Longitudinal Changes in Spirometry in South African Adolescents Perinatally Infected With Human Immunodeficiency Virus Who Are Receiving Antiretroviral Therapy

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(See the Editorial Commentary by McCollum on pages 491–92.)

Background. Despite increased access to highly active antiretroviral therapy (HAART), lung disease remains common in human immunodeficiency virus (HIV)–infected (HIV⁺) adolescents. There is limited information on changes in lung function over time in perinatally HIV⁺ adolescents on HAART. The objective was to investigate the progression of spirometry findings over 2 years in HIV⁺ adolescents on HAART in a prospective cohort, the Cape Town Adolescent Antiretroviral Cohort (CTAAC).

Methods. HIV⁺ adolescents aged 9–14 years, with at least 6 months of HAART, and a comparator group of healthy HIV-uninfected (HIV[−]), age-matched controls were enrolled in CTAAC. Spirometry and bronchodilator testing were done at baseline, 12 months, and 24 months. Mixed-effect models were used to compute longitudinal changes in lung function.

Results. Five hundred fifteen HIV⁺ adolescents, mean age 12 (standard deviation [SD], 1.6) years, 50.4% male, and 110 HIV[−] adolescents, mean age 11.8 (SD, 1.8) years, 45.6% male, were tested at baseline; 477 (93%) HIV⁺ and 102 (93%) HIV[−] adolescents at 12 months; and 473 (92%) HIV⁺ and 97 (88%) HIV[−] adolescents at 24 months. Only 5.4% of the HIV⁺ adolescents had HIV viral load >10 000 copies/mL at baseline. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were lower in the HIV⁺ compared to the HIV[−] adolescents and tracked with no deterioration or catch-up over 2 years. Previous pulmonary tuberculosis (PTB) or lower respiratory tract infection (LRTI) was significantly associated with reduced FEV1 and FVC ($P < .05$ for both).

Conclusions. HIV⁺ adolescents had lower lung function over 2 years than HIV[−] adolescents. This study highlights the need for lung function surveillance and prevention of LRTIs and PTB in HIV⁺ adolescents.

Keywords. HIV; adolescents; chronic lung disease; lung function.

Perinatally acquired human immunodeficiency virus (HIV) has evolved into a chronic disease due to early diagnosis and improved access to effective antiretroviral therapy (ART) [1, 2]. However, of the 2.1 million children <15 years of age living with HIV, only about 43% were on effective ART in 2017 [3]. More than 90% of adolescents with HIV infection (AWH) live in sub-Saharan Africa, with only about 49% accessing effective ART. Chronic lung disease remains one of the most common concerns in AWH in the effective ART era in sub-Saharan Africa [4].

Normal lung growth begins in utero and continues throughout childhood and adolescence till it reaches a plateau in the early 20s and begins to decline [5, 6]. Lung function tracks through life, with those starting at low lung function continuing along

the lower centile into adulthood and also being associated with increased respiratory symptoms and illness [7]. However, most of the evidence on lung function in AWH is from cross-sectional studies, with limited information on longitudinal lung function changes, especially in the context of effective ART. Prior studies have shown that AWH on effective ART have lower lung function compared to HIV-uninfected adolescents [8, 9]. Longitudinal studies are needed to understand the lung function trajectory in AWH and the impact of low lung function and the risk of later respiratory disease. The aim of this study was to investigate the progression and determinants of lung function over 2 years in AWH on effective ART in a South African cohort of perinatally infected adolescents.

METHODS

Children were enrolled from October 2013 to March 2015 in a prospective cohort, the Cape Town Adolescent Antiretroviral Cohort (CTAAC), as previously described [8]. AWH, aged 9–14 years on effective ART for >6 months, in whom informed parental consent was obtained and assent provided, were

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enrolled and followed up every 6 months. Informed consent and assent were renewed annually.

Children were recruited from primary care clinics and hospital-based effective ART clinics in Cape Town, South Africa. An HIV-uninfected age-, sex-, and ethnicity-matched comparator group, with no known preexisting lung disease, was also enrolled. The study was approved by the Faculty of Health Sciences, University of Cape Town Human Research Ethics Committee.

