High-resolution computed tomography features of lung disease in perinatally HIV-infected adolescents on combined antiretroviral therapy

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Abstract

Introduction: Chronic lung disease is common in perinatally HIV-infected children as they increasingly surviving into adolescence. There are few data on the radiologic spectrum of disease in this population.

Methods: Contrasted high-resolution computed tomography (HRCT) was performed in ambulatory South African adolescents enrolled in a prospective study of perinatally-infected adolescents aged 9 to 14 years established on combined antiretroviral therapy (cART) and followed for 36 months. Consecutive participants with reduced lung function (defined by a forced expiratory volume in 1 second [FEV1] of <80% normal and/or lung diffusion capacity [DLCO] <80% normal) underwent HRCT. History, clinical, and laboratory data were collected. Two radiologists blinded to clinical data and to each other, reported scans using standardized methodology; a third radiologist resolved discrepancies.

Results: Amongst 100 participants undergoing HRCT, median age was 13.8 years (12.8-15.1). The median duration on cART was 8.4 years (IQR = 5.7-9.8). Mosaic attenuation was the most common finding (73%). Of these 71 (91%) demonstrated associated air trapping radiologically consistent with bronchiolitis obliterans. Bronchiectasis occurred in 39% with significant correlation between extent of bronchiectasis and mosaic attenuation ($r = 0.57$, $P < .001$). Prior hospitalization for childhood pneumonia at any time before enrollment was associated with mosaic attenuation (OR = 3.9, 95%CI, [1.2-12.5]); prior pulmonary tuberculosis (TB) was associated with the combination of mosaic attenuation and bronchiectasis (OR = 4.9, 95%CI, [1.6-15.7]). Most participants (86%) with mosaic attenuation had stage III or IV HIV disease at time of HIV diagnosis (OR = 3.6; [0.9-14.9]). Inter observer agreement between the two readers was good for bronchiectasis ($K = 0.71$) and moderate for mosaic attenuation ($K = 0.51$).

Discussion: Despite well-controlled HIV and long duration of cART, HRCT changes were common in perinatally HIV-infected adolescents. There was a high prevalence of small airways disease with and without associated bronchiectasis. These changes...
were associated with prior pulmonary TB or prior severe pneumonia. Strategies to prevent and treat early life respiratory infection must be strengthened to reduce the burden of chronic lung disease in HIV-infected adolescents.

KEYWORDS
adolescents, computed tomography, HIV, TB

1 | INTRODUCTION

Perinatally HIV-infected children are surviving into adolescence due to early diagnosis of HIV and use of combination antiretroviral therapy (cART).1,2 Chronic sequelae of HIV, including chronic lung disease are therefore increasingly emerging.3-5 There are very limited data that describe the radiological spectrum of such disease with only two studies of high-resolution computed tomography (HRCT) imaging in adolescents.6,8 In both, ring and tram opacities were the most prevalent findings on CXR, consistent with chronic lung disease manifesting as bronchiectasis. In one study of 56 children, HRCT showed predominantly small airway disease, specifically bronchiolitis obliterans, followed by bronchiectasis.8 The more recent study reported that mosaic attenuation or bronchiectasis was the most common HRCT findings in a combined pediatric and adolescent population of 84 HIV-infected patients on cART.6

Further, knowledge of the type and extent of chronic lung disease in perinatally HIV-infected adolescents is required to better understand the spectrum of disease and strengthen preventive or treatment strategies. The aim of this study was to investigate the spectrum and determinants of HRCT chest findings in a cohort of adolescents vertically infected with HIV who were well established on cART.

