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Risk Factors for Hypoxia and Tachypnea Among Adolescents with Vertically-Acquired HIV in Nairobi

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Abstract

Background—Chronic lung diseases are increasingly recognized complications of vertically-acquired HIV among adolescents in sub-Saharan Africa and may manifest with hypoxia or tachypnea. We sought to determine the prevalence of and risk factors for hypoxia and tachypnea among adolescents with vertically-acquired HIV in Nairobi, Kenya.

Methods—We performed a cross-sectional analysis of 258 adolescents with vertically-acquired HIV who were initiating care at the Coptic Hope Center for Infectious Diseases. Adolescents with documented pneumonia were excluded. Hypoxia was defined as resting oxygen saturation ≤92%, and tachypnea was based on the 99th percentile of age-appropriate respiratory rates. Logistic regression models adjusted for demographics and HIV severity estimated odds ratios (ORs) for risk of hypoxia and tachypnea associated with potential risk factors.

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Results—Overall, 11% of adolescents had hypoxia and 55% had tachypnea. Advanced HIV (adjusted OR [aOR] 2.41) and low CD4 (aOR 1.74) were associated with greater hypoxia risk, but confidence intervals (CI) were wide and included the null (*95% CI* 0.93–6.23 and 0.69–4.39, respectively). Low CD4 (aOR 2.45, *95% CI* 1.39–4.32), current ART use (aOR 0.48, *95% CI* 0.27–0.86) and stunted growth (aOR 3.46, *95% CI* 1.94–6.18) were associated with altered tachypnea risk.

Conclusions—Hypoxia and tachypnea are common among adolescents with vertically-acquired HIV. There was a suggestion that advanced HIV and low CD4 were associated with greater hypoxia risk. Low CD4, lack of ART use and stunted growth are risk factors for tachypnea. Our findings highlight the chronic lung disease burden in this population and may inform diagnostic algorithms.

Keywords

Vertically-acquired HIV; adolescents; chronic lung disease; hypoxia; tachypnea

INTRODUCTION

Over 3 million HIV-infected children and adolescents live in sub-Saharan Africa, and nearly all of them acquired HIV through vertical transmission.[1] Lung diseases, such as lymphocytic interstitial pneumonia, recurrent pneumonia, tuberculosis and bronchiectasis, are well-described among HIV-infected children <10 years old in sub-Saharan Africa[2] and may also affect adolescents. The spectrum of pulmonary complications among HIV-infected adolescents in these settings additionally includes the chronic lung diseases: obliterative bronchiolitis, pulmonary hypertension and asthma.[3] However, limited availability of chest radiography and lung function testing hinders definitive diagnosis.[4]

Respiratory abnormalities, such as hypoxia and tachypnea, are often manifestations of lung disease,[5–7] and their presence may aid in identifying HIV-infected adolescents with chronic lung diseases. Among adolescents with vertically-acquired HIV in Zimbabwe who had no acute respiratory symptoms, 13% had hypoxia at rest and 28% were tachypneic.[3] Over 40% had lung function abnormalities or radiographic evidence of chronic lung disease. However, risk factors for chronic lung diseases and their manifestations are not well-defined among adolescents with vertically-acquired HIV in resource-limited settings. As oxygen saturation and respiratory rate are frequently measured during routine clinic visits, we conducted this study to determine: a) the prevalence of hypoxia and tachypnea among adolescents with vertically-acquired HIV in Nairobi, Kenya; and b) risk factors for hypoxia and tachypnea among these adolescents.

METHODS

Study design and population

We performed a cross-sectional analysis of data from adolescents with vertically-acquired HIV who were initiating care at the Coptic Hope Center for Infectious Diseases in Nairobi from 2004 to 2013. The Hope Center provides comprehensive care to HIV-infected individuals according to Kenyan guidelines.[8] Data were abstracted from electronic research

records populated with information from initial clinic visits. University of Washington and Kenyatta National Hospital Institutional Review Boards approved this study.

We restricted eligibility age to 10–16.9 years old because data supporting vertical HIV transmission, including documentation of HIV risk factors and maternal/sibling HIV status, were systematically collected for this age group. To identify baseline respiratory abnormalities, we excluded adolescents with documented pneumonia at initial clinic visits. Of 258 eligible adolescents, 56 did not have recorded oxygen saturation. We retained these adolescents in our overall cohort as characteristics of adolescents with and without documented oxygen saturation were similar.