Spirometry and bronchodilator testing were done at baseline, 12 months, and 24 months. Testing was done using NDD EasyOne Pro LAB (Switzerland). Testing adhered to European Respiratory Society/American Thoracic Society guidelines [10, 11]. A minimum of 3 trials to a maximum of 8 attempts were done per patient and at least 3 acceptable, reproducible best quality curves were selected by the respiratory technologist. The highest forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) from any of the acceptable maneuvers was reported. Four hundred micrograms of salbutamol was given via spacer and testing was repeated after 15 minutes.

The Global Lung Initiative [6] African American reference population was used to calculate the lower limit of normal for the spirometry outcome measures. Obstructive spirometry pattern was defined as an FEV_1 over FVC ratio less than the lower limit of normal ($FEV_1/FVC < LLN$); a restrictive spirometry pattern was defined as $FVC < LLN$ and normal FEV_1/FVC ratio; and a mixed pattern was defined as $FEV_1/FVC < LLN$, $FVC < LLN$, and $FEV_1 < LLN$. Bronchodilator response was defined as a change in $FEV_1 \geq 12\%$ after 400 μ g salbutamol administered via metered dose inhaler spacer.

Clinical data including age, sex, height, weight, CD4 cell count, and viral load were collected annually. Questionnaires were administered semiannually to study participants to collect data on effective ART adherence, smoking, isoniazid prophylaxis, respiratory symptoms, and other intercurrent events. Effective ART adherence was calculated by assessing 30-day recall of any missed doses. Data on previous pulmonary tuberculosis (PTB) and past lower respiratory tract infection (LRTI), date of effective ART initiation, and doctor-diagnosed asthma were extracted from hospital records and validated study questionnaires. Data on medication use were extracted from health records.

Data Analysis

The two-sample *t* test was used to compute the comparison of lung function outcome between AWH and HIV-uninfected adolescents at baseline and 24 months. Demographic and clinical factors were included to determine associations of lung function. The minimum covariates (age, height, sex, HIV, time, smoke exposure, previous PTB, and previous LRTIs; Supplementary Figure 1) were determined using a directed

acyclic graph [12]. Mixed-effects modeling was used to compute longitudinal changes over 2 years and determinants of lung function outcomes.

RESULTS

Five hundred fifteen AWH, with a mean age of 12 (standard deviation [SD], 1.6) years, and 110 HIV-uninfected adolescents, with a mean age of 11.8 (SD, 1.8) years, were tested at baseline; 477 (93%) AWH and 102 (93%) HIV-uninfected adolescents were tested at 12 months; and 473 (92%) AWH and 97 (88%) HIV-uninfected adolescents were tested at 24 months, with >90% successfully tested (Figure 1). Four hundred eighty-three (96%) AWH and 88 (83%) HIV-uninfected adolescents had successful bronchodilator testing at baseline; 437 (92.6%) AWH and 91 (94.8%) HIV-uninfected adolescents had bronchodilator testing at 12 months; and 402 (92.4%) AWH and 88 (93.6%) HIV-uninfected adolescents had a successful bronchodilator test at 24 months (Table 1).

At 2 years of study, the median duration of effective ART was 9.8 (interquartile range [IQR], 6.8–11.3) years (Table 2). The median age at effective ART initiation was 4.3 (IQR, 1.9–7.6) years. AWH were shorter and had lower body mass index than HIV-uninfected controls at enrollment and at 2 years ($P < .001$; Table 3). Only 5%–6% of adolescents had HIV viral load >10 000 copies/mL at both baseline and 24 months (Table 2). History of hospitalization for LRTI or past PTB prior to enrollment visit was more common in AWH compared with uninfected adolescents ($P < .001$; Table 2). However, intercurrent hospitalization for nontuberculosis LRTI and ambulatory LRTI not requiring hospitalization during the 24-month follow-up period was uncommon in both groups (Table 2). However, AWH had a high incidence rate of intercurrent culture-positive PTB of 3.2% compared to none of the HIV-uninfected adolescents in the 2-year study period. Those with culture-positive *Mycobacterium tuberculosis* over the 2 years had on average a 0.23 lower FEV_1 *z* score (95% confidence interval [CI], $-.57$ to $.10$; $P = .174$, adjusted for time and HIV status, data not shown) compared to those without intercurrent tuberculosis disease.

