Bronchiectasis and other chronic lung diseases in adolescents living with HIV

Engi F Attia[1], Robert F Miller [2,3], Rashida A Ferrand[3,4]

[1] Pulmonary and Critical Care Medicine, University of Washington, Seattle, WA, USA
[2] Research Department of Infection and Population Health, University College London, London, UK
[3] Clinical Research Department, London School of Hygiene & Tropical Medicine, London, UK
[4] Biomedical Research & Training Institute, Harare, Zimbabwe

Corresponding Author:
Dr Rashida Ferrand,
Clinical Research Department,
London School of Hygiene & Tropical Medicine,
Keppel Street,
London WC1E 7HT, UK

Tel: +44 207 927 2577
Email: rashida.ferrand@lshtm.ac.uk

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Abstract

Purpose of review: The incidence of pulmonary infections has declined dramatically with improved access to antiretroviral therapy (ART) and co-trimoxazole prophylaxis, but chronic lung disease (CLD) is an increasingly recognized but poorly understood complication in adolescents with perinatally-acquired HIV.

Recent findings: There is a high prevalence of chronic respiratory symptoms, abnormal spirometry and chest radiographic abnormalities among HIV-infected adolescents in sub-Saharan Africa, where 90% of the world's HIV-infected children live. The incidence of lymphocytic interstitial pneumonitis, the most common cause of CLD in the pre-ART era, has declined with increased ART access. Small airways disease, particularly constrictive obliterative bronchiolitis and bronchiectasis are emerging as leading causes of CLD among HIV-infected adolescents in low- and middle-income countries. Asthma may be more common in high-income settings. Likely risk factors for CLD include recurrent pulmonary infections, air pollution, HIV-related immune dysfunction and untreated HIV infection, particularly during critical stages of lung development.

Summary: Globally, the importance of HIV-associated CLD as a cause of morbidity and mortality is increasing, especially as survival has improved dramatically with ART and growing numbers of children living with HIV enter adolescence. Further research is urgently needed to elucidate the natural history and pathogenesis of CLD, and to determine optimal screening, diagnostic and treatment strategies.

Introduction

Of the estimated 3.4 million children living with HIV globally, 90% live in sub-Saharan Africa [1]. Although the number of children born with HIV is declining due to scale-up of prevention of mother-to-child transmission (PMTCT) programmes, growing numbers of HIV-infected children are surviving to adolescence due to the widespread roll-out of antiretroviral therapy (ART) [2]. In addition, approximately one-third of HIV-infected infants survive to adolescence in the absence of ART, and children infected a decade ago when PMTCT programmes and early infant diagnosis were not available, are now presenting to health services in large numbers for the first time in older childhood and adolescence [3]. Consequently, the burden of paediatric HIV is shifting toward adolescents [2].

While the incidence of acute pulmonary infections in HIV is declining due to the use of co-trimoxazole prophylaxis and ART [4-6,7**], chronic lung disease (CLD) is emerging as an important, but incompletely understood, complication among older children and adolescents living with HIV [8*]. In particular, adolescents with delayed diagnosis of perinatally-acquired HIV have a disproportionately high burden of chronic respiratory disease [8*,9*,10*,11*]. We review the spectrum of and risk factors for HIV-associated CLD among adolescents living with HIV, as well as considerations in diagnosis and management.

Spectrum of chronic lung disease

Recent studies from sub-Saharan Africa highlight a substantial burden of chronic respiratory symptoms and poor lung function among HIV-infected adolescents. Over half of older children and adolescents reported at least one chronic respiratory symptom in recent studies from Zimbabwe, Malawi and Kenya [8*,10*,11*,12*,13*,14*]. Chronic cough and sputum production were reported by 21-60% and breathlessness by 12-18%, but wheezing was uncommon [8*,10*,11*,12*,13*,14*,15*]. The prevalence of tachypnoea is difficult to quantify as definitions vary between studies, but elevated respiratory rates are common [8*,9*,10*,11*, 15*]. Hypoxia after sub-maximal exercise was a striking finding among 12-38% [10*,11*,12*,13*,15*,16*]. One-third of adolescents had abnormal spirometry: forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were lower among those with HIV, compared to age-, sex-, race- and height-adjusted predicted values, and compared to HIV-uninfected controls [8*,15*,17]. While some studies documented a substantial prevalence of airflow

obstruction [10*,11*,12*], others reported a prominence of a restricted pattern [11*,13*,14*]; there was little reversibility with bronchodilators. One study additionally measured lung volumes, compliance and transfer factor for carbon monoxide, finding that each was lower among HIV-infected compared to uninfected participants [18**]. A recent study from the USA also showed a high prevalence of poorly reversible airflow obstruction [19*]. Taken together, these studies suggest that CLD may be more common among HIV-infected adolescents than previously appreciated (Table 1).

