Lung Function in South African Adolescents Infected Perinatally with HIV and Treated Long-Term with Antiretroviral Therapy

Leah Nyawira Githinji¹, Diane M. Gray¹, Sipho Hlengwa¹, Landon Myer², and Heather J. Zar¹

¹Department of Pediatrics and Child Health, Red Cross Children's Hospital and Medical Research Council Unit, Child and Adolescent Health, and ²Division of Epidemiology and Biostatistics, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

ORCID ID: 0000-0003-0480-0868 (L.N.G.).

Abstract

Rationale: Lung disease is a common cause of mortality and morbidity in HIV-infected adolescents, but there is limited information on the spectrum of lung function impairment in adolescents on antiretroviral therapy.

Objectives: To investigate lung function in HIV-infected adolescents on antiretroviral therapy in the Cape Town Adolescent Antiretroviral Cohort (Cape Town, South Africa).

Methods: A total of 515 South African adolescents, aged 9–14 years, stable on antiretroviral therapy for at least 6 months, underwent baseline lung function testing. Measures included spirometry, nitrogen multiple-breath washout, forced oscillation technique, 6-minute walk test, single-breath carbon monoxide diffusion testing, and bronchodilator response testing. A comparator group of 110 age- and ethnicity-matched HIV-uninfected adolescents was also tested.

Results: For the HIV-infected adolescents (mean [SD] age 12 [1.6] years, 52% male), the median (interquartile range) duration of

antiretroviral therapy was 7.6 (4.6–9.2) years. The median (interquartile range) nadir CD4 was 510.5 (274–903) cells/mm³. HIV-infected adolescents had significantly lower FEV₁, FVC, FEV₁/FVC, diffusing capacity of carbon monoxide, respiratory system compliance, and functional residual capacity than HIV-uninfected adolescents ($P < 0.05$ for all associations). HIV-infected adolescents had higher airway resistance and lung clearance index than HIV-uninfected adolescents ($P < 0.05$ for all associations). Although generally small in magnitude, these differences remained significant after adjusting for age, sex, and height. In addition, age, sex, height, and history of past lower respiratory tract infection or pulmonary tuberculosis were associated with reduced lung function.

Conclusions: Perinatally infected South African HIV-infected adolescents on antiretroviral therapy have lower lung function than uninfected adolescents. Prior lower respiratory tract infection or pulmonary tuberculosis is associated with lower lung function.

Keywords: HIV; adolescent; lung function

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Correspondence and requests for reprints should be addressed to Leah Githinji, M.D., University of Cape Town Department of Paediatrics and Child Health, Rondebosch 7700, Cape Town, South Africa. E-mail: gthlea001@myuct.ac.za

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Respiratory disease is the major cause of morbidity and mortality in HIV-infected children and adolescents. This burden of disease occurs predominantly in Sub-

Saharan Africa (1). South Africa has the world's greatest burden of HIV-infected people, with an estimated 6.1 million persons infected, including 410,000

children under 15 years of age (2). Since 2004, access to pediatric antiretroviral therapy (antiretroviral therapy) has expanded globally, resulting in improved

survival of HIV-infected children (3). In South Africa, the number of children under 15 years of age receiving antiretroviral therapy increased from 4,200 in 2004 to 152,000 in 2011 (4). In response to treatment, the incidence of opportunistic infections (OIs) has declined dramatically (5). Accordingly, HIV is evolving into a chronic illness among adolescents (3).

HIV-associated chronic lung disease is common (5–7), but there is limited information on the determinants, spectrum or progression of chronic lung disease (chronic lung disease) in perinatally infected adolescents. Studies of lung function in HIV-infected children in the preantiretroviral therapy era have reported increased airway resistance (8), whereas a few studies on antiretroviral therapy in children found airway obstruction (6, 9–12) and increased bronchodilator responsiveness (13, 14). Studies of adults on antiretroviral therapy (15–17) have documented irreversible airway obstruction, reduced diffusion capacity, and increased bronchodilator response with the most prominent being diffusion impairment (17, 18). Studies of comprehensive lung function testing in HIV-infected adolescents on antiretroviral therapy are limited, despite a high burden of respiratory disease.

