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Adolescent age is an independent risk factor for abnormal spirometry among people living with HIV in Kenya

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Abstract

Objectives: As life expectancy of people living with HIV (PLWH) improves in low- and middle-income countries (LMICs), the spectrum of HIV-related pulmonary complications may reflect a greater burden of chronic lung diseases as in high-income countries. We determined whether the risk of abnormal spirometry was greater among adolescent compared to adult PLWH at the Coptic Hope Center for Infectious Diseases in Nairobi, Kenya, and evaluated the role of other cofactors for abnormal spirometry.

Design: We prospectively enrolled adolescent and adult PLWH for this cross-sectional study.

Methods: Data collection included standardized questionnaires, clinical assessment, and pre- and post-bronchodilator spirometry. Adolescents additionally underwent non-contrast chest CT. Multivariable logistic regression determined associations of adolescent age with abnormal spirometry, adjusting for cofactors.

Results: Of 427 PLWH, 21 (40%) adolescents and 64 (17%) adults had abnormal spirometry. Among adolescents, 80% had abnormal chest CTs, and 79% had ≥1 respiratory symptom. Adolescent age (adjusted OR 3.22; *95% CI* 1.48-6.98) was independently associated with

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abnormal spirometry, adjusting for recent CD4, HIV clinical stage, low BMI, indoor kerosene use, smoking pack-years and prior pulmonary tuberculosis. Additional important cofactors for abnormal spirometry included prior pulmonary tuberculosis (3.15; 1.70-5.58), kerosene use (1.77; 1.04-3.04) and smoking pack-years (1.05; 1.00-1.10). Adolescent age, prior pulmonary tuberculosis, and pack-years were significantly associated with airflow limitation.

Conclusions: Adolescent age was independently associated with increased risk of abnormal spirometry, particularly airflow limitation. Studies to improve prevention, detection and management of chronic lung disease across the lifespan among PLWH are needed in LMICs.

Keywords

HIV; chronic obstructive lung disease; restrictive lung disease; risk factors; adolescents; Africa

INTRODUCTION

Of the 36,700,000 people living with HIV (PLWH), 25,500,000 live in sub-Saharan Africa, including >3,000,000 children and adolescents [1]. With increasing access to antiretroviral therapy (ART), PLWH experience longer life expectancies worldwide, and chronic non-communicable diseases are increasingly prevalent [2]. Although pulmonary infections remain important contributors to morbidity and mortality in low- and middle-income countries (LMICs) [3], the spectrum of HIV-related pulmonary complications may reflect a greater burden of chronic lung diseases (CLD) as in high-income countries [4,5].

Emerging data from cohorts of PLWH in sub-Saharan Africa report a substantial prevalence of abnormal spirometry, a manifestation of CLD. Prevalence estimates for abnormal spirometry are as high as 45%, and vary by age, region, smoking, biofuel exposure and ART use. While abnormal spirometry prevalence among adults ranges from 2% to 35% [6–10], a striking 24–45% prevalence of abnormal spirometry is reported among sub-Saharan African adolescents living with HIV [11–15]. As none of these cohorts enrolled both adolescents and adults, it remains unknown whether adolescents are truly at greater risk of abnormal lung function compared to adults, and if heterogeneity in exposures accounts for these apparent age-related differences in prevalence.

In this study, we determined whether the risk of abnormal spirometry was greater among adolescent compared to adult PLWH receiving routine care at the Coptic Hope Center for Infectious Diseases in Nairobi, Kenya, and evaluated the role of other cofactors for abnormal spirometry.

Some results of this study have been reported as an abstract [16].

METHODS

Expanded methods are in the Supplemental Digital Content (SDC).

Study design and cohort

Adolescent (10–19 years) and adult (≥20 years) PLWH, receiving routine care at the Nairobi-based Hope Center (January-March 2014) were prospectively enrolled for this cross-sectional analysis. The Hope Center provides free ART and comprehensive care to PLWH in a primarily poor, urban area [17]. Individuals with acute respiratory infections, recent tuberculosis or pregnancy were excluded. All participants signed written informed consent/assent. Ethics approvals were obtained from Kenyatta National Hospital/University of Nairobi and University of Washington.

Clinical assessment

Standardized questionnaires assessed risk factors/exposures, including smoking and indoor combustible fuel use. HIV-related variables were abstracted from Hope Center databases. Recent CD4 preceded study visits by ≤120 days. World Health Organization (WHO) Clinical HIV Stage was determined at Hope Center enrollment. Adolescents who reported maternal/sibling HIV infection, no sexual debut and no injection drug use met criteria for perinatally-acquired HIV.