2 | METHODS AND MATERIALS

2.1 | Patient population

This was a prospective study of adolescents enrolled between July 2013 and March 2015 in the Cape Town Adolescent Antiretroviral Cohort (CTAAC). CTAAC is a prospective cohort of 520 perinatally-infected HIV adolescents who were on cART for at least 6 months before enrollment. In addition, 120 age-matched HIV-uninfected adolescents without known pre-existing lung disease were enrolled from similar communities as the HIV-infected adolescents, to serve as controls. Perinatal HIV exposure of the HIV-uninfected participants was not known. All children were followed 6-monthly for 36 months at the MRC Unit for Child and Adolescent Health at Red Cross Children’s Hospital, South Africa, where history, clinical evaluation; lung function, chest X-ray (CXR), and collection of samples were longitudinally done. Written informed consent was obtained from a parent or guardian and assent from a participant. Lung function testing was done at enrollment and at annual follow-up visits. HRCT was added to the CTAAC protocol in January 2015 to better delineate the spectrum of lung disease including the presence of both small and large airways disease. HRCT was performed within 3 months of lung function testing and as such, HRCT corresponded to 12 and 24 month follow-up visits. Due to financial constraint, a sample of 100 sequential participants with abnormal lung function (defined by a forced expiratory volume in 1 second [FEV1] of < 80% normal and/or lung diffusion capacity [DLCO] < 80% of normal) underwent HRCT. Patients with acute respiratory symptoms, renal failure, or a previous reaction to intravenous contrast were excluded.

A history and examination were performed by a study doctor including questions on prior admission for respiratory illness, active or passive smoking (passive smoking documented if a person in the household with the adolescent was a smoker) and history of respiratory symptoms. HIV stage at diagnosis, age at commencement of cART, and cART regimen were obtained from clinic and hospital health records. Hospital records were evaluated for tuberculosis or pneumonia requiring hospitalization. Viral load and CD4 values obtained within 3 months of the HRCT were used.

The study was approved by the Faculty of Health Sciences, Human Research Ethics Committee, University of Cape Town (UCT).

2.2 | HRCT

HRCT was performed, on a 128-slice CT scanner (Siemens Somatom Definition AS Germany). Single phase, contrast-enhanced multidetector volume acquisitions were performed from the thoracic inlet to the diaphragm at full inspiration. Volumetric data were postprocessed to yield thin slice (0.6 mm) images on soft tissue window, thin slice (0.6 mm) lung windows using a high-resolution filter (high-resolution CT), and thicker slice lung windows (5 mm). Three 1 mm slices were additionally performed in full expiration at the level of 2 cm below and 2 cm above the hila to differentiate mosaic pattern caused by bronchiolitis obliterans from inflammatory causes of ground glass attenuation. The protocol was revised to include expiratory slices after the first 21 patients had been scanned and the prevalence of mosaic attenuation had been appreciated.

Radiation limiting measures included: limiting the scan range up to the diaphragm, choosing the single phase scan (no precontrast component), shielding of gonadal structures, selecting pediatric CT scan protocol, which includes automatic exposure control or "care
dose” (automatic dose adjustment according to size of the patient while scan is performed), choosing thin collimation (6 mm), keeping the pitch +/−1.5 (not 1), limiting the field of view (FOV), and placing the patient in the center of the gantry.7

The soft tissue windows were used to evaluate mediastinal structures and confirm or exclude lymphadenopathy. High-resolution reconstructions on lung windows were used to identify large and small airway disease as well as interstitial disease. Thicker slices on lung window was used to identify air-space disease.

Images were stored in a secure patient archiving and communications system (PACS) used for clinical referrals.

### 2.3 HRCT evaluation and scoring

Two radiologists blinded to each other’s reporting and any diagnosis interpreted CT studies according to a standardized case reporting form (CRF) (appendix 1); a third reader evaluated discrepancies. Grading of disease extent was established by a consensus read of the two core radiologists. Definitions for each of the individual findings were predefined according to Fleischner Criteria8 (appendix 2). Quality of HRCT studies was evaluated as satisfactory for evaluation based on the absence of breathing artifact.

Measures included documentation on parenchymal, pleural, and mediastinal abnormalities. Parenchymal abnormalities were divided into airspace disease/consolidation, focal ground glass opacities, nodules, cavities/cyst/bulla, mosaic attenuation, bronchiectasis, reticular infiltrates, and hyperinflation. Mediastinal abnormalities included the presence of lymphadenopathy, which included enlarged as well as small calcified lymph nodes. Specific parenchymal pathology was assessed separately with numeric assignment for percentages of involvement per lobe (1 < 25%; 2 = 25%−50%; 3 = 51%−75%; 4 = >75%). Total extent of disease was calculated as a number from 0 to 20 (based on five lobes with a possible maximum score of 4 in each) and converted to a percentage of total lung volume affected.