The etiology of HIV-associated chronic lung disease is broad, ranging from chronic infection to noninfective causes (5). Diagnosis of chronic lung disease is made in South Africa by clinical criteria, imaging, and lung function tests. Measurement of lung function offers an objective, reproducible, noninvasive measure of lung disease. Comprehensive lung function measures strengthen the ability to detect and diagnose the spectrum of lung function impairment.

The aim of this study was to investigate the spectrum and determinants of lung function in HIV-infected adolescents on antiretroviral therapy in Cape Town, South Africa. Some of the results of these studies have been previously reported in the form of an abstract (19).

Methods

Study Subjects

Patients at the Research Centre for Adolescent and Children Health at Red Cross Children's Hospital, South Africa

Study subjects were recruited between August 2013 and April 2015 into a prospective study: the Cape Town Adolescent Antiretroviral Cohort, a longitudinal cohort study of HIV-infected adolescents on antiretroviral therapy. Eligibility was limited to adolescents, aged 9–14 years, with vertically transmitted HIV, who had been on antiretroviral therapy for at least 6 months, knew their HIV status, and where informed parental consent and participant assent was obtained. After enrollment, patients followed up monthly.

Lung Function Measures

Lung function measurements were generally performed on eligible subjects at the time of enrollment in Cape Town Adolescent Antiretroviral Cohort. Lung function testing was deferred if the participant had an acute respiratory illness; testing, therefore, represented baseline lung function measured at a time when the adolescent was considered to be well.

Age-, sex-, and ethnicity-matched HIV-uninfected adolescents without known pre-existing lung disease were enrolled from the Masiphumelele Youth Centre, a community-based vocational center in Cape Town, to serve as controls. Perinatal HIV exposure of the HIV-uninfected participants was not known.

Lung function testing included: spirometry (FEV₁, FVC, and FEV₁/FVC ratio); single-breath test for diffusing capacity of carbon monoxide (DL_{CO}); multiple-breath nitrogen washout (multiple-breath washout) measuring functional residual capacity (FRC) and ventilation homogeneity with the lung clearance index; the forced oscillation technique (forced oscillation technique testing) measuring respiratory system resistance and compliance; and the 6-minute walk test. Spirometry was repeated 15 minutes after administering 400 µg salbutamol via a metered-dose inhaler equipped with a spacer.

Lung function testing was performed using the NDD Easyone Pro LAB (NDD, Zurich, Switzerland) for spirometry, single-breath CO diffusion test, and multiple-breath washout. Forced oscillation technique testing was completed using custom-made equipment (University of Szeged, Szeged, Hungary) (20). All testing adhered to the American Thoracic Society/European Respiratory Society guidelines (21–27).

The highest FVC and FEV₁ from any of the acceptable maneuvers was reported. Z standardization for spirometry outcome variables was performed with Global Lung Initiative (GLI) software using African American reference population (28). Bronchodilator response was considered positive if there was an increase in FEV₁ of 12% or greater after bronchodilator administration (22). The lower limit of normal (LLN) was calculated using the African American reference cohort in GLI software, 1.64 SD below the mean (28).

Forced oscillation technique testing was performed first with the participant seated, nose clip on, cheeks firmly supported, and breathing quietly through a mouth piece and filter, as per consensus guidelines for testing (25). Three 20-second epochs were collected. Tests were considered acceptable if breathing was regular and free from leak or glottic closure. We collected a minimum of three repeatable tests, defined as visually overlapping spectral recordings within 10% of each other. The analysis model used was frequency range 10–20 Hz for respiratory system resistance and 4–26 Hz for respiratory system compliance. In the absence of appropriate reference ranges, we used our HIV-uninfected adolescents as the reference population.