More adolescents reported symptoms of cough or wheeze at enrollment than at the 2-year follow-up period (Table 3). Less than 7% of AWH used asthma medications at baseline and over 2 years (Table 2). There was higher use of isoniazid prophylaxis in the AWH at baseline than at 2 years (115 [22.9%] and 33 [7.6%], respectively; Table 2). Cotrimoxazole prophylaxis use was 10% at baseline and 7.6% at 2 years in the HIV-infected group (Table 2). Less than 20% of AWH reported chronic or recurrent respiratory symptoms at baseline and at 2 years (Table 3).

AWH had lower FEV_1 , FVC, forced expiratory flow at 25% and 75% of FVC, and FEV_1/FVC *z* scores compared with the uninfected adolescents at all time points (Table 1), with

Figure 1. Description of the study cohort. Abbreviation: HIV, human immunodeficiency virus.

AWH having on average a 0.52 FEV_1 z score lower than the HIV-uninfected adolescents over 2 years (95% CI, $-.76$ to $-.27$; $P < .001$; Table 4). Although HIV infection was associated with lower FEV_1 or FVC, the change in either FEV_1 or FVC at 2 years was similar between AWH and uninfected adolescents as depicted by a near parallel slope (Figure 2) and a nonsignificant interaction between HIV and time at 2 years for both (coefficient, -0.03 [95% CI, $-.17$ to $.23$], $P = .764$ for FEV_1 and -0.14 [95% CI, $-.34$ to $.05$], $P = .154$ for FVC) (Supplementary Table 1).

A history of PTB or severe LRTI prior to enrollment was significantly associated with impaired FEV_1 z score at 2 years (coefficient, -0.27 [95% CI, $-.50$ to $-.03$], $P = .024$ for PTB and -0.37 [95% CI, $-.62$ to $-.13$], $P = .003$ for LRTI) and FVC z

score (coefficient, -0.27 [95% CI, $-.49$ to $-.05$], $P = .015$ for PTB and -0.30 [95% CI, $-.53$ to $-.06$], $P = .013$ for LRTI), adjusting for smoke exposure, time, and HIV infection (Table 5 and Supplementary Table 4A and 4B). AWH with past LRTI requiring hospitalization had lower lung function compared to those with no prior severe LRTI (Figure 3).

More than 65% of AWH had a normal spirometry pattern at baseline, 12 months, and 24 months (Supplementary Table 2). A mixed spirometry pattern was more common in AWH compared with HIV-uninfected adolescents at each time point (Supplementary Table 2 and Figure 4). Obstructive spirometry pattern increased from a prevalence of 4.8% at baseline to 8.1% at 24 months (Supplementary Table 2). Bronchodilator responsiveness at baseline was 16.1% and 11.4% in AWH and

Table 1. Summary of Lung Function at Baseline, 12 Months, and 24 Months

Variable	Baseline			12 mo			24 mo		
	HIV ⁺ (n = 503)	HIV ⁻ (n = 106)	PValue	HIV ⁺ (n = 472)	HIV ⁻ (n = 96)	PValue	HIV ⁺ (n = 435)	HIV ⁻ (n = 94)	PValue
FEV_1 z score	-1.0 (1.3)	-0.5 (1.0)	$<.001$	-0.9 (1.3)	-0.3 (1.0)	$<.001$	-0.8 (1.3)	-0.3 (1.0)	$<.001$
FVC z score	-1.1 (1.3)	-0.8 (1.0)	.060	-0.9 (1.2)	-0.3 (1.0)	$<.001$	-0.7 (1.2)	-0.3 (0.9)	.003
FEF_{25-75} z score	-0.4 (1.4)	0.1 (1.0)	$<.001$	-0.5 (1.4)	-0.1 (1.1)	.015	-0.5 (1.4)	-0.0 (1.1)	.004
FEV_1/FVC z score	0.2 (1.4)	0.9 (1.2)	$<.001$	-0.2 (1.3)	0.0 (1.1)	.231	-0.3 (1.2)	0.0 (1.0)	.008
BDR	n = 483	n = 88		n = 437	n = 91		n = 402	n = 88	
BDR (yes), No. (%)	78 (16.1)	10 (11.4)	.253	45 (10.3)	5 (5.5)	.155	25 (6.2)	5 (5.7)	.849

Data are presented as mean (standard deviation) unless otherwise indicated. P values from 2-samples t test; z scores derived from Global Lung Initiative African American reference values. BDR is positive if change in $FEV_1 \geq 12\%$.

