

# Chronic Lung Disease in Adolescents With Delayed Diagnosis of Vertically Acquired HIV Infection

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(See the Editorial commentary by Gray, on pages 153–4.)

**Background.** Long-term survivors of vertically acquired human immunodeficiency virus (HIV) infection are reaching adolescence in large numbers in Africa and are at high risk of delayed diagnosis and chronic complications of untreated HIV infection. Chronic respiratory symptoms are more common than would be anticipated based on the HIV literature.

**Methods.** Consecutive adolescents with presumed vertically acquired HIV attending 2 HIV care clinics in Harare, Zimbabwe, were recruited and assessed with clinical history and examination, CD4 count, pulmonary function tests, Doppler echocardiography, and chest radiography (CXR). Those with suspected nontuberculous chronic lung disease (CLD) were scanned using high-resolution computed tomography (HRCT).

**Results.** Of 116 participants (43% male; mean age, 14 ± 2.6 years, mean age at HIV diagnosis, 12 years), 69% were receiving antiretroviral therapy. Chronic cough and reduced exercise tolerance were reported by 66% and 21% of participants, respectively; 41% reported multiple respiratory tract infections in the previous year, and 10% were clubbed. More than 40% had hypoxemia at rest (13%) or on exercise (29%), with pulmonary hypertension (mean pulmonary artery pressure >25 mm Hg) in 7%. Forced expiratory volume in 1 second (FEV<sub>1</sub>) was <80% predicted in 45%, and 47% had subtle CXR abnormalities. The predominant HRCT pattern was decreased attenuation as part of a mosaic attenuation pattern (31 of 56 [55%]), consistent with small airway disease and associated with bronchiectasis (Spearman correlation coefficient ( $r^2 = 0.8$ ) and reduced FEV<sub>1</sub> ( $r^2 = -0.26$ ).

**Conclusions.** Long-term survivors of vertically acquired HIV in Africa are at high risk of a previously undescribed small airway disease, with >40% of unselected adolescent clinic attendees meeting criteria for severe hypoxic CLD. This condition is not obvious at rest. Etiology, prognosis, and response to treatment are currently unknown.

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More than 90% of the estimated 2 million global pediatric human immunodeficiency virus (HIV) infections occur in sub-Saharan Africa, predominantly due to mother-to-child transmission [1]. Although untreated HIV infection in infants is associated with a high risk of rapid disease progression [2], up to one-third of HIV-infected infants are “slow progressors,” with an estimated median survival of a decade or more [3–5]. Two percent to 3% of all 10-year-olds living in Southern Africa may be HIV-infected long-term

survivors, the majority still undiagnosed [5, 6]. These estimated burdens reflect high regional HIV prevalence rates in pregnant women during the 1990s and lack of interventions to prevent mother-to-child transmission at that time.

Clinicians in sub-Saharan Africa have become familiar with the clinical manifestations of untreated slow progressors, who typically present in later childhood with pronounced stunting, severe immunosuppression, or chronic complications of untreated HIV [6]. The best-documented regional epidemic is in Zimbabwe, where 43% of 25 000 children attending HIV care clinics in 2008 were aged  $\geq 10$  years [7]. Recently diagnosed or still undiagnosed vertically acquired HIV is now the most common cause of admission to the hospital and the most common cause of in-hospital deaths among adolescents in the region [8]. Undocumented epidemics of similar magnitude are thought to affect neighboring countries.

The natural history of HIV infection in older children is less well defined than for infants or adults. Presentation with chronic cough is common and often leads to presumptive treatment for unconfirmed tuberculosis. Respiratory illness, frequently with a history suggestive of acute-on-chronic lung disease, was the most common cause of death among HIV-infected adolescents admitted to a hospital in Harare [8]. Among younger children, the most common cause of chronic lung disease (CLD) is lymphocytic interstitial pneumonitis (LIP), found in 30%–40% of HIV-infected untreated children [9]. LIP is associated with a slower progression of HIV infection and responds well to antiretroviral therapy (ART) [9, 10]. The cause of HIV-related CLD in older children and adolescents has not previously been investigated.

The aim of this study was to investigate the clinical features and morphologic characteristics of CLD in older children with vertically acquired HIV infection attending HIV care outpatient services in 2 public-sector hospitals in Harare, Zimbabwe.