We followed American Thoracic Society/European Respiratory Society recommendations for acceptability of single-breath CO testing (24). We performed a minimum of two trials that met quality control standards, and were within 3 ml/min/mm Hg or 10%. Up to four attempts could be done per session. Transfer factor for CO (DL_{CO}) was adjusted for patient's hemoglobin done on the day of lung function testing. The average of the two best maneuvers was taken for analysis. LLN was estimated using the equations of Kim and colleagues (29).

Multiple-breath washout testing adhered to international recommendations (23, 27). Tests were considered acceptable if there was a regular breathing pattern, especially for five tidal breaths before washout and the first four breaths of washout, devoid of sighs, apneas, or leaks, and complete washout. We ensured adequate time between tests (at least 4 min) for gas concentration to equilibrate. Multiple-breath washout repeatability was defined by three technically acceptable tests with FRC within 10% of the highest

value and only excluded a test if FRC differed by more than 25% of the median. For lung clearance index repeatability, we excluded a test if lung clearance index differed by more than 1 FRC turnover from median. Where there were two technically acceptable tests, we confirmed FRC repeatability if FRC was within 10% of the highest value, and lung clearance index was within one turnover. In the absence of appropriate reference ranges for African adolescents for multiple-breath washout, we used the HIV-uninfected adolescents as the reference population.

For the 6-minute walk test, participants were instructed to walk to and fro for 6 minutes. This was done in the research center where two marked cones had been placed 30 m apart, as per standardized recommendations (26). Heart rate, respiratory rate, blood pressure, Borg scale for dyspnea, and oxygen saturation were recorded before and at the end of testing. Distance covered in meters was recorded at the end of the test, with published reference data used as normative values (30).

Demographic Data

Demographic and exposure data were measured at enrollment. Smoking history

was collected by self-reported questionnaire completed by the adolescent and by the parent or guardian. Passive smoke exposure was regarded if either reported a smoker in the household; active smoking was attributed if the study participant self-reported smoking. Antiretroviral therapy adherence data were collected via questionnaires to both participant and caregiver and graded according to respondent's subjective rating of adherence as either good or poor. Other covariates were extracted from medical records or measured at study visit. Participants were screened for respiratory symptoms using a validated respiratory questionnaire derived from the International Study of Asthma and Allergies in Childhood study (31).

Statistical Analysis

Data were analyzed using STATA 12.0 (StataCorp, College Station, TX). Lung function measures were summarized with mean (SD) or median (interquartile ranges [IQR]). As no reference data for normative values exists for African adolescent population for lung clearance index and forced oscillation technique, we used our

HIV-uninfected adolescents as our reference population. Z scores for height and weight were calculated using λ - μ - σ growth charts (32).

Comparison of lung function between HIV-infected and -uninfected subjects was computed using independent two-sample *t* test with equal variances, where data were normally distributed and Wilcoxon sum rank test for data that were not normally distributed. Z test was used to compute differences between two proportions. All statistical tests were two sided at an α of 0.05. Univariable and multivariable linear regression was done to explore associations of lung function outcomes using the following covariates: HIV status; age; sex; height Z score; smoking status; nadir CD4 count and viral load before antiretroviral therapy was started; antiretroviral therapy adherence; antiretroviral therapy duration; past lower respiratory tract infections; pulmonary tuberculosis (TB); and self-reported respiratory symptoms.

Ethical approval was obtained from Faculty of Health Sciences, University of Cape Town Human Research and Ethics Committee. Informed consent and assent

Figure 1. Cohort description.

was obtained from study participants and a parent or guardian.

Results

A total of 516 HIV-infected adolescents and 114 demographically matched HIV-uninfected control subjects were enrolled from August 2013 to April 2015. A total of 56 (9.9%) participants did not perform lung function testing and were excluded from this analysis, providing 515 HIV-infected adolescents and 110 HIV-uninfected adolescents with lung function results (Figure 1).

