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Pulmonary Function Impairment In Children And Adolescents Living With Hiv: A Cross-Sectional Study From Eastern India.

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Abstract

Background: HIV-infected children and adolescents remain at risk of pulmonary complications, but published data on lung function in the post-antiretroviral therapy (ART) era, particularly from South Asia, are limited. This study aimed to determine the pattern and prevalence of pulmonary function impairment in HIV-infected children and adolescents on ART, and its association with clinical and immunological parameters. ***Methods:*** This cross-sectional study was conducted over one year (January–December 2019) at the ART centre of a tertiary hospital in Kolkata, India. Thirty HIV-infected children and adolescents aged 10–18 years, receiving ART for at least six months, underwent clinical evaluation, anthropometry, CD4 count, and spirometry. Lung function was assessed using predicted FVC, FEV1, FEV1/FVC, and FEF25–75%. Chi-square, Fisher's exact, and one-way ANOVA tests evaluated associations. ***Results:*** Twenty patients (66.7%) had a normal pattern, 7 (23.3%) a restrictive pattern, and 3 (10.0%) an obstructive pattern. Mean (± standard deviation) FVC%, FEV1%, and FEV1/FVC% were 86.57±18.02, 80.77±18.32, and 93.77±10.60. Impairment was significantly associated with advancing WHO clinical stage (p=0.003), CD4 immunological stage (p=0.001), lower CD4 count (p<0.001), and lower haemoglobin (p=0.006). No significant association was found with sex, area of residence, passive smoking, allergy, body mass index, or ART duration (all p>0.05). ***Conclusions:*** Despite long-term ART, nearly one-third of HIV-infected children and adolescents had impaired lung function, predominantly restrictive. Advanced immunosuppression and anaemia were significantly linked to poorer lung function, supporting periodic spirometric screening in this population.

Keywords: HIV Infections; Child; Adolescent; Respiratory Function Tests; Spirometry; CD4 Lymphocyte Count; Antiretroviral Therapy, Highly Active.

INTRODUCTION

Human immunodeficiency virus (HIV) infection continues to be a major global health problem, with an estimated 1.7 million children below 15 years living with HIV worldwide. [1] India carries the world's third-largest burden of HIV/AIDS, and although West Bengal remains a low-prevalence state, children in this region continue to acquire infection predominantly through mother-to-child transmission. [2]

The lung is one of the principal target organs affected by HIV infection across all age groups.[3,4] In the pre-antiretroviral therapy (ART) era, paediatric pulmonary morbidity was dominated by acute infections such as bacterial pneumonia, Pneumocystis pneumonia, and tuberculosis, contributing to high early mortality. The widespread availability of ART has considerably reduced opportunistic infections and improved survival, allowing a growing cohort of perinatally infected children to survive into adolescence. This changing natural history has, however, unmasked a rising burden of chronic, non-infectious pulmonary disease — including obstructive and restrictive lung function impairment — that had previously been under-recognised.[5]

Cohort studies from sub-Saharan Africa have documented lung function abnormalities in a substantial proportion of HIV-infected children and adolescents even while virologically controlled on ART, most commonly an obstructive pattern.[6,7,8] Adult studies have similarly linked HIV infection to both obstructive and restrictive impairment, with proposed mechanisms including recurrent subclinical pulmonary infection, chronic immune activation, and HIV-related airway inflammation.[9]

Data on lung function among HIV-infected children and adolescents from India, and South Asia more broadly, remain scarce, and no comparable spirometric data were previously available from eastern India. Simple office spirometry could serve as a useful, low-cost screening tool to detect early pulmonary impairment in this growing population of long-term survivors. This study was therefore undertaken to determine the pattern and prevalence of pulmonary function impairment among HIV-infected children and adolescents attending an ART centre in Kolkata, and to examine its association with sociodemographic, clinical, and immunological parameters.

MATERIALS AND METHODS

This cross-sectional, observational, single-centre study was conducted at the ART centre of a tertiary teaching hospital's Department of Paediatric Medicine in Kolkata, India, over one year (January–December 2019). HIV-infected children and adolescents attending the ART centre were enrolled by consecutive sampling. Inclusion criteria were confirmed HIV infection; age 10–18 years, either sex; and receipt of ART for a minimum of six months. Individuals who smoked, had known heart disease, or had any acute or chronic lung disease (e.g., tuberculosis, Pneumocystis pneumonia) evident on history, examination, or chest radiography were excluded. Assuming an expected prevalence of pulmonary function impairment of 8%, 80% power, and a permissible error of 0.1, the minimum calculated sample size was 30 (n = 4pq/d2); 30 patients were accordingly enrolled.