Respiratory abnormalities

We defined hypoxia as resting oxygen saturation ≤92% by pulse oximetry.[9] As normal respiratory rates vary by age during adolescence, we defined tachypnea as a respiratory rate greater than the 99th percentile of age-appropriate values (Table 1).[10] Few published guidelines define hypoxia and tachypnea at Nairobi's altitude of ~1,700 meters;[9] therefore, to minimize the likelihood that our outcome definitions misclassified adolescents with normal oxygen saturation and respiratory rate into abnormal groups, we also considered more conservative cutoffs for oxygen saturation (≤90%) and respiratory rate (Table 1).

Potential risk factors

Baseline demographics included age and gender. Stunted growth and malnutrition were defined as height-for-age and body mass index (BMI)-for-age Z-scores < −2, respectively.[11] HIV severity was categorized per World Health Organization (WHO) clinical staging criteria. Advanced HIV was defined as WHO HIV stages 3 and 4. Current antiretroviral therapy (ART) and co-trimoxazole use were based on self-report. CD4 count (cells/μL) was measured within 30 days of care initiation. We defined low CD4 as <200 cells/μL. Indoor biofuel burning was based on self-reported use of wood, charcoal or kerosene as energy sources within the adolescent's home.

Statistical analysis

To determine independent associations of each of the covariates in Tables 2 and 3 with hypoxia and tachypnea, we generated multivariable logistic regression models. Final models included age (continuous) and gender to account for potential confounding. We also adjusted for WHO HIV stage to minimize potential selection bias, as HIV-infected adolescents who are ill may be more likely to seek medical care.[12] We repeated these analyses using conservative cutoffs for hypoxia and tachypnea.

All analyses were performed using Stata 13 (Stata Corp., College Station, TX).

RESULTS

Cohort characteristics

Most adolescents were at the lower end of included ages (51% were 10–12.9 years old); 49% were male, 40% had stunted growth and 19% were malnourished. Overall, 34% had

WHO HIV stage 3/4, 28% reported current ART use and 51% reported taking co-trimoxazole. Median CD4 was 326 cells/μL (*interquartile range* 125–549), and 33% had CD4 <200 cells/μL. A substantial proportion of data was missing for indoor biofuel burning exposure; among adolescents for whom data were available, 53% reported exposure.

Overall, 22 of 202 adolescents (11%) had hypoxia (oxygen saturation ≤92%), and 143 of 258 (55%) had tachypnea (Table 1). When applying conservative outcome definitions, 13 (6%) had hypoxia and 60 (23%) had tachypnea.

Risk factors for hypoxia

On average, adolescents with hypoxia were younger than those without hypoxia (per one year, adjusted odds ratio [aOR] 0.81, *95% confidence interval* [*CI*] 0.66–0.99; Table 2). Advanced HIV was associated with greater risk for hypoxia: 55% of adolescents with hypoxia but only 31% of those without hypoxia had advanced HIV (aOR 2.41, *95% CI* 0.93–6.23). Ten of the 22 adolescents with hypoxia (45%) had low CD4, in contrast to 31% of those without hypoxia. This association persisted after adjustment for age, gender and WHO HIV stage (aOR 1.74), but, as with advanced HIV, the small number of subjects led to a statistically imprecise result (*95% CI* 0.69–4.39). Adolescents with hypoxia were more likely to report indoor biofuel burning; however, the extent of missing data prohibited any meaningful conclusions to be drawn.

In sensitivity analyses, using oxygen saturation ≤90% as the outcome, the association with advanced HIV was further attenuated (aOR 1.49, *95% CI* 0.65–4.45), while the association with low CD4 was not substantially changed (aOR 1.96, *95% CI* 0.63–6.05). The association with younger age remained similar (aOR 0.68, *95% CI* 0.53–0.87).