The success rate for different pulmonary function tests varied from more than 85% for spirometry and single-breath test for CO to 38% for multiple-breath washout (Figure 1).

The mean (SD) age of participants was 12 (1.7) years; 52% were male (Table 1). Median (IQR) duration of antiretroviral therapy was 7.6 (4.6–9.2) years. Median (IQR) nadir CD4 count was 510 (274–903) cells/mm³.

Past pulmonary TB was reported in 37% of HIV-infected adolescents compared with none of the HIV-uninfected adolescents (Table 1). Prior *Pneumocystis jirovecii* pneumonia (PCP) was only reported in 1.4% of cases. Prior pneumonia was more commonly reported in HIV-infected than in uninfected adolescents. Passive smoke exposure occurred in 25% of HIV-infected children, with a similar prevalence in the HIV-uninfected group (Table 1). A total of 77 (15%) HIV-infected adolescents had a history of self-reported cough as compared with 7.3% HIV-uninfected adolescents ($P = 0.033$). HIV-infected adolescents had more reported wheeze than HIV-uninfected adolescents, although the difference was not statistically significant (10.9 vs. 5.5%; $P = 0.084$; Table 1). A total of 18 (3.5%) HIV-infected participants had digital clubbing compared with only one uninfected adolescent. There was no difference between respiratory rate or oxygen saturation between the two groups.

About one-quarter of HIV-infected adolescents had an FEV₁ less than LLN, significantly more than the HIV-uninfected subjects (27 vs. 12%, $P = 0.001$; Table 2). Overall, 75 (15%) HIV-infected and 9 (8%) HIV-uninfected adolescents had a positive bronchodilator response ($P = 0.058$). Only four HIV-infected adolescents had DL_{CO} below LLN (Table 2). There was no difference in the distance walked or oxygen saturation after 6-minute walk test between the two groups (Table 3).

After adjusting for age, sex, and height, HIV-infection was associated with a lower DL_{CO} (95% confidence interval [CI] = -1.20 to -0.01 ; $P = 0.0048$), lower FEV₁ (95% CI = -0.20 to -0.05 ; $P = 0.001$), lower FRC (95% CI = -0.20 to -0.04 ; $P = 0.004$) and a lower compliance (95% CI = -0.011 to -0.005 ; $P < 0.001$); and a higher resistance at 8 Hz (95% CI 0.15 – 0.68 ; $P = 0.002$) and higher lung clearance index (95% CI = 0.06 – 0.87 ; $P = 0.024$) (Table 4). FEV₁ had a negative correlation with resistance and lung clearance index (see Figures E1 and E2 in the online supplement).

The associations of lung function outcomes in HIV-infected adolescents are shown in Tables E1–E7. Somatic growth, age, and sex were predictors of lung function. In addition, history of previous lower respiratory tract infection or of previous pulmonary TB was associated with decreased FEV₁ (-0.11 , 95% CI = -0.18 to 0.04 , $P = 0.001$; and -0.07 , 95% CI = -0.13 to -0.004 ; $P = 0.037$, respectively; Table E1). Past lower respiratory tract infection was associated with higher lung clearance index and lower DL_{CO} (Tables E2 and E4). Smoke exposure was not associated with lung function (Tables E1–E7).

On average, those who had digital clubbing had lower FEV₁ compared with those who had no clubbing, whereas controlling for sex, age, height, pneumonia and pulmonary TB history, and smoking status (mean FEV₁ = 1.86 vs. 1.20 L; $P < 0.001$; 95% CI = -0.44 to -0.13 ; Table 5). History of self-reported wheeze and asthma was significantly associated with lower FEV₁ (Table 5).