### 2.4 Lung function

Lung function testing was performed within 3 months of the HRCT including spirometry and single breath diffusion capacity of carbon monoxide (DLCO). All testing was performed in compliance with the America Thoracic Society and the European Respiratory Society guidelines.9-11 The highest FVC and FEV1 from any of at least two acceptable, reproducible maneuvers were reported. Z standardization for spirometry variables was estimated with the Global Lung initiative software using African American reference population.12 For DLCO, a minimum of two trials that met quality control standards were performed. Transfer factor for CO was adjusted for patient’s hemoglobin done on the day of lung function testing. The average of the two best maneuvers was recorded for analysis. Lower limit of normal (LLN) was estimated using the equations of Kim et al.13

### 2.5 Statistical analysis

For categorical variables, frequencies and percentages were reported and for continuous variables, medians, and interquartile ranges (IQR) were presented. Bivariate and multivariable logistic regression was computed to assess the association of a specific radiographic pattern with patient characteristics. P-values less than .05 were considered significant. Inter observer agreement for the presence of a radiologic pattern was assessed using the Cohen’s Kappa (K) and agreement categorized as poor (0 < K ≤ 0.20), fair (0.20 < K ≤ 0.40), moderate (0.40 < K ≤ 0.60), good (0.60 < K ≤ 0.80), and excellent (0.80 < K ≤ 1.00).14 Statistical analysis was performed using STATA version 14 software (StataCorp, 2015).

| TABLE 1 Demographics and clinical parameters of participants (n = 100) |
|-----------------------------|-------------------------------|--------------------|
| Demographics               | Median/n (IQR/%)               | Clinical parameters |
| Age (y)                    | 13.84 (12.76-15.10)            | %                 |
| Male                       | 46 (46.0)                      | HIV stage         |
| ART duration (y)           | 8.44 (5.68-9.78)               | I                 |
| HIV stage                  |                                 | II                |
| Male                       | 46 (46.0)                      | III               |
| Clinical parameters        |                                 | IV                |
| Male                       | 46 (46.0)                      | Not known         |
| History of shortness of breath or wheeze in last 6 mo | 22 | | Current ARV regimen |
| CD4 count                  |                                 | 2xNRTI + NRRTI*    |
| <500 cells/mm³             | 17                             | 2xNRTI + PI**     |
| >=500 cells/mm³            | 83                             | Other             |
| Viral Load                 |                                 | Smoke-passive/active |
| <50 copies/mL              | 72                             | Past respiratory illness |
| >=50 copies/mL             | 28                             | Pneumonia requiring hospitalization |
| Abbreviations: ARV, antiretroviral; NRRTI, nucleoside reverse transcriptase inhibitors; TB, tuberculosis. |
| *Two nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. |
| **Two NRTI and protease inhibitors. |
| #Documentation on pneumonia requiring hospitalization available in 91 patients. |
| **Documentation on pulmonary TB available in 99 patients. |
RESULTS

Amongst 100 participants, with a median age at HRCT of 13.8 (IQR = 12.8-15.1) years, 46% were male. The median age at HIV diagnosis was 3.7 years (IQR = 1.6-6.9). The median duration on cART was 8.4 years (IQR = 5.7-9.8); 42% initiated cART before 2 years of age and 72% before 5 years. Most participants (54%) were on a combination of two nucleoside reverse transcriptase inhibitors (NRTI) and a non-nucleoside reverse transcriptase inhibitors (NNRTI), with a smaller proportion (41%) receiving 2 NRTI and a protease inhibitor (PI). Most (86%) had stage III or IV HIV disease at enrollment. In 83%, CD4 count was >500 cells/mm³ and 50/73 (69%) had a viral load <50 copies/mL; there was no association between presence of mosaic attenuation and CD4 count or viral load (OR = 0.8; 95%CI, [0.2-2.7] and OR = 2.0; 95%CI, [0.7-6.0]), respectively with a bivariate analysis (Table 3). When applying multivariable analysis, however, higher viral load was significantly associated with reduced prevalence of mosaic attenuation (OR = 0.36, 95%CI, [0.1-0.9]) adjusting for gender, CD4 count, HIV stage at diagnosis, and past respiratory illness. No association was found between CD4 count and the prevalence of mosaic attenuation (Table 4).