Risk factors for tachypnea

Adolescents with tachypnea were younger on average than those without tachypnea (per one year, aOR 0.80, *95% CI* 0.70–0.91; Table 3). Of adolescents with tachypnea, 51% had stunted growth compared to 26% of those without tachypnea (aOR 3.46, *95% CI* 1.94–6.18). The prevalence of advanced HIV was 34% among those with and without tachypnea. Only 22% with tachypnea were using ART compared to 36% of those without tachypnea (aOR 0.48, *95% CI* 0.27–0.86), and a greater proportion of adolescents with tachypnea had low CD4 (40% *vs* 25%; aOR 2.45, *95% CI* 1.39–4.32). Exposure to indoor biofuel burning was more prevalent among those with tachypnea. Additionally adjusting these models for stunted growth did not appreciably alter associations (data not shown).

When using conservative cut-offs for tachypnea, associations with low CD4 (aOR 2.41, *95% CI* 1.31–4.44), current ART use (aOR 0.26, *95% CI* 0.11–0.62) and stunted growth (aOR 3.78, *95% CI* 1.98–7.22) were largely unchanged, but the association with age was diminished (aOR 0.95, *95% CI* 0.82–1.10).

DISCUSSION

Hypoxia and tachypnea were common in this cohort of adolescents with vertically-acquired HIV in Nairobi. There was a suggestion that advanced HIV and low CD4 were associated

with greater risk of hypoxia. Low CD4, lack of ART and stunted growth were risk factors for tachypnea. These respiratory abnormalities may have clinically relevant implications. In a study of HIV-infected adolescents in Malawi, chronic lung disease phenotypes were characterized as hypoxia- or cough-predominant.[7] Although pathologic correlates were not available in that study or in ours, specific combinations of routinely ascertained signs and symptoms may contribute to future clinical algorithms for identifying adolescents with chronic lung diseases in resource-limited settings. Most risk factors identified in our study are modifiable and may be amenable targets for mitigating the burden of chronic lung diseases.

HIV-related immunosuppression was associated with hypoxia and tachypnea. While WHO HIV stages 3/4 encompass prior severe and AIDS-defining illnesses, low current CD4 imparts contemporaneous risk of opportunistic infections and non-infectious comorbidities.[13] Current CD4 may reflect immunosuppression that has persisted for weeks, months or years. Longstanding HIV infection in children during critical periods of immune system and organ development may influence organ injury and increase risk of chronic lung diseases of the parenchyma, airways and vasculature,[2,3,7,14] potentially impairing gas exchange.[5] Concurrently, pulmonary infections may trigger local inflammation and resultant destructive lung lesions. Though it is unclear from this cross-sectional study if severe immunosuppression indeed predisposes to hypoxia and tachypnea, and whether it is because of immune dysfunction or prior pulmonary infections, our findings suggest that hypoxia and tachypnea in adolescents with advanced HIV or low CD4 are common and may warrant further pulmonary evaluation where available.

We also detected an association of current ART use with lower tachypnea risk. ART scale-up has led to dramatic declines in morbidity and mortality, but <40% of eligible HIV-infected children and adolescents access ART in sub-Saharan Africa.[1] Further, ART initiation at advanced HIV or lower CD4 may attenuate this observed risk reduction, as immune function defects and pulmonary parenchymal damage may not be completely reversible.[3,14] The association of ART with tachypnea suggests that immune modulation and pulmonary infection mitigation by ART has important implications for pulmonary pathophysiology, underscoring potential benefits of early, universal ART.

We also found that stunted growth was a strong predictor of tachypnea. In our cohort, 40% of adolescents had stunted growth, which is reported in as many as 50% of HIV-infected children and is linked with advanced HIV.[15] Adolescents with stunted growth who acquired HIV vertically may have impaired lung development, as lung development is physiologically associated with growth velocity and height attainment. If adequate growth attainment does not occur by five years of age, impaired lung function may persist into adulthood,[16] raising the concern that sequelae of stunted growth identified during adolescence may be irreversible. Stunted growth reflects long-term exposures and may capture elements of socioeconomic status, such as wealth, education and environmental conditions.[17]

Finally, we found that younger age was associated with greater hypoxia and tachypnea risk, potentially suggesting a survivor bias. In sub-Saharan Africa, adolescents with delayed diagnosis of vertically-acquired HIV often present at advanced HIV stages[12] with stunted

growth, frequent infections and respiratory abnormalities.[18] These “slow progressors” comprise up to 36% of infants with vertically-acquired HIV and may survive a median 16 years without ART.[19] As adolescents with untreated HIV have a high mortality risk,[12] many with undiagnosed, advanced HIV will have died, some with respiratory abnormalities, prior to seeking care. However, we pose this hypothesis cautiously as the association with age was attenuated when data were analyzed using conservative cutoffs for tachypnea (though the association remained for hypoxia).