Written informed consent was obtained from parents/guardians, with assent from participating children and adolescents, in accordance with the Declaration of Helsinki. The study was approved by the Institutional Ethics Committee [name/number/date to be inserted].

A detailed history and clinical examination were performed for each participant, and WHO clinical staging (I–IV) was assigned.3 Height and weight were measured and body mass index (BMI) calculated. CD4 T-lymphocyte count was estimated by flow cytometry and CD4 percentage calculated; participants were categorised by age-specific CD4 cut-offs into WHO immunological stages (not significant, mild, advanced, severe).3 Haemoglobin was estimated from venous blood samples.

Spirometry was performed using an ultrasonic flow-sensor spirometer (EasyOn-PC; ndd Medizintechnik AG, Zurich, Switzerland), following standard acceptability and reproducibility criteria, with a minimum of three technically acceptable manoeuvres and the best of three trials taken for analysis.[10] FVC, FEV1, FEV1/FVC ratio, and FEF25–75% were expressed as percentage of predicted values adjusted for age, sex, height, and race. Cases were classified as normal, obstructive, or restrictive based on standard criteria: an obstructive pattern was defined as FEV1 <80% predicted with FEV1/FVC <90% predicted and normal or reduced FVC; a restrictive pattern was defined as FVC <80% predicted with FEV1/FVC ≥90% predicted and normal or reduced FEV1; and a normal pattern was defined as FEV1, FVC, and FEV1/FVC all within predicted limits.

Data were analysed using SPSS version 27.0 (IBM Corp., Chicago, IL, USA) and GraphPad Prism version 5. Continuous variables are expressed as mean ± standard deviation and compared across pattern groups using one-way ANOVA; categorical variables are expressed as frequency and percentage and compared using the chi-square test or Fisher's exact test, as appropriate. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

Table 1. Baseline demographic, clinical, and immunological characteristics of the study population (n=30)

Characteristic	n (%) / Mean (± SD)
Age group (years)	
10–13	27 (90.0)
14–18	3 (10.0)
Sex	
Male	17 (56.7)
Female	13 (43.3)
Religion	
Hindu	22 (73.3)
Muslim	8 (26.7)
Area of residence	
Rural	17 (56.7)
Urban	13 (43.3)
Mode of HIV acquisition	
Vertical transmission	26 (86.6)
Blood transfusion	4 (13.4)

History of passive smoking	13 (43.3)
History of allergy	8 (26.7)
History of MDI use	4 (13.3)
WHO clinical stage	
I	18 (60.0)
II	7 (23.3)
III	5 (16.7)
CD4 immunological stage	
I	18 (60.0)
II	10 (33.3)
III	2 (6.7)
Mean height, cm (± SD)	136.43 (± 9.79)
Mean weight, kg (± SD)	32.13 (± 6.33)
Mean BMI, kg/m2 (± SD)	17.12 (± 2.03)
Mean haemoglobin, g/dL (± SD)	10.73 (± 0.97)
Mean CD4 count, cells/mm3 (± SD)	747.03 (± 339.89)
Duration of ART	All ≥ 5 years

BMI = body mass index; ART = antiretroviral therapy; MDI = metered-dose inhaler; WHO = World Health Organization; SD = standard deviation.

Table 2a. Distribution of pattern of pulmonary function impairment

Pattern of pulmonary function	n	Percentage
Normal	20	66.7
Restrictive	7	23.3
Obstructive	3	10.0
Total	30	100.0

Table 2b. Mean percentage predicted spirometry parameters

Spirometry parameter (% predicted)	Mean	± SD
FVC %	86.57	18.02
FEV1 %	80.77	18.32
FEV1/FVC %	93.77	10.60
FEF25–75 %	84.67	20.77

FVC = forced vital capacity; FEV1 = forced expiratory volume in one second; FEF25–75 = forced expiratory flow at 25–75% of FVC; SD = standard deviation.