Amongst participants with mosaic attenuation, 56% was on two NRTI and a NNRTI while 38% was on a PI. There was no association between cART regimen and mosaic attenuation (OR = 0.7; 95%CI, [0.3-1.2] and OR = 0.95, 95%CI, [0.1-10.0] for cART regimens respectively), age at cART initiation (OR = 0.6, 95%CI, [0.3-1.6]) or duration of cART (OR = 0.96, 95%}

3.1 HRCT findings

All HRCT studies were of satisfactory quality, most had inspiratory and expiratory scans, Figure 1. The most prevalent finding was mosaic attenuation pattern in 73% on either inspiratory or expiratory scans. (Figure 2A-C). Air trapping (accentuated mosaic attenuation) was found in 91% with mosaic attenuation who had expiratory imaging. In 4/73 (6%) patients, mosaic attenuation occurred only in expiratory views (Figure 3A and 3B).

Bronchiectasis was reported in 39% of which 22 (56%) of these involved less than 25% of total lung volume (Figure 4A and 4B). Associated mosaic attenuation was demonstrated in 37/39 patients (95%) with bronchiectasis with significant correlation between extent of mosaic attenuation and bronchiectasis ($r = 0.57$, $P < 0.001$). The prevalence and extent of specific radiologic abnormalities are summarized in Table 2.

Amongst those with mosaic attenuation, 60/73 (82%) had a CD4 count >500 cells/mm³ and 50/73 (69%) had a viral load <50 copies/mL; there was no association between presence of mosaic attenuation and CD4 count or viral load (OR = 0.8; 95%CI, [0.2-2.7] and OR = 2.0; 95%CI, [0.7-6.0]), respectively with a bivariate analysis (Table 3). When applying multivariable analysis, however, higher viral load was significantly associated with reduced prevalence of mosaic attenuation (OR = 0.36, 95%CI, [0.1-0.9]) adjusting for gender, CD4 count, HIV stage at diagnosis, and past respiratory illness. No association was found between CD4 count and the prevalence of mosaic attenuation (Table 4).

Amongst participants with mosaic attenuation, 56% was on two NRTI and a NNRTI while 38% was on a PI. There was no association between cART regimen and mosaic attenuation (OR = 0.7; 95%CI, [0.3-1.2] and OR = 0.95, 95%CI, [0.1-10.0] for cART regimens respectively), age at cART initiation (OR = 0.6, 95%CI, [0.3-1.6]) or duration of cART (OR = 0.96, 95%
CI, [0.8–1.1]). No association was found between stage of HIV disease at enrollment and mosaic attenuation (OR = 3.6, 95% CI, [0.9–14.8]).

In bivariate analysis, pneumonia requiring hospitalization at any time before enrollment was associated with mosaic attenuation (OR = 3.9, 95% CI, [1.2–12.5]) and strongly associated with the combination of mosaic attenuation and bronchiectasis (OR = 4.1, 95% CI, [1.7–10.4]). Similar associations were demonstrated when a multivariable analysis was applied with pneumonia requiring hospitalization strongly associated with the combination of mosaic attenuation and bronchiectasis (OR = 2.9, 95% CI, [1.1–9.0]) adjusting for gender, CD4 count, viral load, and HIV stage at diagnosis. A previous history of pulmonary tuberculosis (TB) was also associated with the combination of mosaic attenuation and bronchiectasis (OR = 4.9, 95% CI, [1.6–15.7]) but no association with the presence of mosaic attenuation alone (OR = 2.2, 95% CI, [0.9–5.7]). A history of wheezing or shortness of breath was associated with mosaic attenuation (OR = 4.7, 95% CI, [1.0–21.8]).