Abbreviations: BDR, bronchodilator responsiveness; FEF_{25-75} , forced expiratory flow at 25% and 75% of forced vital capacity; FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity; HIV, human immunodeficiency virus.

Table 2. Characteristics of Participants Tested at Both Baseline and 24 Months, by Human Immunodeficiency Virus Status

Characteristic	Baseline			24 mo		
	HIV ⁺ (n = 503)	HIV ⁻ (n = 106)	PValue	HIV ⁺ (n = 435)	HIV ⁻ (n = 94)	PValue ^a
Age, y, mean (SD)	12.0 (1.6)	11.9 (1.8)	.533	14.1 (1.6)	13.8 (1.8)	.171
Male sex	261 (51.9)	48 (45.2)	.216	217 (49.9)	42 (44.7)	.360
Age at effective ART initiation, y, median (IQR)	4.3 (1.9–7.6)	...		4.3 (2.0–7.6)	...	
Effective ART duration, y, median (IQR)	7.7 (4.6–9.3)	...		9.8 (6.8–11.3)	...	
CD4 count, cells/ μ L, median (IQR)	712 (556–959)	...		695.5 (529.5–887.5)	...	
Viral load, copies/mL						
<50	383 (76.1)	...		260 (59.8)	...	
50–1000	55 (10.9)	...		108 (24.8)	...	
1001–10 000	37 (7.4)	...		24 (5.5)	...	
>10 000	27 (5.4)	...		27 (6.2)	...	
Missing	1 (0.2)	...		16 (3.7)	...	
Poor ART adherence	116 (23.0)	...		41 (9.4)	...	
Effective ART regimen						
2 $\times$ NRTI + NNRTI	307 (61.2)	...		249 (57.2)	...	
2 $\times$ NRTI + PI	166 (33.1)	...		151 (34.7)	...	
Other	29 (5.8)	...		35 (8.1)	...	
Tobacco smoke exposure ^b						
Passive	127 (25.3)	21 (19.8)	.236	86 (19.8)	14 (14.9)	.274
Active	2 (0.4)	...		5 (1.2)	...	
History of LRTI requiring hospitalization prior to baseline visit	145 (28.8)	1 (0.9)	<.001	...	...	
Past history of PTB prior to baseline visit	303 (60.2)	2 (1.9)	<.001	...	...	
History of asthma, self-reported (ever)	62 (12.3)	6 (5.7)	.048	32 (7.4)	7 (7.5)	.976
Family history of asthma	78 (15.5)	13 (12.3)	.395	...	...	
Isoniazid prophylaxis	115 (22.9)	4 (3.8)	<.001	33 (7.6)	0	.006
Inhaled corticosteroids	13 (2.6)	2 (1.9)	.674	11 (2.5)	4 (4.3)	.360
Short-course steroids	13 (2.6)	...		6 (1.4)	...	
Inhaled salbutamol	33 (6.6)	2 (1.9)	.060	28 (6.4)	2 (2.1)	.104
Oral salbutamol	12 (2.4)	...		6 (1.4)	...	
Cotrimoxazole prophylaxis	50 (9.9)	0		33 (7.6)	0	
Intercurrent events, during the cumulative 2 y (n = 609)						
Hospitalization						
Nontuberculosis LRTI	...	...		5 (0.8)	1 (0.2)	<.001
Unconfirmed tuberculosis	...	...		13 (2.1)	0	
Asthma	...	...		1 (0.2)	1 (0.2)	1.000
Ambulatory LRTI	...	...		13 (2.1)	4 (0.7)	<.001
Culture-positive <i>Mycobacterium tuberculosis</i>	...	...		19 (3.1)	0	

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; LRTI, lower respiratory tract infection; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PTB, pulmonary tuberculosis; SD, standard deviation.

^aP value *t* test or χ^2 test.

^bSelf-reported smoking history.