## METHODS

### Study Participants

Consecutive patients aged 10–19 years attending 2 HIV care outpatient clinics at Parirenyatwa Hospital and Harare Central Hospital (Harare, Zimbabwe) were enrolled (maximum 8 per day for logistic ease). Exclusion criteria were horizontally acquired HIV infection, pregnancy, being too ill to participate (requiring immediate hospitalization), living outside Harare, and having pulmonary Kaposi sarcoma, recently diagnosed smear-positive tuberculosis, or acute respiratory tract infection.

### Clinical Data Collection

Interview data recorded the reasons for HIV testing, duration of ART, respiratory symptoms, and exercise tolerance (New York Heart Association [NYHA] scale [11]). Standard

respiratory examination and anthropometric assessment, including height, weight, and Tanner staging, were performed. All participants underwent CD4 count measurement (CyFlow counter, Partec GmbH), spirometry, Doppler echocardiography, and chest radiography (CXR); high-resolution computed tomography (HRCT) was performed if CLD was suspected. The World Health Organization (WHO) Adult Classification was used to stage HIV infection [12]. HIV infection was presumed to be vertically acquired if the following case definition was met: maternal and/or sibling death or known maternal HIV infection, plus no history of sexual debut or blood transfusion, and at least 2 of the following: frequent infections during early childhood, stunting, or pubertal delay [6].

### Pulmonary Function Tests

Oxygen saturation ( $O_2$  sat) and respiratory rate were measured at rest and after exercise (a 200-m brisk walk). Participants with a respiratory rate  $>25$  breaths/minute or  $O_2$  sat  $<92\%$  at rest were not exercised.

Spirometry was performed using a Microloop spirometer (Mk8, MicroMedical). Participants were actively encouraged during the maneuver verbally and with pictorial incentives to blow out maximally. A nose clip was used; 3 reproducible, technically adequate measurements were taken in the standing position, and the maximal values were recorded. At least 30 seconds were allowed between each maneuver.

### Laboratory Investigations

Participants with cough of any duration were asked to provide 2 sputum specimens. Bacterial pathogens were identified using standard techniques [13]. Concentrated decontaminated sputum specimens were examined using Auramine and Ziehl-Neelsen staining and cultured on Lowenstein-Jensen media, with positive mycobacterial cultures confirmed by genotyping using the Hain assay (Hain LifeScience GmbH).

### Radiologic Data

Participants with clinically suspected CLD or CXR abnormality (assessed locally) were invited to undergo HRCT scanning (Siemens Emotion 6). Those with suspected active mycobacterial disease were excluded. In separate sessions, CXR and HRCT scans were scored independently by 2 thoracic radiologists blinded to clinical data. CXR abnormalities were quantified using a previously developed scoring system [14]. HRCT abnormalities were categorized on the basis of patterns reflecting either airway pathology or parenchymal disease using standard definitions (see Supplementary Data) [15].

### Statistical Analysis

The  $z$  scores for height-for-age and weight-for-age were calculated using British Growth Reference Curves [16]. Scores of  $\leq 2$  were considered to represent stunting and wasting,

respectively. Predicted spirometric indices were calculated using age-, sex-, and height-adjusted standards in healthy Malawian schoolchildren [17]. Quantitative interrelationships were examined using Spearman rank correlation coefficient: HRCT lobar scores were summed to provide global HRCT scores for specific variables. Interobserver variation for HRCT and CXR abnormalities with a prevalence of  $\geq 15\%$  was examined using the kappa ( $\kappa$ ) coefficient of agreement.

### Clinical Case Definitions

#### Acute Respiratory Tract Infection

Acute onset of respiratory tract infection ( $< 2$  weeks) was defined as the presence of  $\geq 2$  of the following: fever, cough, purulent sputum, and clinical response to antibiotics (amoxicillin and/or erythromycin).

#### Tuberculosis

Definite tuberculosis was defined as a positive, genotype-confirmed culture for *Mycobacterium tuberculosis*; probable active mycobacterial disease was defined as 2 sputum smears positive for acid-fast bacilli on Ziehl-Neelsen staining without culture confirmation.

#### Clinically Suspected CLD

CLD was defined as at two or more of chronic cough (present most days for 3 months of the year in the past 2 years), recurrent respiratory tract infections ( $>$  antibiotic courses in the last year) and moderate to severe limitation in physical activity caused by breathlessness (NYHA class 2–4), and/or an existing diagnosis and/or signs of cor pulmonale (finger clubbing, raised jugular venous pressure), or hypoxia ( $O_2$  sat  $\geq 92\%$ ) at rest, or desaturation ( $O_2$  sat  $\geq 5\%$ ) on exercise.