Oxygen saturation was measured at rest and after sub-maximal exercise. Low BMI was defined as BMI<18.5 kg/m^2 for adults and BMI-for-age *Z*-score<−2 for adolescents [18].

Spirometry

Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured before and 15 minutes after administration of 400 μg salbutamol via LiteAire® spacer according to American Thoracic Society standards using an ndd EasyOne® spirometer [19].

Global Lung Initiative equations were used to determine predicted FEV_1 and FVC, FEV_1/FVC less than lower limit of normal (<LLN), FEV_1<LLN and FVC<LLN [20]. We defined airflow limitation as FEV_1/FVC<LLN. We considered spirometry as abnormal if any of these patterns was present pre-bronchodilator to allow comparison with studies that have not uniformly administered bronchodilators. Bronchodilator responsiveness was identified if post-bronchodilator FEV_1 or FVC increased 200 mL and 12% among adults and if FEV_1 increased >10% among adolescents [21,22].

Chest CT scans

Given the prevalence of respiratory abnormalities among adolescents, we obtained non-contrast high-resolution chest computed tomography (CT) in adolescents who consented/assented. Scans were interpreted by a board-certified radiologist with expertise in thoracic radiology blinded to clinical data.

Statistical analysis

Characteristics were compared by age group and abnormal spirometry, using χ^2 or Fisher's exact tests for categorical, t-tests with unequal variance for spirometry and Wilcoxon rank-sum tests for other continuous variables.

Bivariate logistic regression evaluated associations of adolescent age and cofactors that we hypothesized *a priori* would be associated with abnormal spirometry (CD4 <200, WHO HIV Stage ¾, ART, low BMI, combustible fuel use, cigarette smoking, ART, and prior pulmonary infections). We compared any abnormal versus normal spirometry, and individual abnormal patterns versus normal (SDC Table S1). To avoid overfitting adjusted models that determined associations between adolescent age and abnormal spirometry, cofactors were retained if they did not co-vary or if they had substantive effects on other variables. We determined correlations between spirometry and CT findings among adolescents. Analyses were performed using Stata 14.1 (College Station, TX).

RESULTS

Clinical characteristics by age group

Median age was 13 years among 52 adolescents and 40 years among 375 adults; 54% of adolescents were male compared to 33% of adults (Table 1, SDC Figure S1). No adolescents smoked, and there was no difference in prevalence of indoor combustible fuel burning. BMI was low in 23% of adolescents compared to 5% of adults. Nearly all adolescents met criteria for perinatally-acquired HIV. Compared to 55% of adults, only 25% of adolescents had nadir CD4 <200 cells/μL; 7% of adolescents had recent CD4 <200. Adolescents had nearly universal ART and co-trimoxazole use. Yet, compared to adults, adolescents had a significantly higher prevalence of respiratory symptoms and oxygen saturation ≤92%, especially after sub-maximal exercise.

Spirometry outcomes

Substantially more adolescents had abnormal spirometry compared to adults (40% *vs* 17%, $p<0.001$; Table 2). Airflow limitation was present in 23% of adolescents and 10% of adults pre-bronchodilator ($p=0.008$), and in 27% and 7% post-bronchodilator, respectively ($p<0.001$). Among adolescents and adults with pre-bronchodilator airflow limitation, 50% and 74% had persistent airflow limitation after bronchodilator, respectively. Overall bronchodilator responsiveness was similar among adolescents and adults. Adolescents had a significantly higher prevalence of FEV_1<LLN and FVC<LLN.

Cofactors for abnormal spirometry

Participants with abnormal spirometry were more likely to be adolescents compared to those with normal spirometry (25% *vs* 9%, $p<0.001$; Table 1). Smoking status did not differ by spirometry, even when restricted to adults. Smokers with abnormal spirometry reported greater pack-years ($p=0.06$). Participants with abnormal spirometry were more likely to use kerosene, and have prior pulmonary tuberculosis, obstructive CLD diagnoses, low BMI and respiratory symptoms compared to those with normal spirometry.

Independent risk for abnormal spirometry patterns

In multivariable analysis, adolescent age (adjusted OR 3.22; *95% CI* 1.48–6.98), prior pulmonary tuberculosis (3.15; 1.70–5.58), kerosene use (1.77; 1.04–3.04) and smoking pack-years (1.05; 1.00–1.10) were associated with abnormal spirometry (SDC Table S2). Adolescent age, prior tuberculosis, and pack-years were associated with airflow limitation.