HIV-uninfected adolescents, respectively (Table 1). This decreased to 6.2% and 5.7%, respectively, in the AWH and HIV-uninfected adolescents at 24 months, indicating an increase in fixed airway obstruction over the 24 months. On average, those with abnormal spirometry pattern had a higher odds of having either wheeze, shortness of breath, cough on most days, and history of doctor-diagnosed asthma, adjusted for HIV status ($P < .05$ for all; Table 6). History of doctor-diagnosed asthma (odds ratio [OR], 2.19 [95% CI, 1.16–4.14]) or past severe LRTI requiring hospitalization (OR, 1.71 [95% CI, 1.02–2.88]) were significantly associated with bronchodilator responsiveness (Supplementary Table 3).

DISCUSSION

This study provides novel 2-year follow-up data showing that spirometry in adolescents perinatally infected with HIV established on effective ART tracks lower compared to uninfected adolescents. Prior LRTI requiring hospitalization or PTB was associated with low FEV₁ or FVC. Reassuringly, this cohort had minimal chronic respiratory symptoms and few intercurrent ambulatory or hospitalized LRTIs during the 2-year follow-up. The cohort was well established on effective ART with a mean duration of effective ART of 9 years.

Table 3. Clinical Characteristics of Participants Tested at Both Baseline and 24 Months

Characteristic	Baseline			24 mo		
	HIV ⁺ (n = 503)	HIV ⁻ (n = 106)	PValue	HIV ⁺ (n = 435)	HIV ⁻ (n = 94)	PValue ^a
Height, cm, mean (SD)	140.0 (10.3)	144.6 (11.9)	.001	150.6 (9.8)	153.0 (9.7)	.030
BMI, kg/m ² , mean (SD)	17.7 (3.2)	19.5 (4.2)	<.001	19.4 (3.5)	21.1 (4.6)	<.001
Current history of cough on most days ^b	74 (14.7)	8 (7.6)	.050	51 (11.7)	11 (11.7)	.995
History of wheezing (ever) ^b	55 (10.9)	6 (5.7)	.100	31 (7.1)	7 (7.5)	.913
Wheezing in the last 12 mo ^b	31 (6.2)	3 (2.8)	.174	19 (4.4)	4 (4.3)	.961
SOB in the last 12 mo ^b	3 (0.6)	2 (1.9)	.181	6 (1.4)	3 (3.2)	.218
Digital clubbing at baseline	18 (3.6)	0 (0)	.048	...	...	
Respiratory rate, breaths/min	21.5 (3.5)	20.9 (5.2)	.142	21.0 (1.1)	20.9 (0.9)	.565
Oxygen saturation, %	98.6 (0.9)	98.8 (0.4)	.036	98.3 (1.7)	98.5 (0.7)	.199
Tanner stage						
I	242 (48.1)	34 (32.1)	.003	62 (14.3)	11 (11.7)	.516
II	123 (24.5)	30 (28.3)	.406	81 (18.6)	15 (16.0)	.544
III	69 (13.7)	18 (17.0)	.383	87 (20.0)	23 (24.5)	.333
IV	39 (7.8)	17 (16.0)	.007	110 (25.3)	26 (27.7)	.633
V	23 (4.6)	6 (5.7)	.633	83 (19.1)	16 (17.0)	.643
Missing	7 (1.4)	1 (0.9)	.713	12 (2.8)	3 (3.2)	.819

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; SD, standard deviation; SOB, shortness of breath.

^aSymptoms are self-reported at each time point.

^bt test or χ^2 test.

The stable trajectory of spirometry outcomes over 2 years suggests that damage to the lung, reflected as lower lung function in the HIV-infected group, may have occurred early in life due to uncontrolled HIV infection as effective ART was only initiated on average at 4 years of age in this cohort. In addition, it suggests that in AWH well established on effective ART, lung growth continues to occur and tracks similar to HIV-uninfected youth. Early damage may have been caused by HIV exposure in utero in the developing lung or in the early childhood years prior to initiation of effective ART. This damage may be attributed to early childhood infection, by HIV-associated inflammation and immune dysregulation, or opportunistic infections in the AWH, who had high rates of prior PTB or LRTI compared with HIV-uninfected participants, as has been reported in other studies [9, 13]. This is supported by the fact that previous LRTI or PTB was associated with lower lung function. The effect of HIV on lung function was reduced after adjusting for LRTI

and PTB, suggesting that pulmonary infection may be a major mechanism by which HIV reduces lung function.