### Ethical Considerations

Written informed consent was obtained from all participants and from guardians of participants aged  $< 16$  years. Ethical approval was obtained from the Medical Research Council of Zimbabwe, the London School of Hygiene and Tropical Medicine Ethics Committee, and the Biomedical Research and Training Institute Institutional Review Board.

## RESULTS

### Demographic and Clinical Characteristics

Five individuals were excluded (1 with a recent diagnosis of tuberculosis, 3 who did not obtain parental consent, and 1 with likely horizontally acquired HIV infection). Characteristics of the 116 participants (mean age,  $14 \pm 2.6$  years, 43% male) are summarized in Table 1. None were cigarette smokers or had smoke exposure from indoor open fires. HIV was diagnosed a median of 23 months (interquartile range [IQR], 10–45) before recruitment, and 99 patients (85%) had WHO stage 3/4

**Table 1. Baseline Demographic and Clinical Characteristics of Study Participants (N = 116)**

Baseline Characteristic	No. (%)
Age, years	
$\leq 12$	34 (29)
13–15	39 (34)
16–18	43 (37)
Male	50 (43)
Orphanhood	
Both parents alive	9 (8)
Single orphan	51 (44)
Double orphan	56 (48)
Educational level	
None	3 (2)
Primary	52 (45)
Secondary	61 (53)
Age at HIV diagnosis, y, median (IQR)	12 (10–15)
Taking co-trimoxazole prophylaxis	111 (96)
Taking ART	80 (69)
Type of ART	
2 NRTI + 1 NNRTI	72 (62)
2 NRTI + PI	6 (5)
Height-for-age z score, median (IQR)	−1.96 (−2.9 to −1.3)
Weight-for-age z score, median (IQR)	−1.74 (−2.9 to −0.79)
BMI z score, median (IQR)	−0.69 (−1.7 to 0.1)
Pubertal delay (Tanner stage 1/2 in $\geq 14$ y) <sup>a</sup>	21 (18)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

<sup>a</sup> Data missing for 2 participants.

disease. Reasons for HIV testing were presumed tuberculosis in 20 (17%), repeated chest infections or coughing in 23 (20%), other illnesses in 60 (52%), and following HIV diagnosis in a parent or parental death in 13 (11%). Eighty (69%) participants were taking ART for a median duration of 20 months (IQR, 5–40). Overall, median CD4 count was 384 cells/ $\mu$ L (IQR, 180–584) and did not differ between those who were receiving ART (median CD4 count, 402 cells/ $\mu$ L) and those who were not (median CD4 count, 351 cells/ $\mu$ L) ( $P < .58$ ).

Eighty-two (71%) participants had a prior diagnosis of CLD made by a physician, and 42 (36%) had been treated for suspected tuberculosis at least once. Disabling respiratory insufficiency was common (Table 2): 24 (21%) reported reduced exercise tolerance (NYHA class  $> 2$ ), 41 (35%) were dyspneic at rest and/or hypoxic at rest, and 21 (29%) had a  $\geq 5\%$  fall in  $O_2$  sat following exercise. Abnormal lung function (forced expiratory volume in 1 second [ $FEV_1$ ]  $< 80\%$  predicted) was noted in 52 (45%) participants. Of ART-naive participants with CD4 counts  $> 350$  cells/ $\mu$ L, 8 of 18 (44%)