Kerosene use and prior tuberculosis were associated with FEV_1<LLN. Prior tuberculosis and low BMI were associated with FVC<LLN.

Adolescent chest CTs

Of 52 adolescents, 46 underwent chest CT. Of these, 80% had ≥1 CT abnormality: 22 (48%) had mosaic attenuation, 10 (22%) groundglass opacities, 9 (20%) bronchial wall thickening, 8 (17%) micronodules, 5 (11%) emphysema, 4 (9%) bronchiectasis. Mosaic attenuation correlated with post-bronchodilator airflow limitation (r=0.6, p=0.02); emphysema correlated with FEV_1<LLN (r=0.7, p=0.02). No other correlations between spirometry and CT abnormalities were detected.

DISCUSSION

Adolescents had a disproportionately high prevalence of abnormal spirometry, low oxygen saturation and respiratory symptoms compared to adults, despite nearly universal ART and immune reconstitution/preservation. Adolescent age was independently associated with increased risk of abnormal spirometry, particularly airflow limitation, adjusting for HIV-related variables, malnutrition, smoke exposures and prior pulmonary tuberculosis. The direct comparison of adolescents and adults from a single cohort is a key strength of our study and supports that abnormal spirometry prevalence is greater in adolescents with perinatally-acquired HIV compared to adults with behaviorally-acquired HIV. These data suggest that exposure to heterogeneous factors during lung growth with concomitant HIV may contribute to greater CLD risk in adolescent compared to adult PLWH in sub-Saharan Africa [23].

Pathophysiologic mechanisms of CLD among adolescents with perinatally-acquired HIV are largely unknown. However, perinatal and early life insults are linked with impaired lung function and CLD throughout the lifespan in HIV-uninfected populations [24,25]. Perinatal insults may alter epigenetic determinants with potential long-term implications, including changes in lung structure/function [26]. Further, HIV, an independent risk factor for CLD [5,6,9,15], is implicated in epigenetic dysregulation [27]. These concurrent exposures may confer disparately greater CLD risk among adolescents who acquired HIV during critical periods of lung and immune development, though early ART initiation may mitigate this risk [14,23].

The physiologic and structural abnormalities identified in adolescents are consistent with obliterative bronchiolitis, a recently recognized etiology of CLD among adolescents with perinatally-acquired HIV in LMICs [11]. Adolescents, nearly all of whom acquired HIV perinatally in our cohort, had a high burden of abnormal spirometry, particularly airflow limitation that did not improve post-bronchodilator. They frequently had abnormal CTs, with a predominance of mosaic attenuation that correlated with post-bronchodilator airflow limitation but not bronchodilator responsiveness. These findings together argue against asthma as a primary CLD etiology in this population, though asthma likely plays a role [11–13,15,22]. Although emphysema and bronchiectasis were rare, emphysema correlated with FEV_1<LLN (an indicator of impaired airflow). CLD characterization is critical for guiding management.

Prior pulmonary tuberculosis was an important cofactor for abnormal spirometry, in line with findings from other African studies [9,15,28]. Lung infections, including tuberculosis, may be in the causal pathway by which HIV augments risk for abnormal spirometry through airway and/or parenchymal destruction [28–30]. Three-quarters of individuals with HIV-associated tuberculosis live in sub-Saharan Africa and the burden of CLD associated with tuberculosis is anticipated to grow as PLWH age, pointing to opportunities to improve outcomes through integration of HIV and tuberculosis programmatic efforts.

Indoor kerosene use was also associated with abnormal spirometry, including FEV_1<LLN. The impact of household air pollution on lung health is a recognized contributor to mortality, and is associated with impaired lung function, CLD and pneumonia, especially in LMICs [3,31–33]. Although considered a cleaner alternative to biofuels, kerosene combustion emits more volatile organic compounds, which may explain its link to airflow limitation, tuberculosis and pediatric pneumonia [3,31,34–36].

Not unexpectedly, greater pack-years were associated with higher risk of airflow limitation despite low smoking intensity and prevalence [3,37,38]. Gaining popularity, cigarette smoking is positioned to emerge as an important contributor to CLD in LMICs [38–40]. Smoking prevention and cessation are essential.

Low BMI was associated with FVC<LLN, considered a marker of restricted spirometry. Although this finding may be influenced by differing definitions of low BMI in adolescents and adults, malnutrition has been linked with abnormal spirometry patterns [9,41–43]. Children living with HIV have a high risk of malnutrition, and those with CLD experience a 20–30% increase in nutritional needs [43,44]. These unmet needs may persist into adolescence, perpetuating malnutrition and CLD risk.