The term CLD comprises a spectrum of lung diseases whose prevalence varies between LMICs and high-income countries. The pathogenesis is multifactorial, but HIV-related immune dysfunction is likely important.

Bronchiectasis

Bronchiectasis is a well-recognized and irreversible cause of CLD among HIV-infected children and adolescents [20]. The bronchial architecture is distorted with bronchial diameter enlargement relative to the adjacent pulmonary artery, which appears as a "ring" or "tramline" pattern on chest radiography [21*,22*]. A study from the USA in the pre-ART era reported that 6% of 749 HIV-infected children without pre-existing lung disease developed radiographically or histologically determined bronchiectasis during an average of six years of follow-up [23]. In contrast, in two recent studies conducted in Zimbabwe and Malawi among older children and adolescents with perinatally-acquired HIV, one-half had chest radiographic features consistent with bronchiectasis [8*,11*]. Two-thirds of children in the African studies were on ART for at least a median duration of 20 months and had median CD4 >350 cells/μL. The lower prevalence of bronchiectasis in the USA study despite unavailability of ART was probably due to earlier engagement with healthcare services, prompt treatment of infections and greater attention to maintaining adequate nutrition.

Multiple insults can result in bronchiectasis, including recurrent pulmonary infections, chronic aspiration, and congenital or acquired immunodeficiency syndromes [17,20,21*,22*,23,24]. HIV is associated with an increased risk of tuberculosis, and recurrent viral and bacterial pulmonary infections [7**,17,23,24,25*,26]. However, some data suggest that HIV predisposes to bronchiectasis independently of infection, likely due to HIV-mediated defects in innate immunity and accompanying airway neutrophilic inflammation [17,21*,22*,27].

Bronchiectasis in adolescents can also occur as a late complication of lymphocytic interstitial pneumonitis (LIP) [24]. Bronchiectasis accounts for a substantial proportion of chronic respiratory symptoms, reduced quality of life and risk of premature death [22*].

Constrictive obliterative bronchiolitis

In 2012, Ferrand and colleagues first reported a high prevalence of chronic respiratory symptoms among perinatally HIV-infected children diagnosed in adolescence, nearly three-quarters of whom were taking ART [8*]. This was the first study to perform high-resolution computed tomography (HRCT) in this context. Among the 56 adolescents with chronic respiratory symptoms, the most common HRCT finding was a mosaic pattern of decreased attenuation in 55% (Figure 1). Decreased attenuation was associated with reduced FEV_1 and chronic cough [16*]. Together with hypoxia and irreversible airflow obstruction, these findings are consistent with constrictive obliterative bronchiolitis (cOB). This was the first study to demonstrate cOB as a major cause of CLD. To our knowledge, there are no reports of HIV-associated cOB among adolescents in high-income settings, although the findings by Shearer and colleagues could partly be explained by small airways disease [19*]. Due to the cross-sectional nature of these data, however, it is not possible to determine whether findings reflect abnormalities persisting from insults during childhood or recent-onset disease [28*].

The pathogenesis and natural history of cOB among HIV-infected adolescents is not well understood. This rare, usually progressive, and fibrotic and inflammatory condition involves the small airways involved in gas exchange, namely the terminal and respiratory bronchioles, but spares the lung parenchyma [29]. These bronchiolar lesions are patchy and may be missed on transbronchial biopsy. Clinically, cOB presents with progressive dyspnea and cough over weeks to months, and hypoxia may be detected in severe cases. The predominant diagnostic features of cOB are poorly reversible airflow obstruction, a mosaic pattern of decreased attenuation on HRCT, and air trapping on pulmonary function testing and/or expiratory HRCT images (Figure 1). Chest radiographs are often normal, or may demonstrate only hyperinflation, until cOB is advanced. It has been mainly described in lung and stem cell transplant patients with chronic rejection and graft-versus-host disease, and as a sequela of community-acquired respiratory viral infections (i.e., influenza, parainfluenza, adenovirus, respiratory syncytial virus) and cytomegalovirus infection. It is very rarely reported among HIV-uninfected children after community-acquired respiratory viral infections. The high incidence of viral infections among children and adolescents with HIV may play an important