Discussion

This study provides comprehensive lung function data on a large cohort of unselected perinatally HIV-infected adolescents

Table 1. Characteristics of study population

	HIV Infected (n = 515)	HIV Uninfected (n = 110)	P Value
Age, yr	12.0 (1.6)	11.8 (1.8)	0.355
Height for age Z score	−1.3 (1.0)	−0.5 (1.1)	<0.001
Weight for age Z score	−0.8 (1.1)	0.1 (1.2)	<0.001
Male, n (%)	266 (52.1)	48 (45.3)	0.127
Smoke exposure			
None, n (%)	379 (74.3)	83 (78.3)	0.388
Passive, n (%)	127 (24.9)	20 (18.9)	0.185
Active, n (%)	2 (0.4)	1 (0.9)	0.458
Past lower respiratory tract infection, n (%)	147 (28.8)	1 (0.9)	<0.001
Past pulmonary TB, n (%)	301 (37.1)	0 (0)	<0.001
PCP, n (%)	7 (1.4%)	0 (0)	0.220
History of cough, n (%)	77 (15.0)	8 (7.3)	0.033
History of wheeze, n (%)	56 (10.9)	6 (5.5)	0.084
History of asthma, n (%)	51 (9.9)	7 (6.4)	0.246
Shortness of breath, n (%)	17 (3.3)	2 (1.8)	0.411
Clubbing, n (%)	18 (3.5)	1 (0.9)	0.152
Respiratory rate, breaths/min	21.5 (3.4)	20.8 (5.1)	0.189
Oxygen saturation (%)	98.6 (0.9)	98.8 (0.5)	0.063
CD4 nadir count, (cells/mm ³), n = 442	510.5 (274–903)		
CD4 current, (cells/mm ³), n = 510	713 (561–957.5)		
Viral load zenith, (copies/mL), n = 195	226 (40–3927)		
antiretroviral therapy duration, (years), n = 497	7.6 (4.6–9.2)		
Age at antiretroviral therapy initiation, (years)	5.0 (3.5)		
Poor antiretroviral therapy adherence, n (%)	51 (10.8)		

Definition of abbreviations: PCP = *Pneumocystis jirovecii* pneumonia; TB = tuberculosis. Values are mean (SD) or median (interquartile range); P value computed by two sample test for proportions or independent two sample t test.

Table 2. Baseline lung function tests

	HIV Infected (n = 499)	HIV Uninfected (n = 106)	P Value
Spirometry			
FEV ₁ , L	1.6 (0.5)	1.9 (0.5)	<0.0001
% predicted FEV ₁	87 (17)	94 (13)	<0.001
FEV ₁ Z score	−1.0 (1.3)	−0.5 (1.0)	<0.001
Children with FEV ₁ below LLN, n (%)	134 (27)	13 (12)	0.001
FVC, L	1.8 (0.48)	2.0 (0.6)	<0.001
% predicted FVC	87 (16.0)	90 (13.0)	0.071
FVC Z score	−1.1 (1.3)	−0.8 (1.04)	0.064
FVC below LLN, n (%)	140 (28.0)	23 (22.0)	0.180
FEV ₁ /FVC	89 (8.7)	93 (6.3)	<0.001
FEV ₁ /FVC Z score	0.2 (1.4)	0.9 (1.2)	<0.001
FEV ₁ /FVC < LLN, n (%)	50 (9.8)	4 (3.8)	0.041
Single-breath CO diffusion test	n = 454	n = 98	
D _{LCO} , ml CO/min/mm Hg	16.6 (3.4)	18.1 (4.2)	0.002
D _{LCO} Z score	−0.6 (0.5)	−0.3 (0.7)	0.002
D _{LCO} /VA, (ml CO/min/mm Hg)/L	5.9 (0.8)	5.8 (0.9)	0.078
D _{LCO} /VA Z score	0.7 (1.1)	0.5 (1.2)	0.078
Multiple-breath washout, median (IQR)	n = 193	n = 41	
FRC, L	1.0 (0.8 to 1.2)	1.2 (0.9 to 1.5)	0.007
FRC Z score	−0.6 (−1.1 to −0.2)	−0.2 (−0.8 to −0.7)	0.001
Lung clearance index turnovers	7.4 (6.8 to 8.1)	6.9 (6.3 to 7.6)	0.002
Lung clearance index Z score	0.6 (−0.2 to −1.6)	−0.2 (−0.8 to −0.9)	0.002
Forced oscillation technique, median (IQR)	n = 397	n = 104	
Resistance at 8 Hz, cmH ₂ O/L/s	5.0 (4.2 to 5.7)	4.4 (3.5 to 5.4)	0.0001
Reactance at 8 Hz, cmH ₂ O/L/s	−2.0 (−2.7 to −1.5)	−1.7 (−2.2 to −1.2)	0.0001
Mean respiratory system resistance, cmH ₂ O/L/s	4.3 (3.7 to 5.0)	3.8 (3.1 to 4.9)	0.0005
Compliance, ml/cmH ₂ O	11.1 (8.7 to 14.0)	13.5 (10.0 to 21.0)	<0.0001