Nodules were reported in 48 patients of which all had minimal disease, except for one patient diagnosed with miliary TB. Airspace opacification occurred in 16% but with minimal extent of disease. Cysts (11%) or pleural disease (4%) was uncommon. No reticular interstitial infiltrates or fibrosis was reported. Emphysema was reported in 2 participants, both of minimal extent and with mosaic attenuation. These participants had stage III HIV were on cART for more than 8 years and had CD4 counts >500 cells/mm³ and viral load of <50 copies/mL at the time of HRCT. Mediastinal or perihilar lymphadenopathy occurred in 45% with 32 (71%) of these calcified (Figure 5). No association with previous TB and lymphadenopathy was found (P = .36). Thirty of these (67%) demonstrated a combination of mosaic attenuation and adenopathy, but there was no association with this combination and prior TB (P = .123).

Inter observer agreement between the first two readers was good for bronchiectasis (K = 0.71) and moderate for mosaic attenuation (K = 0.51), nodules (K = 0.43), or lymphadenopathy (K = 0.53).

In this study of HRCT findings in perinatally HIV-infected with well-controlled disease, mosaic attenuation was the predominant HRCT finding with or without associated bronchiectasis. This...
**TABLE 2** Prevalence and extent of findings on HRCT

| Finding                  | N = 100 | Extent = /<25% | 26%-50% | 51%-75% | = >/75% |
|--------------------------|---------|----------------|---------|---------|---------|
| Parenchymal Airspace consolidation | 16%     | 16            | -       | -       | -       |
| Ground glass opacity     | 4%      | 4             | -       | -       | -       |
| Nodules                  | 48%     | 47            | -       | -       | -       |
| Cysts/cavities/bullae    | 11%     | 11            | -       | -       | -       |
| Hyperinflation           | 10%     | -             | -       | -       | -       |
| Airway involvement       |         |               |         |         |         |
| Mosaic attenuation       | 73%     | 35            | 26      | 10      | 2       |
| Bronchiectasis           | 39%     | 22            | 9       | 8       | -       |
| Pleural Effusion/thickening| 4%     | -             | -       | -       | -       |
| Mediastinal Lymphadenopathy| 45%   | -             | -       | -       | -       |
| Calcified lymph node     | 32%     | -             | -       | -       | -       |

Abbreviation: HRCT, high-resolution computed tomography.

**TABLE 3** Unadjusted odds ratios predicting mosaic attenuation and a combination of mosaic attenuation and bronchiectasis

|                               | Mosaic attenuation | Mosaic attenuation and bronchiectasis |
|-------------------------------|--------------------|---------------------------------------|
|                               | Odds ratio 95% CI  | Odds ratio 95% CI                      |
| Age                           | 0.88 [0.659-1.168] | 1.29 [0.983-1.692]                    |
| Male                          | 0.73 [0.299-1.756] | 1.41 [0.623-3.180]                    |
| Respiratory rate              | 0.99 [0.88-1.11]   | 0.88 [0.780-0.994]                    |
| HAART duration                | 0.96 [0.82-1.13]   | 1.09 [0.941-1.262]                    |
| CD4 count                     |                    |                                      |
| <=500 cells/mm³               | 1.00 Ref           | 1.00 Ref                              |
| >=500 cells/mm³               | 0.803 [0.237-2.717]| 0.809 [0.279-2.345]                   |
| Viral load                    |                    |                                      |
| <=50 copies/mL                | 1.00 Ref           | 1.00 Ref                              |
| >=50 copies/mL                | 2.024 [0.681-6.016]| 1.733 [0.712-4.220]                   |
| HIV stage at diagnosis of HIV |                    |                                      |
| I&II                          | 1.00 Ref           | 1.00 Ref                              |
| III&IV                        | 3.636 [0.896-14.76]| 5.231 [0.626-43.72]                   |
| Age at ARV initiation         |                    |                                      |
| 0-5 y                         | 1.00 Ref           | 1.00 Ref                              |
| 6-14 y                        | 0.642 [0.252-1.634]| 0.796 [0.324-1.956]                   |
| Current ARV regimen           |                    |                                      |
| 2xNRTI + NNRTI                | 0.683 [0.276-1.691]| 1.417 [0.611-3.283]                   |
| 2xNRTI + PI                   | 0.951 [0.090-9.950]| 0.667 [0.065-6.871]                   |
| Other                         |                    |                                      |
| Passive smoke exposure        | 1.231 [0.432-3.509]| 0.944 [0.368-2.420]                   |
| Past respiratory illness      | 2.579* [1.002-6.635]| 3.441* [1.469-8.056]                  |
| Pneumonia requiring hospitalization | 3.868* [1.194-12.532] | 4.133* [1.646-10.38] |
| Prior pulmonary TB            | 2.224 [0.868-5.699]| 4.923* [1.548-15.66]                  |
| History of shortness of breath or wheeze | 4.717* [1.002-21.77] | 2.544 [0.970-6.675]                  |