**Table 2. Respiratory Symptoms and Signs in Study Participants**

Characteristic	Patients, No. (%)
<b>Clinical history</b>	
Previously treated for tuberculosis <sup>a</sup>	42 (36)
<b>History of other cardiorespiratory conditions</b>	
Treatment for asthma	11 (9)
Treatment for PCP	7 (6)
Dilated cardiomyopathy	1 (1)
Hospitalized for LRTI in the past year	19 (16)
>2 courses of antibiotics for LRTI in the past year	48 (41)
Recurrent <sup>b</sup> cough ± purulent sputum	77 (66)
<b>NYHA class<sup>c</sup></b>	
1	72 (62)
2	20 (17)
3	22 (19)
4	2 (2)
<b>Symptoms (current/recent)</b>	
Cough	84 (72)
Sputum	54 (47)
Exertional chest tightness	49 (42)
<b>Clinical assessment</b>	
Clubbing	12 (10)
Bibasal crackles	37 (32)
Wheeze on auscultation	2 (2)
Tachycardia (HR >100), at rest	35 (30)
Respiratory rate >25/min at rest	33 (28)
Resting O <sub>2</sub> sat <92% at rest	15 (13)
Drop of ≥5% O <sub>2</sub> sat on exercise testing (n = 72) <sup>d</sup>	21 (29)
<b>Pulmonary arterial pressure (n = 110)<sup>e</sup></b>	
<20 mm Hg	94 (86)
20–25 mm Hg	8 (7)
>25 mm Hg	8 (7)
<b>FEV<sub>1</sub>, % predicted</b>	
80–100	64 (55)
50–79	40 (35)
<50	12 (10)
<b>PEFR, % predicted</b>	
80–100	83 (72)
50–79	28 (24)
<50	5 (4)

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1 second; HR, heart rate; LRTI, lower respiratory tract infection; NYHA, New York Heart Association; PCP, pneumocystis pneumonia; PEFR, peak expiratory flow rate.

<sup>a</sup> Three participants treated twice.

<sup>b</sup> Most days in at least 3 mo in the year in past 2 years.

<sup>c</sup> NYHA functional classification: 1 = no symptoms and no limitation in physical activity; 2 = mild symptoms and slight limitation during physical activity; 3 = marked limitation of activity due to symptoms; 4 = severe limitations in activity, symptoms at rest.

<sup>d</sup> Three not mobile; 26 had respiratory rate >25; 7 had O<sub>2</sub> sat <92% and RR >25; 8 had O<sub>2</sub> sat <92%.

<sup>e</sup> Measured on Doppler echocardiography.

had clinically defined CLD and 5 of 18 (28%) had an abnormal HRCT scan. There was no association between FEV<sub>1</sub> and duration of ART or current CD4 count ( $P = .65$  and  $P = .31$ , respectively). On Doppler echocardiography, 16 patients (14%) had raised mean pulmonary artery pressure >20 mm Hg and 7% had pulmonary hypertension (mean pulmonary artery pressure >25 mm Hg) [18].

### Microbiologic Findings

Sputum, obtained from 54 (46%) participants, was culture positive for bacteria/fungi in 18 (33%): *Haemophilus influenzae* (n = 6), *Staphylococcus aureus* (n = 5), *Moraxella catarrhalis* (n = 5), *Pseudomonas aeruginosa* (n = 3), *Streptococcus pneumoniae* (n = 2), *Klebsiella pneumoniae* (n = 1), *Listeria monocytogenes* (n = 1), and *Candida albicans* (n = 3). Mycobacterial cultures were positive in 12 patients: *M. tuberculosis* was grown from 8 participants (smear positive = 7); additionally, 31 (27%) participants had organisms seen on sputum microscopy (staining on both auramine-O and Ziehl-Neelsen stains, but negative culture results from specimens taken at recruitment). Of these, *Mycobacterium gordonae* was cultured from 4 (3%) participants, and 18 (16%) had confirmation of positive microscopy but negative cultures when repeat sputum specimens were taken before commencement of antituberculous treatment and processed in a second independent mycobacterial culture laboratory. Unprocessed sputum specimens were sent to the second laboratory because of the unexpectedly high prevalence of smear positivity and concern about possible laboratory artifact (morphology was reported to be unusual for *M. tuberculosis*) or a nosocomial epidemic of *M. tuberculosis*.

### Radiologic Findings

Abnormalities on chest radiography were reported in 55 participants (47%), the most common being ring and tramline opacities. Features of posttuberculous lung disease (such as volume loss and fibrosis) were not prominent, despite the high proportion of participants who had been treated for tuberculosis.