role in development of cOB, particularly in those with delayed diagnosis and treatment of HIV [25*]. Additionally, decreased attenuation was strongly correlated with bronchiectasis and bronchial wall thickening and dilatation on HRCT [8*], suggesting a continuum of pathological processes that links small and large airways involvement. Although disease course and prognosis of cOB are not known among HIV-infected adolescents, in other populations, cOB responds poorly to therapy and is associated with a high risk of mortality over months to years.

Lymphocytic interstitial pneumonitis

Globally, LIP was the most common cause of CLD among HIV-infected children during the pre-ART era [20,30,31]. It is generally responsive to ART, although severe LIP may require adjunct corticosteroid therapy. The overall incidence of LIP has declined dramatically with the scale-up of ART, and in recent studies, LIP appears to be uncommon among older children and adolescents with HIV. A review of chest radiographic findings in HIV-infected children and adolescents reported that pulmonary tuberculosis and LIP accounted for 70% and 15% of cases, respectively [32*]. However, three-quarters of included studies were conducted during the pre- and early ART era or in ART-naïve individuals. In two recent studies of generally ART-experienced HIV-infected adolescents from Zimbabwe, HRCT was strongly suggestive of LIP in <3% [8*,16*].

Asthma

Conflicting data suggest that asthma risk may be higher among HIV-infected compared with HIV-uninfected children and adolescents, especially in high-income settings [33,34]. Among 1201 HIV-infected adolescents living in the USA, of whom 87% were perinatally-infected and 85% were taking ART, asthma was a common comorbid condition with an incidence of 1.2/100 person-years [35**]. In a study of Thai children with perinatally-acquired HIV, early initiation of ART was associated with higher CD4, and the prevalence of asthma (27%) exceeded that of uninfected Thai children (18%) [36*]. Asthma tended to be more common among individuals with preserved immune function, and may be linked to immune reconstitution [36*,37-39]. However, the prevalence may have been overestimated in these studies, as diagnosis was based on self-report, diagnostic codes or prescription of asthma-related medications. In a study that performed spirometry in 216 perinatally HIV-infected adolescents in the USA, only 30% of those with airflow obstruction had bronchodilator reversibility (overall, 9% of those with interpretable spirometry) [19*]. In Zimbabwe, 3-5% of older children and adolescents with perinatally-acquired HIV reported a history of asthma [13*,15*], similar to the prevalence estimated in the general African paediatric population [40]. Reversibility

with bronchodilators was uncommon in African studies reporting airflow obstruction among HIV-infected adolescents, with the exception of one South African study in which 15% had reversibility [10*,11*,12*,13*,18**]. While asthma prevalence may be underestimated in LMICs where few systematic surveys have been completed, it is plausible that incidence is low, but could increase with industrialization, as observed in South Africa.

Pulmonary hypertension

HIV-related pulmonary arterial hypertension is rare with an estimated prevalence of 0.5% among adults in high-income countries; however, small studies from sub-Saharan Africa suggest a prevalence of 5-13% [41,42*]. Pulmonary hypertension is rarely described in HIV-infected children and adolescents [43]. A study in Zimbabwe reported that 4% of perinatally HIV-infected adolescents had elevated estimated pulmonary artery systolic pressure (>30 mmHg) on echocardiography [44]. Overall, 30% had right ventricular dilatation, and 24% had concurrent impaired left ventricular function. In another study, 28% of HIV-infected children and adolescents had right ventricular dilatation, and two-thirds had concomitant left heart abnormalities [45*]. Pulmonary hypertension prevalence, however, remains uncertain as echocardiography may over- or underestimate prevalence [46], and use of pulmonary angiography, the diagnostic gold standard, is limited in LMICs. HIV-related pulmonary hypertension in adolescents may be multifactorial as a sequela of HIV itself or secondary to HIV-associated immune dysfunction and/or cardiopulmonary disease [42,47].