Definition of abbreviations: D_{LCO} = diffusing capacity of carbon monoxide; FRC = functional residual capacity; IQR = interquartile range; LLN = lower limit of normal; VA = alveolar volume. Values are mean (SD) unless otherwise indicated. P values computed by t test or Wilcoxon sum rank test, depending on data normality. Forced oscillation technique testing and multiple-breath washout compared to control data. Spirometry reference equation: Quanjer and colleagues, 2012 (28). D_{LCO} referenced to Kim and colleagues, 2012 (29).

established on antiretroviral therapy, showing that lung function outcomes are impaired compared with HIV-uninfected adolescents, including expiratory flow volumes, ventilation homogeneity,

resistance, and compliance. Although the mean percent predicted FEV₁ in the HIV-infected adolescents were within normal limits, approximately 25% had reduced lung function. Furthermore, the lung

clearance index was increased in HIV-infected children reflecting ventilation impairment. The higher resistance and lower compliance found in HIV-infected adolescents suggests smaller airways or chronic inflammation.

Overall, lung function impairment was mild in the HIV-infected cohort compared with the uninfected patient cohort. The HIV-infected cohort represented a relatively healthy group of perinatally infected adolescents with minimal symptoms, which may partly explain the relatively mild lung function impairment.

Other African studies in Malawian and Zimbabwean HIV-infected adolescents (6, 11, 33) have reported more severe symptoms and lung function impairment. In a study (6) of 116 Zimbabwean HIV-infected adolescents (69% on antiretroviral therapy), 52 (45%) were reported to have an FEV₁ less than 80%. A cross-sectional study of 145 Malawian HIV-infected adolescents, of which 72% were on antiretroviral therapy, reported 18% to have obstructive disease (11). Patient selection, with more severely symptomatic children being selected for lung function, may have influenced measurements in these studies.

The relatively preserved lung function in our cohort may also be a result of long-term antiretroviral therapy use, good adherence to antiretroviral treatment, and access to health care, enabling timely diagnosis and treatment of intercurrent infections. Although our HIV-infected adolescents had been on antiretroviral therapy for approximately 8 years, the median age of initiation of antiretroviral therapy occurred only at around 5 years of age, suggesting that use of antiretroviral therapy, even when initiated late in childhood, is an important strategy to preserve lung health. The reasons for documented low lung function in HIV-infected children may be related to prior illness, or HIV infection specifically. OIs have been reported to increase cytokines in serum and sputum, so promoting HIV mediated chronic airway inflammation (15).