One hundred participants (86%) met study case definitions for suspected CLD (see the “Methods” section), of whom 56 (56%) had HRCT performed: the investigation was withheld in 23 because of positive sputum microscopy infection control hazard, and an additional 21 participants were referred but did not attend, including 1 who had died. The median interval between CXR and HRCT in the remaining 56 participants was 2 months. Interobserver agreement was good for presence of specific HRCT abnormalities (bronchiectasis,  $\kappa = 0.74$ ; bronchial wall thickening,  $\kappa = 0.70$ ; small airway (centrilobular



**Table 3. Prevalence of Abnormalities on Chest Radiography and High-Resolution Computed Tomography in 56 Patients Undergoing Full Imaging Evaluation**

Radiologic Abnormality	Prevalence of Abnormality, No. (%)	With >5% Extent of Abnormality, No. (%)
<b>CXR</b>		
Rings/tramline opacities	18 (32)	18 (32)
Consolidation	7 (12)	6 (11)
Volume loss	7 (12)	NA
Paucity of vascular markings	5 (9)	NA
Noncavitating nodules	4 (7)	4 (7)
Ground-glass opacification	2 (4)	2 (4)
Hyperexpansion	2 (4)	NA
Reticular pattern	0 (0)	0 (0)
<b>HRCT</b>		
<b>Airway abnormality</b>		
Decreased attenuation	31 (55)	27 (48)
Bronchiectasis	24 (43)	NA
Bronchial wall thickening	20 (36)	NA
Small airway plugging	13 (23)	NA
Large airway plugging	6 (11)	NA
<b>Parenchymal abnormality</b>		
Consolidation	18 (32)	4 (7)
Noncavitating nodules	11 (20)	2 (4)
Reticular pattern	1 (2)	0 (0)
Emphysema	8 (14)	1 (2)
Cysts	6 (11)	3 (5)
Ground-glass opacification	6 (11)	1 <sup>a</sup> (2)
Cavitation	3 (5)	0 (0)

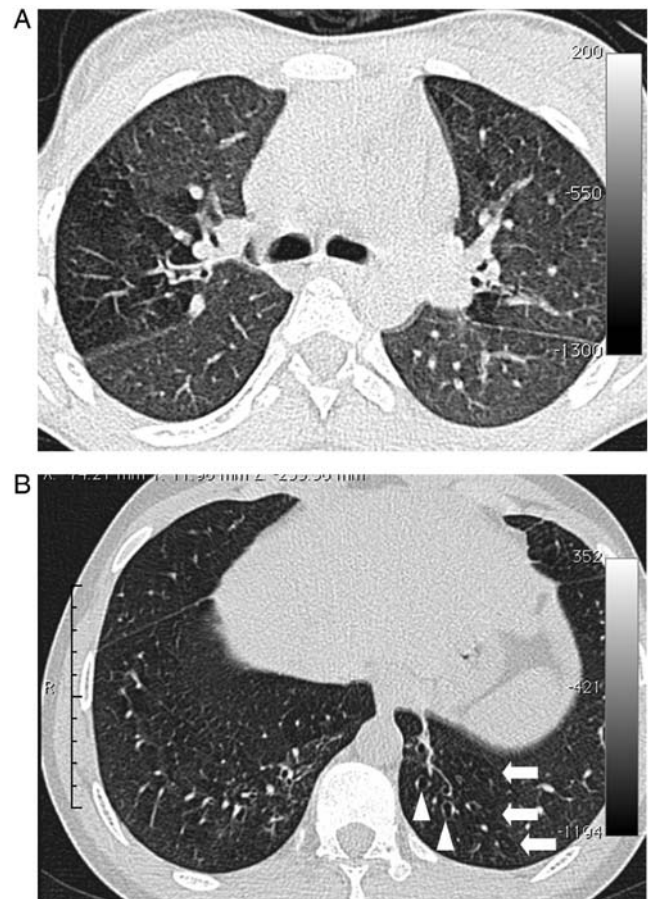
Abbreviation: CXR, chest radiography; HRCT, high-resolution computed tomography; NA, not applicable.

<sup>a</sup> 90% extent.

plugging,  $\kappa = 0.66$ ; consolidation,  $\kappa = 0.56$ ; decreased attenuation,  $\kappa = 0.75$ ; noncavitating nodules,  $\kappa = 0.57$ ).

### **CXR and HRCT Abnormalities in Participants Meeting Case Definition for CLD**

Radiologic findings in the 56 participants who received HRCT scans are summarized in Table 3. Of note, the prevalence of CXR abnormalities was not significantly different between participants meeting case definitions for CLD who received HRCT scans and those who met case definitions but did not



**Figure 1.** Lung high-resolution computed tomography findings in participants. *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).

undergo HRCT (data not shown). Decreased attenuation consistent with small airway disease was the most common and most extensive HRCT abnormality, followed by (and associated with) large airway abnormalities (bronchial wall thickening, small and large airway plugging, and bronchiectasis; Figure 1, Table 3). Our protocol obtained HRCT images at full inspiration (having not anticipated the high prevalence of small airway disease), but pronounced decreased attenuation was observed in 4 HRCT scans serendipitously performed in the expiratory phase. Ground-glass opacification and nodules were seen in a minority of cases, and features suggesting interstitial lung disease were also rare.