Our study has several limitations. We lacked an HIV-uninfected comparison group. We may have misclassified a few adolescents as having perinatally-acquired HIV, but the male:female ratio was nearly 1:1 in adolescents and 1:2 in adults, consistent with perinatally- and behaviorally-acquired HIV, respectively. Exposures/cofactors were ascertained by self-report, and CTs were interpreted using visual assessment by one radiologist. Finally, population size and outcome events may have provided insufficient statistical power to detect some associations.

In conclusion, adolescent age is an independent risk factor for abnormal spirometry, particularly airflow limitation, among PLWH, suggesting that adolescents with perinatally-acquired HIV represent a unique group at risk for CLD [11–15,23]. As more children with perinatally-acquired HIV survive into adolescence in LMICs [45], it is imperative to understand CLD pathophysiology across the lifespan of PLWH, and to improve strategies to mitigate the growing CLD burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics of participants

Characteristic	Overall cohort *n* = 427	Adolescents 10-19 years old *n* = 52	Adults ≥20 years old *n* = 375	*p*-value	Abnormal spirometry *n* = 85	Normal spirometry *n* = 342	*p*-value
Age (years), median (IQR)	39 (32 – 45)	13 (11 – 14)	40 (35 – 46)	--	37 (20 – 42)	40 (33 – 46)	<0.001
Adolescents (10-19 years old), n (%)	52 (12)	--	--	--	21 (25)	31 (9)	<0.001
Male, n (%)	151 (35)	28 (54)	123 (33)	0.003	28 (33)	123 (36)	0.6
Current/former smoker, n (%)	47 (11)	0	47 (13)	--	10 (11)	37 (11)	0.8
Smoking pack-years among current/former smokers, median (IQR)	5 (2 – 11)	0	5 (2 – 11)	--	10 (5 – 20)	5 (2 – 8)	0.06
Energy source for indoor heating/cooking [*], n (%)							
Any combustible fuel	362 (85)	46 (88)	316 (84)	0.5	75 (88)	287 (84)	0.3
Kerosene	210 (49)	22 (42)	188 (50)	0.3	50 (59)	160 (47)	0.047
Wood	53 (12)	10 (19)	43 (11)	0.1	11 (13)	42 (12)	0.9
Charcoal	263 (62)	34 (65)	229 (61)	0.5	50 (59)	213 (62)	0.6
Self-reported prior pulmonary infections, n (%)							
Pneumonia (presumed bacterial)	109 (25)	18 (35)	91 (24)	0.1	25 (29)	84 (25)	0.4
Tuberculosis	96 (22)	14 (27)	82 (22)	0.4	35 (41)	61 (18)	<0.001
Self-reported history of obstructive lung disease (asthma or COPD), n (%)	29 (7)	2 (4)	27 (7)	0.6	11 (13)	18 (5)	0.01
Low BMI[†], n (%)	32 (7)	12 (23)	20 (5)	<0.001	15 (18)	17 (5)	<0.001
Stunted growth (height-for-age *Z*-score <−2)[‡], n (%)	--	13 (25)	--	--	6/21 (29)	7/31 (23)	0.7
Respiratory abnormalities, n (%)							
Any chronic respiratory symptom	232 (54)	41 (79)	191 (51)	<0.001	58 (68)	174 (51)	0.004
Cough	144 (34)	32 (62)	112 (30)	<0.001	46 (54)	98 (29)	<0.001
Sputum production	107 (25)	28 (54)	79 (21)	<0.001	28 (33)	79 (23)	0.06
Wheezing	89 (21)	16 (31)	73 (19)	0.05	28 (33)	61 (18)	0.002
Chest tightness	63 (15)	12 (23)	51 (14)	0.07	19 (22)	44 (13)	0.03
mMRC Dyspnea Scale Score[§] ≥1	90 (21)	15 (29)	75 (20)	0.1	28 (33)	62 (18)	0.003
SpO2 ≤92%, resting	14 (3)	5 (10)	9 (2)	0.02	3 (4)	11 (3)	1.0
SpO2 ≤92%, after sub-maximal exercise	82 (19)	20 (38)	62 (17)	<0.001	21 (25)	61 (18)	0.2
HIV-related variables							