Only a minority of adolescents had bronchodilator responsiveness, similar to that reported in a Malawian study (11). A number of mechanisms may predispose to irreversible airway damage in this group, including recurrent infection, fibrosis, and increased oxidative stress mediated by down-regulation of glutathione pathways by HIV (34). Irreversible airway damage

Table 3. The 6-minute walk test

The 6-Min Walk Test	HIV Infected (n = 339)	HIV Uninfected (n = 99)	P Value
Distance walked, m	433.7 (57.0)	443.5 (60.5)	0.138
Pulse before test, beats per min	78.1 (12.2)	83.0 (13.5)	<0.001
Pulse after test, beats per min	82.3 (13.9)	87.2 (14.4)	0.002
Oxygen saturation after test (%)	98.7 (0.8)	98.8 (0.6)	0.473
MAP before test, mm Hg	77.6 (7.9)	81.4 (7.9)	<0.001

Definition of abbreviation: 6-Min = 6-minute; MAP = mean arterial pressure. P values computed using independent two-sample t test.

Table 4. Effect of HIV infection on lung function

	HIV Infected	HIV Uninfected	Coefficient	95% CI	P Value
FEV ₁ , L	1.6 (0.5)	1.9 (0.5)	−0.13	−0.20 to −0.05	0.001
DL _{CO} , ml CO/min/mm Hg	16.6 (3.4)	18.1 (4.2)	−0.60	−1.20 to −0.01	0.048
FRC, L	1.01 (0.8 to 1.2)	1.2 (0.9 to 1.5)	−0.12	−0.20 to −0.04	0.004
lung clearance index, turnovers	7.4 (6.8 to 8.1)	6.9 (6.3 to 7.6)	0.47	0.06 to 0.87	0.024
Resistance at 8 Hz, cmH ₂ O/L/s	5.0 (4.2 to 5.7)	4.4 (3.5 to 5.4)	0.41	0.15 to 0.68	0.002
Reactance at 8 Hz, cmH ₂ O/L/s	−2.0 (−2.7 to −1.5)	−1.7 (−2.2 to −1.2)	−0.31	−0.53 to −0.08	0.008
Compliance ml/cmH ₂ O	11.1 (8.7 to 14.0)	13.5 (10.0 to 21.0)	−7.63	−10.48 to −0.79	<0.001

Definition of abbreviations: CI = confidence interval; DL_{CO} = diffusing capacity of carbon monoxide; FRC = functional residual capacity. P values after statistical adjustment for age, sex, and height (multivariate linear regression).

may also reflect bronchiolitis obliterans, which has been commonly reported in a Zimbabwean cohort (6).

In our cohort, previous respiratory tract infection was common and associated with lower lung function. Prior lower respiratory tract infection or pulmonary TB was strongly associated with reduced lung function, both of which were more common in HIV-infected participants. This is consistent with data from HIV-uninfected children showing lower respiratory tract infection in childhood to be associated with lower lung function in later life (35, 36).

Bacterial pneumonia in HIV-infected adults has been associated with permanent declines in FEV₁, FVC, FEV₁/FVC, and DL_{CO} (37). OIs, such as PCP, have also been associated with increased metalloproteinases and chronic airflow obstruction in HIV-infected adults (38). Very few HIV-infected adolescents reported prior PCP in this cohort. Furthermore, HIV-infected adolescents had higher airway resistance, possibly due to smaller airways from impaired growth, repeated lower respiratory tract infections, OIs, or increased airway inflammation. Higher airway resistance has been demonstrated in HIV-infected children before widespread use of antiretroviral therapy (8).

Although low lung function on spirometry was common in HIV-infected adolescents, diffusion abnormalities were uncommon. Very few children were active smokers, and only approximately one-quarter reported passive smoke exposure; in contrast, HIV-infected adult studies have reported diffusion impairment in the context of high smoke exposure (17). The absence of an association between passive smoking and lung function outcomes may possibly reflect underreporting of smoke exposure, which was self-reported. The lack of association could also reflect a shorter-term, lower-dose exposure among adolescents compared with that reported in the adult emphysema literature. Diffusion abnormalities reported in both smoking and nonsmoking HIV-infected adults have been explained by the presence of radiological emphysema due to loss of capillary blood volume (39).