On HRCT, the extent of decreased attenuation was strongly correlated with extent of bronchiectasis (Spearman correlation

coefficient,  $r_s = 0.80$ ;  $P < .001$ ) and with other features indicating large airway pathology (severity of bronchial wall dilatation ( $r_s = 0.80$ ;  $P < .001$ ) and bronchial wall thickening ( $r_s = 0.73$ ;  $P < .001$ ). The association between extent of decreased attenuation and a composite score of the extent of small and large airway plugging on HRCT (“secretion score”) was weaker but statistically significant ( $r_s = 0.48$ ;  $P < .001$ ). The extent of bronchiectasis was also significantly associated with secretion score ( $r_s = 0.60$ ;  $P < .001$ ). Ring/tramline opacities on CXR were associated with secretion score ( $P = .006$ ) but not with any other HRCT abnormalities, including decreased attenuation, bronchiectasis, bronchial wall thickening, or bronchial dilatation. Consolidation on CXR was also significantly correlated with HRCT secretion score ( $P = .005$ ).

#### **Association Between HRCT Patterns and FEV<sub>1</sub>**

The extent of decreased attenuation was inversely correlated with FEV<sub>1</sub> ( $r_s = -0.26$ ;  $P = .06$ ), as was consolidation ( $r_s = -0.3$ ;  $P = .05$ ). No other HRCT features, including bronchiectasis, correlated with FEV<sub>1</sub>.

## **DISCUSSION**

The major finding of this study was the high burden of severe respiratory insufficiency among HIV-infected older children receiving HIV care after delayed diagnosis of presumed vertically acquired HIV infection. Two-thirds had chronic cough; recurrent lower respiratory tract infections and active mycobacterial disease were common, including persistent culture-negative smear positivity potentially reflecting nontuberculous mycobacterial disease. Pulmonary function tests were abnormal in 45% of participants, and a similar proportion had resting or exertional hypoxia. Pulmonary arterial hypertension was present in 7%. HRCT suggested small airway disease as the predominant underlying pathology, a previously undescribed finding with major implications for the health and long-term survival of perinatally HIV-infected adolescents.

We had anticipated a high prevalence of LIP in our cohort because it is the most common cause of HIV-associated CLD in younger children and because slow HIV progression and LIP are strongly correlated [9, 10, 19]. However, there was a striking absence of features (cysts and ground-glass opacification) to support active LIP or subsequent fibrosis [20]. This may reflect the natural history of LIP for self-resolution and prompt response to ART [21]. Instead, the most prevalent abnormality on HRCT was patchy (mosaic) decreased attenuation, for which the differential diagnosis is small airway disease, chronic pulmonary thromboembolic lung disease, or infiltrative lung disease. Of these, small airway disease is by far the most likely because of the significant association with (1)

FEV<sub>1</sub> (an index of airflow limitation) and (2) large airway abnormalities such as bronchiectasis.

The most common small airway disease is asthma, but the relatively stable clinical condition of hypoxic participants (attending a routine outpatient clinic and not in acute distress when recruited) argues against this diagnosis, as does the low prevalence of wheezing. Moreover, we have since confirmed a similarly high prevalence of hypoxic lung disease and shown lack of responsiveness to inhaled bronchodilators (excluding asthma) among older children and adolescents receiving HIV care in Blantyre, Malawi [22]. This leaves obliterative bronchiolitis as the most common cause of CLD in this patient group [23, 24].

Obliterative bronchiolitis is a life-threatening condition that responds poorly to treatment. It can progress to hypoxic respiratory failure and cor pulmonale or it can develop acutely and then remain at a relatively stable level of disability (eg, when due to adenovirus infection). In young children it may impair subsequent lung development. Obliterative bronchiolitis can result from a number of insults, including drug reactions; inhalation of allergens or toxins; and infection with a number of pathogens including adenovirus, mycoplasma, respiratory syncytial virus, or influenza. It is also an integral feature of the pathology of cystic fibrosis and chronic rejection following lung transplantation, with some evidence for genetic predisposition to severe forms [25]. It is thought to result from epithelial injury in the small airways, which undergo repair with fibrosis, leading to narrowing and airflow limitation [26]. Obliterative bronchiolitis has not been recognized in European or American cohorts of HIV-infected children, suggesting either geographic variability (eg, infantile adenoviral obliterative bronchiolitis has a Southern hemisphere predominance) or that ART during early childhood is preventive [27].