Risk factors for HIV-associated chronic lung disease among adolescents

The burden of CLD among HIV-infected adolescents appears to be greater in LMICs. This may be due to a higher prevalence of risk factors, including pulmonary infections, household air pollution, malnutrition and stunting [1,7**,48]. Additionally, in contrast with high-income settings where the majority of HIV-infected children initiate ART in infancy, a substantial proportion of children are diagnosed with HIV and initiate ART in later childhood. Among adolescents with delayed diagnosis of perinatally-acquired HIV in sub-Saharan Africa, older age and low FEV_1 and FVC *z*-scores appear to be associated [9*,11*,13*,15*]. This might reflect accumulation of insults over time and survivor bias. Multiple risk factors may interact to predispose to CLD (Figure 2).

Pulmonary infections

Pulmonary pathogens can trigger local inflammation, resulting in scarring and destruction of lung tissue [49]. Pulmonary infections, including *Pneumocystis jirovecii* pneumonia (PCP), bacterial pneumonia, and tuberculosis are associated with permanent lung function abnormalities among HIV-infected adults [50,51]. Recurrent and severe pulmonary infections early in life are also associated with impaired lung function, and these early impairments may track through later life [52*,53]. Increasing availability of ART and co-trimoxazole have resulted in a decline in the incidence of bacterial pneumonia, pulmonary tuberculosis, and PCP [54,55]. In LMICs, pulmonary infections remain common despite decreases in incidence, and risk of pulmonary infections is particularly high among those with delayed diagnosis and treatment of HIV [26,56*].

HIV infection, systemic immune activation and chronic inflammation

HIV infection is associated with systemic immune activation and chronic inflammation [57-59]. This is driven by translocation of microbial products, including lipopolysaccharide, into the systemic circulation through a gastrointestinal mucosa made "leaky" as a result of HIV HIV-mediated inflammation of gut lymphoid tissue [59-61]. The resultant immune dysregulation is associated with end-organ damage [58,62-64], and may be important mechanistically in CLD development. HIV itself is an independent risk factor for COPD among adults [6,65,66]. Preliminary data suggest that HIV is also independently associated with CLD in children and adolescents [12*,15*,18**]. Infancy and early childhood are critical periods for organ and immune system development. HIV-mediated immune dysregulation may place children at high risk of lung damage, particularly those with untreated HIV, and recurrent pulmonary infections may further accelerate lung function decline. These pathophysiological mechanisms may partly explain why adolescents in LMICs, where HIV diagnosis and ART initiation are often delayed [67*,68], have a higher prevalence of CLD.

While ART reduces markers of inflammation, residual systemic immune activation and chronic inflammation persist [61,69]. The impact of ART on the course of CLD remains unclear. An African study reported a lower prevalence of cough, breathlessness and hypoxia, but no difference in lung function among HIV-infected adolescents who had received ART for a median of five years compared to an age-matched

group of ART-naïve adolescents [14*]. Among HIV-infected Kenyan adolescents and adults, perinatally-acquired HIV and nadir CD4 <200 cells/μL were associated with airflow obstruction despite near universal ART use [12*]. Additionally, in Zimbabwe and South Africa, adolescents with HIV had significantly decreased FEV_1 and FVC *z*-scores, lung volumes, and compliance compared to uninfected peers, despite a greater than six-year median duration of ART use [15*,18**].

Tobacco smoke and air pollution

Exposure to tobacco smoke, both prenatally and during infancy, is associated with impaired lung function in one year olds [52*]. Cigarette smoking is a recognized risk factor for chronic obstructive pulmonary disease (COPD) and lung function decline among adults. Levels of cigarette smoking are increasing among adolescents, particularly in LMICs [70]. Therefore, tobacco smoke exposure will likely become an increasingly important contributor to development of CLD.

Exposure to household air pollution during early life has been associated with mortality and pulmonary infections, which in turn may impair lung function [48,71*,72]. Strong evidence also supports the association between household air pollution and CLD, including COPD in adults and wheezing in children [48]. To date, no studies have demonstrated a link between household air pollution and CLD among HIV-infected adolescents, likely due to confounding by other exposures and difficulties in measuring exposures.

Malnutrition and stunted growth

Both malnutrition and stunting are common among children and adolescents living with HIV in LMICs, with prevalence estimated as high as 42% and 73%, respectively [10*,73-76]. Malnutrition during the first year of life is associated with decreased lung function at one year of age [52*]. In a Kenyan study, stunting was associated with tachypnoea among HIV-infected adolescents [9*]. Stunting is a marker of delayed somatic growth; therefore, stunted children are likely to have smaller lungs [77*], which may subsequently predispose to CLD.