Table 3. Univariate association between sociodemographic, clinical, and immunological variables and pattern of pulmonary function impairment

Variable	Test used	p value	Significance
Area of residence (rural vs urban)	$\chi 2$	0.685	NS
Sex	$\chi 2$	0.930	NS
History of passive smoking	$\chi 2$	0.930	NS
History of allergy	$\chi 2$	0.947	NS
History of MDI use	$\chi 2$	0.539	NS
CD4 immunological stage	$\chi 2$	0.001	**S**
WHO clinical stage	$\chi 2$	0.003	**S**
Mean BMI	ANOVA	0.051	NS
Mean haemoglobin	ANOVA	0.006	**S**
Mean CD4 count	ANOVA	<0.001	**S**
Mean age at diagnosis of HIV	ANOVA	0.345	NS
Mean duration of ART	ANOVA	0.259	NS

$\chi 2$ = Chi-square test; ANOVA = one-way analysis of variance; NS = not significant ($p \geq 0.05$); S = statistically significant ($p < 0.05$); BMI = body mass index; MDI = metered-dose inhaler; ART = antiretroviral therapy.

Table 4. Mean CD4 count, haemoglobin, and BMI according to pattern of pulmonary function impairment

Parameter (Mean ± SD)	Normal (n=20)	Obstructive (n=3)	Restrictive (n=7)	p
CD4 count (cells/mm3)	901.20 ± 297.75	576.00 ± 231.88	379.86 ± 92.50	<0.001
Haemoglobin (g/dL)	11.04 ± 0.88	10.93 ± 1.12	9.76 ± 0.46	0.006
BMI (kg/m2)	17.10 ± 1.55	20.67 ± 0.55	15.67 ± 1.89	0.051

BMI = body mass index; SD = standard deviation.

Thirty HIV-infected children and adolescents aged 10–18 years were enrolled, comprising 17 males (56.7%) and 13 females (43.3%). Twenty-two participants (73.3%) were Hindu and 8 (26.7%) Muslim; 17 (56.7%) resided in rural areas and 13 (43.3%) in urban areas. The majority (86.6%) had acquired HIV infection through vertical transmission, and the remainder (13.4%) through blood transfusion. Thirteen participants (43.3%) had a history of passive smoke exposure, 8 (26.7%) a history of allergy, and 4 (13.3%) a history of metered-dose inhaler (MDI) use. All participants had been on ART for a minimum of five years at the time of assessment. Baseline characteristics are summarised in Table 1.

Eighteen participants (60.0%) were in CD4 immunological stage I, 10 (33.3%) in stage II, and 2 (6.7%) in stage III; correspondingly, 18 (60.0%) were in WHO clinical stage I, 7 (23.3%) in stage II, and 5 (16.7%) in stage III. Mean CD4 count was 747.03 ± 339.89 cells/mm3 and mean haemoglobin was 10.73 ± 0.97 g/dL. Mean height, weight, and BMI were 136.43 ± 9.79 cm, 32.13 ± 6.33 kg, and 17.12 ± 2.03 kg/m2, respectively.

On spirometry, 20 participants (66.7%) had a normal pattern, 7 (23.3%) a restrictive pattern, and 3 (10.0%) an obstructive pattern. Mean percentage predicted FVC, FEV1, FEV1/FVC, and FEF25–75% were 86.57 ± 18.02, 80.77 ± 18.32, 93.77 ± 10.60, and 84.67 ± 20.77, respectively (Table 2).

On univariate analysis (Table 3), the pattern of pulmonary function impairment showed no significant association with area of residence, sex, history of passive smoking, history of allergy, history of MDI use, BMI, age at diagnosis of HIV, or duration of ART (all p>0.05). In contrast, pattern of impairment was significantly associated with CD4 immunological stage (p=0.001) and WHO clinical stage (p=0.003): 85.0% of participants with CD4 stage I disease had normal lung function, compared with 30.0% of those with stage II and none with stage III disease; similarly, 80.0% of those with WHO clinical stage I disease had normal lung function, compared with 42.9% of stage II and 20.0% of stage III participants.

Mean CD4 count and mean haemoglobin also differed significantly across pattern groups (Table 4). Mean CD4 count was 901.20 ± 297.75 cells/mm3 in the normal group, 576.00 ± 231.88 cells/mm3 in the obstructive group, and 379.86 ± 92.50 cells/mm3 in the restrictive group (p<0.001). Mean haemoglobin was 11.04 ± 0.88, 10.93 ± 1.12, and 9.76 ± 0.46 g/dL in the normal, obstructive, and restrictive groups, respectively (p=0.006). Mean BMI did not differ significantly across groups (17.10 ± 1.55, 20.67 ± 0.55, and 15.67 ± 1.89 kg/m2, respectively; p=0.051).