Emphysema may not be important in the etiology of chronic lung disease in HIV-infected adolescents, given the imaging findings that have been previously published that show predominantly bronchiolitis obliterans (6). Other mechanisms postulated include alveolar–capillary membrane inflammation due to OIs, such as PCP or pulmonary TB (18, 39). The lower DL_{CO} in HIV-infected adolescents in

our study cohort may represent loss of alveolar volume, as a consequence of previous respiratory infection or ongoing inflammation.

The 6-minute walk test is an insensitive measure of cardiopulmonary compromise, which only becomes impaired in moderate to severe disease. Therefore, the finding that the distance walked and arterial oxygen saturation on the 6-minute walk test were similar in HIV-infected children and control subjects probably reflects the lack of severe cardiorespiratory compromise and relatively mild lung disease.

Limitations

One limitation of the study is that childhood history of prior lower respiratory infection or pulmonary TB was based on recall. Despite this, there was a strong association between prior lower respiratory tract infection or pulmonary TB and impaired lung function.

A second limitation is the lack of appropriate normative reference values in African population for lung function, but the study is strengthened by the inclusion of an age-matched control group. Furthermore, the use of the GLI African American data for spirometry normal values provided an appropriate reference standard.

Table 5. Effect of self-reported respiratory symptoms on lung function in HIV-infected adolescents

Symptoms	FEV ₁ Coeff*	95% CI	DL _{CO} Coeff*	95% CI	Lung Clearance Index Coeff*	95% CI
History of asthma	−0.19	−0.30 to −0.09	−0.17	−1.03 to 0.68	0.52	−0.06 to 1.10
History of wheeze	−0.21	−0.31 to −0.12	−1.02	−1.79 to −0.26	−0.12	−0.66 to 0.42
History of cough	−0.05	−0.13 to 0.04	0.05	−0.66 to 0.76	0.45	−0.02 to 0.92
Digital clubbing	−0.29	−0.44 to −0.13	−1.82	−3.12 to −0.52	0.15	−0.86 to 1.17

Definition of abbreviations: CI = confidence interval; Coeff = coefficient; DL_{CO} = diffusing capacity of carbon monoxide.

*Adjusted for sex, age, height, history of lower respiratory tract infections, and pulmonary tuberculosis and antiretroviral therapy duration.

We did not obtain official birth records on the HIV-uninfected participants to establish HIV exposure perinatally; however, given the very long time from exposure to enrollment in this cohort, any possible residual effect of HIV exposure on lung health is unclear, and likely to be minimal. A further limitation is that few children met the strict criteria for multiple-breath washout quality analysis, as any who had sighs, glottis closure, or hyperventilation during testing were excluded. This occurred in both HIV-infected adolescents and control subjects. However, success rates in performing spirometry were more than 95%, and there were also high rates of success for DL_{CO} , forced oscillation technique testing, and 6-minute walk test.

Another limitation is the inability to correlate lung function with precise

radiological abnormalities, as we did not obtain radiological imaging due to concerns about exposure to radiation and cost. These findings may not be generalizable to other settings in Sub-Saharan Africa, where adolescents may be more severely symptomatic and have more delayed access to antiretroviral therapy and to health care. Nevertheless, the results suggest that antiretroviral therapy may be effective for preserving lung health even when started late in childhood.

Conclusions

South African HIV-infected adolescents on antiretroviral therapy have significantly lower lung function than HIV-uninfected adolescents. Despite being well controlled on antiretroviral therapy, lung function impairment is common in HIV-infected adolescents on antiretroviral therapy, with

almost 25% having relatively mild impairment in lung function compared with age- and ethnicity-matched control subjects. Previous lower respiratory infection and pulmonary TB were associated with lower lung function. With the growing number of perinatally HIV-infected adolescents in Africa facing improved survival and well-being on antiretroviral therapy, investigating the implications of these findings on long-term respiratory health in this population is a priority that we are currently undertaking. ■

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