Assessment and management of chronic lung disease

Awareness of the burden and spectrum of HIV-associated CLD is limited. Several studies have proposed criteria for defining CLD in children and adolescents [8*,11*,56*], but a sensitive and specific clinical algorithm has not been established. Chest radiographic abnormalities are nonspecific for many CLD subtypes and may be visible only in late stages of disease. Availability of diagnostic modalities such as spirometry and HRCT is limited in LMICs.

In the absence of appropriate diagnostics, chronic respiratory symptoms are frequently empirically treated with repeated courses of antibiotics and anti-tuberculosis therapy in high HIV prevalence settings where tuberculosis is common [8*,15*,17]. The pathogenesis of CLD is poorly understood, and there are no specific management guidelines. However, prevention of pulmonary infections by ensuring routine vaccinations, early ART initiation and continued co-trimoxazole use may mitigate the burden of CLD among HIV-infected adolescents [78].

Future directions

Prospective studies to understand the natural history, pathology and pathogenesis of CLD in HIV-infected adolescents are needed. Standardization of the definition of CLD and of data collection/measurement will allow for comparability across studies and merging of data to achieve greater power to detect associations. Additionally, locally-derived references for defining abnormal lung function in children are needed in LMICs. The 2016 WHO HIV guidelines recommend treatment of all individuals regardless of age or immune status, which should facilitate earlier ART initiation. However, once established, CLD does not appear to be completely reversed by ART. Screening algorithms for CLD for children and adolescents need to be developed, and interventions such as long-term macrolide therapy, prophylactic antibiotics, pulmonary rehabilitation and tobacco smoke avoidance/cessation programmes require evaluation.

Conclusion

Recent studies demonstrate a high burden of CLD and its manifestations among HIV-infected older children and adolescents, particularly in LMICs. CLD represents a spectrum of conditions with overlapping risk factors and pathogenic mechanisms. As greater numbers of HIV-

infected children survive to adolescence, the prevalence of CLD in this age-group is likely to increase. Further research is urgently needed to develop optimal diagnostic and therapeutic strategies so as to avoid compromising the substantial gains in mortality accomplished with ART among HIV-infected children.

Key points

1. Chronic lung disease is increasingly recognized as a complication among older children and adolescents with perinatally-acquired HIV.

2. The burden of chronic lung disease disproportionally affects those living in LMICs.

3. The most common causes of chronic lung disease appear to be large and small airways disease, which may be poorly responsive to antiretroviral therapy once established

4. The prevalence and incidence of lymphocytic interstitial pneumoniitis appear to have decreased dramatically with the global scale-up of antiretroviral therapy.

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Conflicts of interest

Dr Miller is a panel member for Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents (Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America) and has received honoraria from Gilead, ViiV, Merck, and Janssen for non-promotional lectures on clinical aspects of HIV infection. For the remaining authors, none were declared.

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resource-limited setting and compare these findings in HIV-uninfected, age-, sex-, and ethnicity-matched controls. Despite an 8-year median duration of ART and current CD4 of 714 cells/mm^3, HIV-infected adolescents had significantly decreased lung volumes, airflow and compliance compared to HIV-uninfected comparators.