Obliterative bronchiolitis is prone to misdiagnosis and diagnostic delay because patients often appear well at rest with only subtle clinical and plain radiologic abnormalities [28]. In our study, the main HRCT finding had no CXR correlate, except in the subgroup with concurrent bronchiectasis. Decreased attenuation on HRCT was reported from lobes without overt bronchiectasis, implying that small airway disease precedes development of bronchiectasis [29], a phenomenon well recognized in obliterative bronchiolitis due to cystic fibrosis and adenovirus infection [25, 30].

HIV has not previously been recognized as predisposing to childhood obliterative bronchiolitis, but untreated HIV-infected children frequently experience multiple bacterial and viral respiratory tract infections over many years [6]. We postulate that these infections, together with HIV-induced impairment of innate immune responses [31, 32], predispose to chronic lower respiratory tract inflammation that in turn

increases susceptibility to further respiratory tract infections. Small airway disease may then result from cumulative inflammatory damage incurred during unusually frequent or severe viral/bacterial infections (similar to HIV-negative children with adenovirus, measles, or *Bordetella* infection). Alternatively, HIV-infected children may be predisposed to an inflammatory obliterative bronchiolitis that does not require a secondary pathogen other than HIV itself. In either event, host pulmonary inflammatory responses may be modulated by HIV and potentially by genetically determined immunologic responses. Persistent airway inflammation facilitates airway remodeling and development of bronchiectasis [33–36].

Previous studies of HIV-related CLD in this age group are limited to CXR findings [9, 37, 38], which are insensitive and subject to observer error and inconsistent use of terminology [39]. The strengths of this study are its prospective design, unselected recruitment, exclusion of acutely unwell patients, use of HRCT, and low interobserver variability in CXR and HRCT scoring. Limitations include the cross-sectional design, incomplete uptake of HRCT in participants meeting definitions for chronic lung disease, and lack of histologic confirmation. Although histology provides the “gold standard” for diagnosis of obliterative bronchiolitis, open or thorascopic lung biopsy or postmortem examination is required because of the patchy and peripheral nature of the disease process [40]. Increasingly, HRCT without biopsy is considered to be sufficiently characteristic to be used for initial diagnosis, and the chronic symptoms, structural damage, mosaic pattern of decreased attenuation, and strong association with FEV<sub>1</sub> provide strong evidence for obliterative bronchiolitis in our patients [41]. Finally, although we were careful to avoid further selection bias, our recruitment was limited to adolescents known to be receiving HIV care services, whereas the majority of African adolescent survivors of perinatal HIV infection are still undiagnosed [7].

Our study showed a substantial burden of CLD in vertically HIV-infected adolescents, even at high CD4 counts and following several years of ART. Other than a single case report in an HIV-infected 11-year-old, this is the first description of small airway disease as a cause of HIV-associated CLD [42]. As HIV epidemics mature, increasing numbers of previously undiagnosed HIV-infected older children are being identified [6]. Our findings suggest that HIV-infected children with chronic respiratory symptoms or evidence of airflow obstruction should be investigated for possible obliterative bronchiolitis as well as for mycobacterial disease. Earlier diagnosis of HIV infection may be crucial to preventing the development of CLD and suggests that international recommendations (which currently do not support immediate initiation of ART in children diagnosed over the age of 2 years) need to take the high risk of CLD and potential for prevention with early ART

initiation into account. The lack of association between CD4 count or duration of ART and pulmonary function infers that once established, lung damage may be irreversible. Possible intervention strategies include aggressive management of intercurrent infection and use of prophylactic antibiotics, which may delay progression of airway disease and reduce morbidity, and, potentially, corticosteroids [43]. Further investigation of the natural history, histopathology, geographic distribution, pathogenesis, and management of this newly described and highly prevalent HIV-associated CLD is needed.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online ([http://www.oxfordjournals.org/our\\_journals/cid/](http://www.oxfordjournals.org/our_journals/cid/)). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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