Characteristic	Overall cohort *n* = 427	Adolescents 10-19 years old *n* = 52	Adults ≥20 years old *n* = 375	*p*-value	Abnormal spirometry *n* = 85	Normal spirometry *n* = 342	*p*-value
CD4 cell counts [//]							
Nadir CD4 <200 cells/μL, n (%)	213 (51)	13 (25)	200 (55)	<0.001	38 (47)	175 (52)	0.4
Nadir CD4 (cells/μL), median (IQR)	194 (82 – 310)	294 (200 – 494)	180 (74 – 296)	<0.001	210 (87 – 366)	191 (76 – 303)	0.2
Recent CD4 <200 cells/μL, n (%)	46 (11)	3 (7)	43 (12)	0.5	11 (14)	35 (11)	0.3
Recent CD4 (cells/μL), median (IQR)	454 (304 – 677)	678 (430 – 952)	439 (297 – 633)	<0.001	506 (331 – 713)	448 (298 – 667)	0.3
WHO HIV Clinical Stage [**], n (%)							
1/2	261 (63)	34 (65)	227 (63)	0.7	41 (51)	220 (66)	0.01
3/4	154 (37)	18 (35)	136 (37)		40 (49)	114 (34)	
Current co-trimoxazole use, n (%)	398 (93)	50 (96)	348 (93)	0.2	82 (96)	316 (93)	0.3
Current ART use, n (%)	367 (86)	48 (94)	319 (85)	0.09	74 (87)	293 (86)	0.9
ART duration (years) [††], median (IQR)	4 (2 – 8)	5 (3 – 8)	4 (2 – 7)	0.02	5 (3 – 8)	4 (2 – 7)	0.1
Known duration of HIV infection (years) [††], median (IQR)	7 (3 – 10)	13 (11 – 14)	6 (3 – 9)	<0.001	8 (4 – 13)	6 (3 – 10)	0.006

[*] Participants could have reported use of >1 energy source

[†] Adolescents = BMI-for-age *Z*-score <-2 (wasted); adults = BMI <18.5 kg/m^2 (underweight)

[‡] Stunted growth presented for adolescents only

[§] Modified Medical Research Council (mMRC) Dyspnea Scale Score ≥1 corresponds to dyspnea when hurrying on level ground or with lesser exertion

[//] CD4 cell counts missing for n=11 overall

[**] WHO HIV Clinical Stage missing for n=12 overall

[††] ART duration and known duration of HIV missing for n=4 overall

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Table 2.

Spirometry results by age group

	Overall cohort *n* = 427	Adolescents 10 – 19 years old *n* = 52	Adults ≥20 years old *n* = 375	*p*-value
Abnormal spirometry[*], n (%, 95% *CI*)	85 (20, 16 – 24)	21 (40, 28 – 54)	64 (17, 14 −21)	<0.001
Airflow limitation (FEV1/FVC<LLN), n (%, 95% *CI*)				
Pre-bronchodilator (pre-BD)	51 (12, 9 – 15)	12 (23, 14 – 37)	39 (10, 8 – 14)	0.008
Post-bronchodilator (post-BD)	42 (10, 7 – 13)	14 (27, 17 – 41)	28 (7, 5 – 11)	<0.001
FEV_1 in L, pre-BD, mean (SD)	2.62 (0.71)	1.83 (0.55)	2.73 (0.66)	--
FEV_1, % predicted pre-BD, mean (SD)	95 (16)	88 (18)	96 (16)	0.001
FEV_1 < LLN, n (%, 95% *CI*)	55 (13, 10 – 16)	14 (27, 17 – 41)	41 (11, 8 – 15)	0.001
FVC in L, pre-BD, mean (SD)	3.26 (0.85)	2.20 (0.54)	3.41 (0.77)	--
FVC, % predicted pre-BD, mean (SD)	98 (15)	94 (15)	98 (15)	0.05
FVC < LLN, n (%, 95% *CI*)	38 (9, 7 – 12)	9 (17, 9 – 30)	29 (8, 5 – 11)	0.02
Bronchodilator responsiveness[†], n (%, 95% *CI*)	73 (17, 14 – 21)	11 (21, 12 – 34)	62 (17, 13 – 21)	0.4
Bronchodilator responsiveness in abnormal spirometry, n (%, 95% *CI*)	29/85 (34, 25 – 45)	7/21 (33, 16 – 56)	22/64 (34, 24 – 47)	1.0
Bronchodilator responsiveness in normal spirometry, n (%, 95% *CI*)	44/342 (13, 10 – 17)	4/31 (13, 5 – 30)	40/311 (13, 10 – 17)	1.0

[*] Abnormal spirometry includes pre-BD FEV_1/FVC<LLN, FEV_1<LLN and FVC<LLN.

[†] Bronchodilator responsiveness present if FEV_1 and/or FVC increased by ≥12% and 200 mL after bronchodilator administration.