DISCUSSION

This cross-sectional study found that nearly one-third of HIV-infected children and adolescents on long-term ART had impaired lung function — 23.3% restrictive and 10.0% obstructive — despite being clinically stable and on treatment. This predominance of a restrictive rather than obstructive pattern is consistent with the only comparable Indian data available, from Kumar and Premdeep, who reported restrictive lung disease in 12 of 20 HIV-infected children and no obstructive disease.[11] This contrasts with most reports from sub-Saharan Africa, where obstructive lung disease has predominated: Githinji et al., studying 515 HIV-infected South African adolescents, reported obstructive disease in 10% and restrictive disease in only around 1%,[7] while Mwalukomo et al., in 145 Malawian adolescents, reported obstructive disease in 18%.[8] The mean percentage predicted FVC, FEV1, and FEV1/FVC in the present study were, however, closely comparable to those reported by Githinji et al. (FEV1 87 ± 17%, FVC 87 ± 16%, FEV1/FVC 89 ± 8.7% in their HIV-infected cohort),[7] suggesting broadly similar overall severity of impairment despite the difference in predominant pattern.

More severe impairment has been reported from Zimbabwe and Malawi, where 45% and 18% of adolescents respectively had reduced FEV1 or obstructive disease; [6,8] in contrast, only 10% of the present cohort had obstructive impairment, and all participants were on ART. This relatively preserved lung function may reflect long-term ART use with good adherence, and a low prevalence of prior severe opportunistic pulmonary infection in this cohort — a recognised driver of HIV-related chronic airway inflammation.[9]

Anthropometric parameters (height, weight, BMI) showed no significant association with lung function pattern, nor did area of residence or passive smoke exposure, in agreement with earlier paediatric HIV cohorts; this may reflect the relatively low intensity and under-reporting of smoke exposure among adolescents compared with adults.[6] History of

allergy and MDI use were similarly not associated with lung function pattern in this cohort, although the small sample size limits the ability to exclude such an association.

A key finding was the strong, statistically significant association between declining CD4 count/advancing CD4 immunological stage and pulmonary function impairment (p=0.001 and p<0.001, respectively), and between advancing WHO clinical stage and impairment (p=0.003). Only 30% of participants with CD4 stage II and none with stage III disease had normal spirometry, compared with 85% of those with stage I disease. This is consistent with earlier reports linking advanced immunosuppression to pulmonary dysfunction: Rosen et al. found reduced diffusion capacity in patients with CD4 counts <200 cells/mm3,[12] and Nieman et al. reported that reduced diffusion capacity independently predicted faster progression to AIDS.[13] These findings collectively support CD4 status and WHO clinical stage as useful clinical markers of pulmonary risk in this population.

Lower mean haemoglobin was also significantly associated with impaired lung function (p=0.006), paralleling a previous report from Zambia in which low haemoglobin independently predicted mortality in HIV-infected children.[14] Whether anaemia is a marker of more advanced disease, a direct contributor to functional respiratory impairment, or both, cannot be determined from a cross-sectional design.

Some studies have reported a higher incidence of asthma among HIV-infected children on ART,[15,16,17] but this study found no association between duration of ART and lung function pattern — consistent with a South African cohort in which neither use nor duration of ART was associated with abnormal spirometry.[18] The absence of an ART-naive comparator group in this study, however, precludes any firm conclusion regarding a causal role of ART itself.

This study has several limitations. Its cross-sectional design allowed evaluation only at a single time point, without longitudinal follow-up. The sample size was small (n=30) and no HIV-uninfected or ART-naive comparator group was included, limiting causal inference. HIV viral load was not measured, which would have strengthened correlation with immunological and functional status.

CONCLUSION

In conclusion, despite being on long-term antiretroviral therapy, nearly one-third of HIV-infected children and adolescents in this cohort had impaired lung function, predominantly restrictive in pattern. Advancing CD4 immunological stage, advancing WHO clinical stage, lower CD4 count, and lower haemoglobin were significantly associated with pulmonary function impairment, underscoring that lung function may deteriorate with progression of HIV disease even in the ART era. Routine, low-cost spirometric screening may help identify early pulmonary impairment in HIV-infected children and adolescents, particularly those with advancing immunosuppression or anaemia, allowing timely evaluation and intervention.

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Author Contributions

[Insert per ICMJE criteria, e.g.: AB — concept and design, data acquisition, analysis and interpretation, drafting the manuscript; KD — concept and design, supervision, critical revision for important intellectual content; SB — supervision, critical revision for important intellectual content. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.]

Conflict of Interest

The authors declare that they have no conflict of interest. [confirm before submission]

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