The incidence of culture confirmed that tuberculosis in AWH was high over the study period. This is in keeping with published evidence [14] that, while long-term effective ART is associated with a reduction in tuberculosis risk, the incidence remains high in HIV-infected populations. South Africa has a high HIV and tuberculosis burden [15], and previous reports

Table 4. Effect of Human Immunodeficiency Virus on Lung Function Over 2 Years (n = 609)

Measure of Lung Function	Coefficient	(95% CI)	PValue ^a
FEV ₁ z score	-0.52 ^b	(-.76 to -.27)	<.001
FVC z score	-0.37 ^b	(-.60 to -.14)	.001
FEF ₂₅₋₇₅ z score	-0.42 ^b	(-.68 to -.17)	.001
FEV ₁ /FVC z score	-0.41 ^b	(-.64 to -.19)	<.001

Abbreviations: CI, confidence interval; FEF₂₅₋₇₅, forced expiratory flow at 25% and 75% of forced vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

^aLinear mixed-effects model.

^bAdjusted for age, sex, height, time.

Figure 2. Line plots of the trend of lung function over 2 years showing forced expiratory volume in 1 second and FVC absolute values (A and B, respectively) and z scores (C and D, respectively). Baseline: HIV infected (HIV⁺), n = 503 and HIV uninfected (HIV⁻), n = 106; 12 months: HIV⁺, n = 472 and HIV⁻, n = 96; 24 months: HIV⁺, n = 435 and HIV⁻, n = 94. Abbreviations: FVC, forced vital capacity; HIV, human immunodeficiency virus; lb/ub, lower 95% confidence interval /upper 95% confidence interval.

Table 5. Association of Forced Expiratory Volume in 1 Second (FEV₁), Forced Vital Capacity (FVC), and FEV₁/FVC z Scores at 24 Months (n = 515)

Variable	FEV ₁ z Score		FVC z Score		FEV ₁ /FVC z Score	
	Coefficient	P Value ^a	Coefficient	P Value ^a	Coefficient	P Value ^a
HIV infection	−0.12	.510	0.01	.946	−0.34	.036
Time at 12 mo	0.04	.296	0.25	<.001	−0.51	<.001
Time at 24 mo	0.17	<.001	0.41	<.001	−0.61	<.001
Tobacco smoke exposure ^b	0.01	.931	0.08	.192	−0.18	.022
Previous PTB	−0.27	.024	−0.27	.015	−0.01	.904
Previous LRTI	−0.37	.003	−0.30	.013	−0.27	.020

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HIV, human immunodeficiency virus; LRTI, lower respiratory tract infection; PTB, pulmonary tuberculosis.

^aMultivariate linear mixed model.

^bSelf-reported passive smoke exposure (active smoking had too few numbers, thus not reported).

have shown that the adolescent age group has a higher rate of tuberculosis disease [16]. Of concern was the very low use of cotrimoxazole or isoniazid prophylaxis as effective preventive interventions in this cohort. The low use of cotrimoxazole may reflect current program guidelines as prophylaxis is stopped after immune reconstitution, which had occurred in most participants, as reflected by the median CD4 count of around 700 cells/ μ L.

The higher occurrence of obstructive and mixed-pattern spirometry in AWH may be due to higher rates of bronchiectasis or postinfective bronchiolitis obliterans (BO) in the HIV-infected group. High rates of bronchiectasis in HIV-infected children have been reported [4, 17]. A study on chest computed tomography in AWH reported predominantly mosaic attenuation due to possible BO that was inversely correlated with FEV₁ [4]. Bronchiolitis obliterans is a nonreversible condition due to fibrosis. In our study cohort, bronchodilator

responsiveness at 2 years was <10%, suggesting irreversible airway pathology, possibly related to BO. Others have reported irreversible airway pathology in HIV-infected youth compared to HIV-exposed uninfected youth [18]. The high rate of restrictive spirometry pattern in both the AWH and HIV-uninfected adolescents at baseline may be for technical reasons as most participants had never done a lung function test before enrollment but became familiar with the technique of performing spirometry and were able to produce better-quality tests in subsequent visits.

The improvement of respiratory symptoms over the 2-year period in our cohort may have been due to close follow-up of study participants, good clinical management, and appropriate treatment or referral when the participant was sick or symptomatic. This cohort also had good adherence to effective ART, reflected by most adolescents having low HIV viral load.