No consensus guidelines designate cutoffs for abnormal oxygen saturation or respiratory rate at Nairobi’s moderate altitude. However, altitude-specific models estimate a hypoxia threshold of 95% oxygen saturation,[9] indicating that this altitude is unlikely to impact hypoxia prevalence. We observed tachypnea among 55% of adolescents compared to 28% in the Zimbabwean study. Applying that study’s cut-off (>25 breaths per minute) in our cohort yields a 42% tachypnea prevalence. Though unlikely, it remains possible that Nairobi’s altitude accounts for a fraction of our observed tachypnea prevalence.

Our study has several other limitations. First, the sample size was relatively small, representing only adolescents initiating care at the Hope Center who met criteria for vertically-acquired HIV. Second, vertically-acquired HIV criteria were based on self-report, which may have resulted in some misclassification. However, the median age for sexual debut in Kenya is 17–24 years old,[20] supporting that the majority of adolescents in our cohort acquired HIV vertically. Third, the substantial proportion of missing data for indoor biofuel burning limited our ability to draw conclusions about associations regarding this exposure. Finally, despite controlling for potential confounding factors, there may still be residual confounding of associations.

In conclusion, hypoxia and tachypnea were common among adolescents with vertically-acquired HIV. The association of advanced HIV, low CD4 and lack of ART with greater risk of hypoxia or tachypnea suggests that sequelae of uncontrolled HIV may contribute to pulmonary injury. Stunted growth, especially in HIV, may impact lung development. As the prevalence of adolescents with vertically-acquired HIV in sub-Saharan Africa is not anticipated to decline for another decade,[19] further studies are needed to understand implications of these respiratory abnormalities and to determine whether they can be utilized systematically to identify chronic lung diseases among HIV-infected adolescents in resource-limited settings.

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Table 1

Definition of tachypnea (in breaths per minute)

Age group (years)	Elevated respiratory rate based on respiratory rate >99th percentile of age-appropriate normal values*	Conservative cutoffs for elevated respiratory rate (used in sensitivity analysis)
10 – 12.9	>25	>27
13 – 14.9	>23	>25
15 – 16.9	>22	>24

*based on international systematic review of resting respiratory rates of children and adolescents[9]

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Table 2

Demographic and clinical characteristics among adolescents with and without hypoxia (*n* = 202)

	Hypoxia (*n* = 22)		No hypoxia (*n* = 180)		Crude OR (*95% CI*)	aOR – adjusted for age, gender and WHO HIV clinical stage (*95% CI*)
	n	**%**	***n***	**%**		
Age * (years), median (IQR)	12.6 (11.0 – 13.1)		13.2 (11.4 – 14.7)		0.79 (0.64 – 0.96)	0.81 (0.66 – 0.99)‡
Age (years), by category						
10 – 12.9	16	73%	84	47%	--	--
13 – 14.9	5	23%	56	31%	--	--
15 – 16.9	1	4%	40	22%	--	--
Gender						
Male	14	64%	89	49%	1.79 (0.71 – 4.48)	1.45 (0.55 – 3.79)§
Female	8	36%	91	51%	Referent	Referent
Height-for-age *Z*-score						
< −2 (stunted growth)	9	41%	60	36%	1.26 (0.51 – 3.12)	1.21 (0.50 – 2.89)
≥ −2	13	59%	109	64%	Referent	Referent
Missing	0	--	11	--		
BMI-for-age *Z*-score						
< −2 (malnutrition)	6	27%	32	19%	1.59 (0.58 – 4.41)	1.22 (0.46 – 3.25)
≥ −2	16	73%	136	81%	Referent	Referent
Missing	0	--	12	--		
WHO HIV Clinical Stage						
Stage 3/4 (advanced HIV)	12	55%	55	31%	2.71 (1.10 – 6.65)	2.41 (0.93 – 6.23)¥
Stage 1/2	10	45%	124	69%	Referent	Referent
Missing	0	--	1	--		
CD4+ cell count						
<200 cells/μL	10	45%	54	30%	1.91 (0.78 – 4.71)	1.74 (0.69 – 4.39)
≥200 cells/μL	12	55%	124	70%	Referent	Referent
Missing	0	--	2	--		
Current ART use						
Yes	7	32%	50	28%	1.21 (0.47 – 3.16)	0.91 (0.35 – 2.35)