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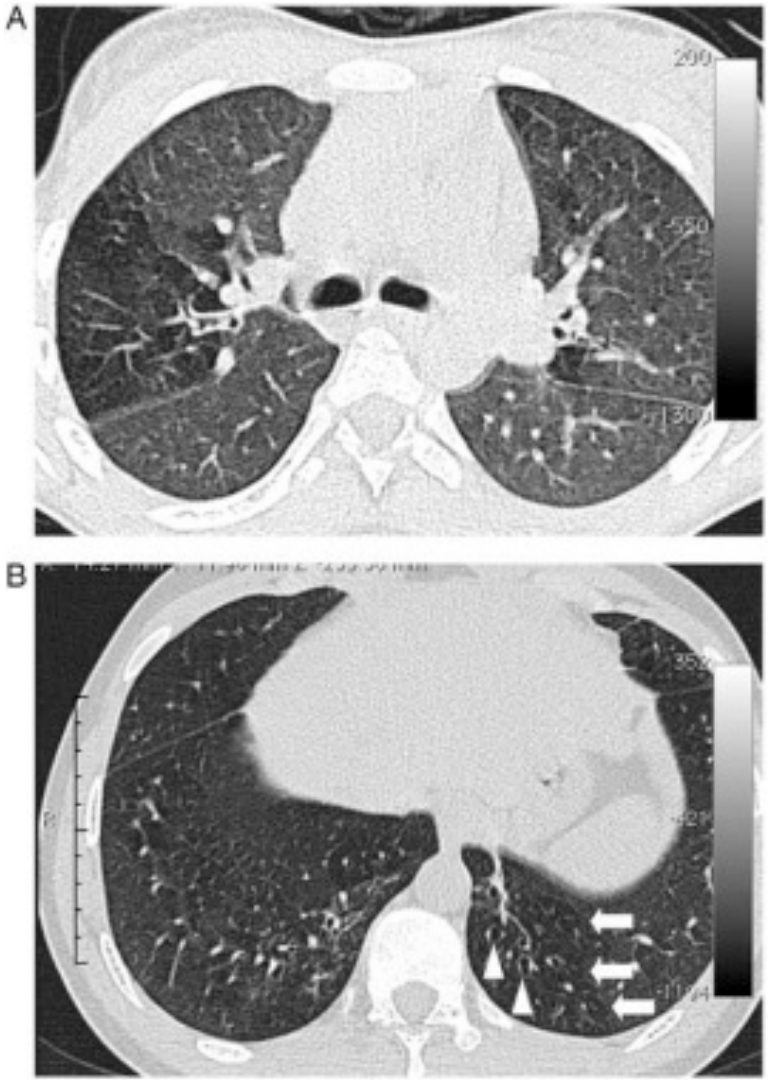
Study, year	Location, participant N	Characteristics of HIV-infected adolescents	Respiratory symptoms/signs	Abnormal spirometry
Ferrand, et al. [8*], 2012	Harare, Zimbabwe N=116	• Mean age: 14 ± 2.6 years • 43% male • Mean age at HIV diagnosis: 12 years • Perinatally-acquired HIV: 100% • 69% on ART for median duration of 2 years	• 66% chronic cough • 21% reduced exercise tolerance • 10% digital clubbing • 13% SaO_2 <92% at rest • 29% hypoxia after sub-maximal exercise • 28% respiratory rate >25 bpm	• OBSTRUCTED: 52/116 (45%) based on FEV_1 <80% predicted – Predicted values based on age-, sex-, and height-adjusted standards in healthy Malawian schoolchildren
McHugh, et al. [10*], 2016	Harare, Zimbabwe N=385	• Median age: 11 [6-15] years • 48% male • Median age at HIV diagnosis: 11 years • Perinatally-acquired HIV: 95% • All ART-naïve	• 54% cough >1 month • 16% MRC dyspnoea score ≥2 • 14% SaO2 <88% • 10% with SaO2 <88% after sub-maximal exercise	• OBSTRUCTED: 23/238 (10%) had FEV_1 and FEV_1/FVC <1.64 SD below mean – 3 had bronchodilator reversibility • RESTRICTED: 43/238 (18%) had FVC <1.64 SD below mean and normal FEV_1/FVC
Mwalukomo, et al. [11*], 2016	Blantyre, Malawi N=160	• Median age: 11 [10-12] years • 50% male • Median age at HIV diagnosis: 8 years • Perinatally-acquired HIV: 56% • 74% on ART for median duration of 4 years	• 38% cough • 34% moderate/severe dyspnoea • 22% digital clubbing • 21% SaO_2 <92% • 36% respiratory rate >24 bpm	• OBSTRUCTED: 26/145 (18%) had FEV_1 and FEV_1/FVC <LLN using GLI 2012 equations • RESTRICTED: 29/145 (20%) had FVC <LLN and FEV_1/FVC ≥LLN using GLI 2012 equations • 15 of 55 with abnormal spirometry had bronchodilator reversibility, but overall median increase in FEV_1 only 3%
Attia, et al. [12*], 2015	Nairobi, Kenya N=55	• Median age: 13 [11-14] years • 54% male • Age at HIV diagnosis: Not reported • Perinatally-acquired HIV: 100% • 95% on ART	• 60% cough • 51% sputum production • 31% wheeze (self-reported) • 11% SaO_2 ≤92% • 38% SaO2 ≤92% after sub-maximal exercise	• OBSTRUCTED: – 10/55 (18%) pre-bronchodilator FEV_1/ FVC <0.7 – 8/55 (15%) post-bronchodilator FEV_1/FVC <0.7
Rylance S, et al. [14*], 2016	Harare, Zimbabwe N=385 ART-naïve and 202 ART-treated	• Median age: 11 [9-13] years • 45% male • Median age at HIV diagnosis: 11 years among ART-naïve *vs* 6 years among ART-treated • Perinatally-acquired HIV: 100% • Median duration of ART use: 6 years among ART-treated	ART-naïve compared to ART-treated: • Daily cough in 53 *vs* 15% • Dyspnoea in 12 *vs* 15% • Resting hypoxia in 14 *vs* 1% • Greater exercise limitation (walked 460 *vs* 770 m on shuttle walk testing)	ART-naïve compared to ART-treated: • Abnormal spirometry in 26 *vs* 24% • OBSTRUCTED: 24/262 (9%) *vs* 7/177 (4%) • RESTRICTED: 43/262 (16%) *vs* 36/177 (20%) – based on reduced FVC
Rylance J, et al. [15*], 2016	Harare, Zimbabwe N=202 HIV-	• Median age: 11 [9-13] years • 51% male • Median age at HIV diagnosis:	HIV-infected compared to HIV-uninfected: • Daily cough in 15 *vs* 1%	HIV-infected compared to HIV-uninfected: • OBSTRUCTED: 4/177 (4%) *vs* 1/130 (1%) • RESTRICTED: 36/177 (20%) *vs* 14/130 (11%)

