0.064	-0.34 (-0.73, 0.06)	0.098
>500m	0.56 (-0.08, 1.20)	0.086	0.58 (-0.04, 1.21)	0.067
HIV-related factors				
Percentage of life on ART (n= 155)	0.14 (-0.06, 0.35)	0.164	0.16 (-0.05, 0.36)	0.127
WHO HIV stage 3/4	0.00 (-0.39, 0.39)	0.992	0.037 (-0.36, 0.44)	0.853
Recent CD4 <200[b] (n=161)	-0.43 (-1.11, 0.24)	0.208	-0.41 (-1.08, 0.25)	0.222
Recent CD4/CD8 <0.4 (n=161)	-0.11 (-0.52, 0.30)	0.590	-0.12 (-0.54, 0.30)	0.573
Nadir CD4 <200[b] (n=143)	-0.11 (-0.52, 0.30)	0.594	-0.06 (-0.49, 0.37)	0.787
Nadir CD4/CD8 <0.4 (n=142)	0.09 (-0.26, 0.44)	0.604	0.10 (-0.25, 0.45)	0.589
Clinical factors				
BMI-for-age Z-score	0.29 (0.13, 0.46)	<0.001	0.38 (0.20, 0.55)	<0.001
Height-for-age Z-score	-0.08 (-0.27, 0.11)	0.412	-0.05 (-0.24, 0.14)	0.602
History of pneumonia	-0.11 (-0.50, 0.27)	0.562	-0.20 (-0.60, 0.21)	0.337
Hospitalized for pneumonia	0.10 (-0.33, 0.53)	0.650	0.02 (-0.40, 0.44)	0.916
History of pulmonary TB	0.02 (-0.40, 0.45)	0.924	-0.04 (-0.47, 0.39)	0.845
History of asthma	-0.56 (-1.18, 0.07)	0.079	-0.50 (-1.10, 0.10)	0.103
Breathlessness	-0.13 (-0.69, 0.44)	0.663	-0.14 (-0.69, 0.42)	0.625
Cough	-0.01 (-0.42, 0.39)	0.945	-0.001 (-0.42, 0.42)	0.995
Phlegm	-0.23 (-0.70, 0.23)	0.322	-0.20 (-0.68, 0.28)	0.415
Chest tightness	0.27 (-0.14, 0.68)	0.199	0.32 (0.09, 0.73)	0.126
Wheezing	-0.20 (-0.63, 0.22)	0.346	-0.19 (-0.60, 0.23)	0.370
Productive cough	-0.12 (-0.55, 0.30)	0.596	-0.16 (-0.57, 0.25)	0.434
SpO2 after sub-maximal exertion	0.02 (-0.01, 0.05)	0.174	0.02 (-0.01, 0.05)	0.143
Clubbing	-1.26 (-2.48, -0.05)	0.042	-1.42 (-2.61, -0.23)	0.019
Abnormal lung sounds	-0.66 (-1.10, -0.23)	0.003	-0.63 (-1.08, -0.18)	0.006

*Adjusted for Age and Sex

[#]Household income in 1 month. 5000 Ksh ≈ $47 USD

[a] units in 10 hours/week

[b] units in cells/µL

n=163 unless otherwise specified

Figure 1. Participant diagram for inclusion into the study