Birth cohort studies from high-income countries in HIV-uninfected populations have shown that lung function tracks from childhood to adulthood [7, 19–21]. Therefore, the lung function of AWH, which was lower than that in HIV-uninfected adolescents, is likely to continue to track along the lower centile over time, provided there are no further insults. Longitudinal studies in HIV-infected children and adolescents are, however, lacking. With the expected physiological growth and development of the lung from in utero to early adulthood [5], it is unclear what effect HIV or opportunistic infections may have on normal physiological growth. In our study, there was no catch-up or deterioration over 2 years between the HIV-infected and the uninfected adolescents, but a longer follow-up period is needed. The lack of deterioration in lung function over the 2 years may reflect that this is a relatively healthy HIV-infected cohort (as evidenced by minimal respiratory morbidity in the 2-year period) who were stable on effective ART for a mean duration of 9 years.

Strengths of the study include a prospective collection of objective measures of lung function, high cohort retention with close follow-up over 2 years, and a well-controlled HIV cohort. Limitations of the study are that data included spirometry

Figure 3. Lung function at baseline, 12 months, and 24 months by past severe LRTI status in the adolescents with human immunodeficiency virus infection (showing FVC [A] and FEV₁ [B] z scores). P values calculated from two-sample independent *t* test. Missing LRTI data: 29 (5.8%) at baseline, 26 (5.5%) at 12 months, 23 (5.3%) at 24 months. Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; lb/ub, lower 95% confidence interval /upper 95% confidence interval; LRTI, lower respiratory tract infection.

Figure 4. Spirometry pattern by HIV status at baseline, 12 months, and 24 months. Abbreviation: HIV, human immunodeficiency virus.

only, but this is the most widely used measure of lung function; further bronchodilator responsiveness was also assessed in this study. In the absence of a local South African adolescent spirometry reference equation, we used the Global Lung Initiative 2012 [6] African American reference values, which have been shown to be acceptable for sub-Saharan Africa [22]. Further limitation was the lack of chest computed tomographic imaging to define lung abnormalities and correlate with lung function. These findings may not be generalizable to HIV-infected adolescent populations that are not well controlled on effective ART, where more severe lung function abnormalities have been found [23, 24]. However, as effective ART programs are strengthened, increasing numbers of adolescents perinatally infected with HIV can be expected to be on therapy and to develop this spectrum of lung disease.

CONCLUSIONS

AWH had lower spirometry at all time points compared to HIV-uninfected adolescents over 2 years. Lung growth was,

however, preserved in the HIV-infected group and similar in both groups. Previous PTB or previous LRTI was associated with reduced FEV₁ and FVC. There was a high incidence rate of culture-confirmed tuberculosis in the AWH. Interventions to prevent childhood LRTI or tuberculosis must be strengthened to optimize lung health. Further longitudinal studies on lung function in HIV-infected children and adolescents on effective ART are needed to show the long-term effect of HIV or opportunistic infections on subsequent respiratory health and to enable timely treatment of lung disease. Surveillance of lung function in AWH from early adulthood and throughout adulthood is necessary to detect disease early.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. L. N. G.: acquisition of data, analysis and interpretation of data, and writing of the manuscript; D. M. G.: conception and design of study and writing of the manuscript; S. H.: acquisition of data; T. M.: statistical analysis; H. J. Z.: conception and design of the study, acquiring of funding for the Cape Town Adolescent Antiretroviral cohort (CTAAC) study, and writing of the manuscript.

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Table 6. Association of Abnormal Spirometry Pattern and Respiratory Symptoms/Signs at Baseline

Respiratory Symptom/Sign ^a	No.	OR	(95% CI)	P Value ^b
History of ever wheeze (yes)	608	2.4	(1.25–4.68)	.009
Cough on most days (yes)	607	2.7	(1.62–4.62)	< .001
History of asthma ever (yes)	607	3.1	(1.64–5.83)	< .001
History of shortness of breath ever (yes)	608	4.7	(1.44–15.25)	.010
Digital clubbing (yes)	609	5.6	(.89–35.94)	.068

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAll symptoms are self-reported except digital clubbing.

^bAdjusted for human immunodeficiency virus status and time.

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