	infected and 150 age-matched HIV-uninfected	6 years • Perinatally-acquired HIV: 99.5% • All HIV-infected receiving ART; ART initiated at a median age of 6 years	• Dyspnoea in 15 *vs* 0% • Sputum production in 10 *vs* 1% • Respiratory rate >25 bpm in 14 *vs* 6% • Greater exercise limitation (walked 771 *vs* 889 m on shuttle walk testing)	– based on reduced FVC • 11/31 (36%) *vs* 2/6 (33%) had bronchodilator reversibility (only those with abnormal spirometry were tested)
Githinji, et al. [18**], 2016	Cape Town, South Africa N=515 HIV-infected and 110 age-, sex-, ethnically-matched HIV-uninfected controls	• Mean age: 12 ± 1.6 years • 52% male • Age at HIV diagnosis: Not reported • Perinatally-acquired HIV: 100% • Median duration of ART use: 8 years	Not reported	<u>HIV-infected compared to HIV-uninfected</u>: • OBSTRUCTED: 44/515 (9%) among HIV-infected – FEV_1: 1.60 L in HIV-infected *vs* 1.86 L in HIV-uninfected • RESTRICTED: 75/515 (15%) among HIV-infected based on measured lung volumes – FVC: 1.80 L in HIV-infected *vs* 2.00 L in HIV-uninfected • 75/515 (15%) *vs* 9/110 (8%) had bronchodilator reversibility → Overall, HIV-infected had reduced lung function (i.e., lung volumes, airflow, compliance) compared to HIV-uninfected
Shearer, et al. [19*], 2015	United States (multiple sites) N=216 HIV-infected and 151 HIV-exposed uninfected	• Median age: 17 [14-19] years • 42% male • Age at HIV diagnosis: Not reported • Perinatally-acquired HIV: 100% • ART use: Not reported	Not reported	<u>HIV-infected compared to HIV-uninfected</u>: • OBSTRUCTED: 42/188 (22%) *vs* 28/132 (21%) had FEV_1 <80% <u>or</u> FEV_1/FVC <0.8 • RESTRICTED: 18/188 (10%) *vs* 17/132 (13%) had FVC <80% <u>and</u> FEV_1/FVC ≥0.8 • 17/188 (9%) *vs* 21/132 (17%) had bronchodilator reversibility – Predicted values calculated based on normative equations generated using values from healthy children in NHANES III



A, Image section at the level of the carina in a 15-year-old female. There is a clear zone of decreased attenuation in the right upper lobe (and, to a lesser extent, the left lung). In regions of decreased attenuation there is reduction in the caliber of pulmonary vessels; there was no bronchiectasis in this patient. B, Image section in a 19-year-old male through the lower zones demonstrating focal areas of decreased attenuation in both lungs (arrows) and bronchiectasis in the left lower lobe (arrowheads).

Figure 1: Aetio-pathogenesis of chronic lung disease in HIV-infected adolescents (+ Increases risk; - decreases risk)