	Hypoxia (*n* = 22)		No hypoxia (*n* = 180)		Crude OR (*95% CI*)	aOR – adjusted for age, gender and WHO HIV clinical stage (*95% CI*)
	n	**%**	***n***	**%**		
No	15	68%	130	72%	Referent	Referent
Current co-trimoxazole use						
Yes	12	55%	94	52%	1.10 (0.45 – 2.68)	0.85 (0.34 – 2.14)
No	10	45%	86	48%	Referent	Referent
Indoor biofuel burning						
Yes	7	70%	40	50%	2.33 (0.56 – 9.75)	1.81 (0.43 – 7.62)
No	3	30%	40	50%	Referent	Referent
Missing	12	--	100	--		

*OR per 1 year increase in age

‡Only adjusted for gender and WHO HIV clinical stage

§Only adjusted for age and WHO HIV clinical stage

¥Only adjusted for age and gender

Table 3

Demographic and clinical characteristics among adolescents with and without tachypnea ($n = 258$)

	Tachypnea (n = 143)		No tachypnea (n = 115)		Crude OR (*95% CI*)	aOR – adjusted for age, gender and WHO HIV clinical stage (*95% CI*)
	n	**%**	***n***	**%**		
Age * (years), median (IQR)	12.7 (11.0 – 14.0)		13.2 (11.8 – 15.4)		0.81 (0.72 – 0.92)	0.80 (0.70 – 0.91)[≠]
Age (years), by category						
10 – 12.9	78	55%	54	47%	--	--
13 – 14.9	44	31%	24	21%	--	--
15 – 16.9	21	15%	37	32%	--	--
Gender						
Male	71	50%	56	49%	1.04 (0.64 – 1.70)	0.93 (0.55 – 1.56)[§]
Female	72	50%	59	51%	Referent	Referent
Height-for-age *Z*-score						
< −2 (stunted growth)	70	51%	28	26%	3.07 (1.78 – 5.30)	3.46 (1.94 – 6.18)
≥ −2	66	49%	81	74%	Referent	Referent
Missing	7	--	6	--		
BMI-for-age *Z*-score						
< −2 (malnutrition)	27	21%	18	17%	1.31 (0.68 – 2.54)	1.24 (0.62 – 2.50)
≥ −2	104	79%	91	83%	Referent	Referent
Missing	12	--	6	--		
WHO HIV Clinical Stage						
Stage 3/4 (advanced HIV)	48	34%	38	34%	1.00 (0.59 – 1.68)	0.96 (0.56 – 1.65)[¥]
Stage 1/2	95	66%	75	66%	Referent	Referent
Missing	0	--	2	--		
CD4+ cell count						
<200 cells/μL	57	40%	28	25%	2.01 (1.17 – 3.47)	2.45 (1.39 – 4.32)
≥200 cells/μL	86	60%	85	75%	Referent	Referent
Missing	0	--	2	--		
Current ART use						
Yes	32	22%	41	36%	0.52 (0.30 – 0.90)	0.48 (0.27 – 0.86)

	Tachypnea (*n* = 143)		No tachypnea (*n* = 115)		Crude OR (*95% CI*)	aOR – adjusted for age, gender and WHO HIV clinical stage (*95% CI*)
	n	**%**	***n***	**%**		
No	111	78%	74	64%	Referent	Referent
Current co-trimoxazole use						
Yes	71	50%	60	52%	0.90 (0.55 – 1.48)	0.83 (0.49 – 1.39)
No	72	50%	55	48%	Referent	Referent
Indoor biofuel burning						
Yes	26	59%	24	47%	1.63 (0.72 – 3.69)	1.72 (0.73 – 4.07)
No	18	41%	27	53%	Referent	Referent
Missing	99	--	64	--		

*OR per 1 year increase in age

‡Only adjusted for gender and WHO HIV clinical stage

§Only adjusted for age and WHO HIV clinical stage

¥Only adjusted for age and gender