Abbreviations: ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; TB, tuberculosis.

*Statistically significant.
pattern reflects patchy decreased attenuation which may be caused by small airway disease, parenchymal disease, or pulmonary vascular disease.\textsuperscript{15,16} Expiratory views confirmed air trapping in more than 90% of cases in whom expiratory imaging was performed, consistent with a diagnosis of bronchiolitis obliterans (BO). These findings are similar to those described in two cohorts of HIV-infected children in Zimbabwe in which decreased attenuation was the more common finding, although the prevalence of mosaic attenuation was lower at 43% and 55%.\textsuperscript{4,6} Differences in patient selection, with higher numbers of documented previous TB (71% in our cohort compared with 36%) or prior hospitalization for pneumonia (35% compared with 16%) may explain these differences.

In patients with bronchiectasis, associated mosaic attenuation occurred in almost all (95%). The extent of bronchiectasis correlated strongly with the extent of decreased attenuation, again supporting the likelihood of small airways disease preceding bronchiectasis.\textsuperscript{6,17} TB has been reported as an important etiology for the development of BO in endemic regions in HIV-negative patients.\textsuperscript{18-20} Although there was no association between prior TB and mosaic attenuation alone, the strong association with the combination of mosaic attenuation and bronchiectasis suggests that TB may lead to severe chronic lung disease. There was also a strong association between prior severe pneumonia and mosaic attenuation, as well as the combination of mosaic attenuation and bronchiectasis. Interestingly when multivariate logistic regression was applied, an increased viral load was found to be associated with decreased prevalence of mosaic attenuation which is in contrast to the hypothesis that the HIV virus itself may be responsible for small airways disease in this population.\textsuperscript{21}

More than 80% with mosaic attenuation on HRCT had stage III or IV HIV disease and the median age at diagnosis and treatment with cART was after 3 years of age. However, participants were well established on cART for more than 8 years, with well-controlled HIV at the time of imaging. This suggests that uncontrolled HIV associated with recurrent lower respiratory tract infections in the first few years of life may be a critical factor in the evolution of chronic lung disease and specifically in the development of BO. In the absence of longitudinal follow-up scans the evolution of BO cannot be evaluated; the findings likely represent chronic static pathology from a prior insult.

Cross-sectional observational studies in adults have suggested that cART may be associated with the development of BO or airflow obstruction.\textsuperscript{22,23} Our study, however, demonstrated no correlation between the duration, age at commencing treatment or regimen of cART with BO. This is consistent with later longitudinal studies demonstrating a protective effect of cART on lung health, with less lung function deterioration in adults.\textsuperscript{16,24,25} In addition, HIV has been shown to be an independent risk factor for the development of emphysema, in adults with poor virological control.\textsuperscript{26} Two of our
patients had features of emphysema; both with associated mosaic attenuation which might suggest early chronic obstructive airway disease.

Despite 72% adolescents having a history of previous TB, there was no association with TB and calcified lymph nodes, but this may be due to the large number of children with prior TB, and the relatively small sample size. Post tuberculous scarring reported or cavitary disease was not found. Although nodules were the second most prevalent finding, the extent in all, but a single patient with suspected miliary TB, was minimal. A recent study reported that pulmonary nodules frequently occurred in healthy children; thus these findings may be consistent with the occurrence of incidental nodules. Lymphocytic interstitial pneumonitis (LIP) was formerly an important cause of nodules in HIV-infected children before cART but is no longer commonly seen due to use of cART.6,21,28

Strengths of the study are that all HRCT studies were of good quality, interpretation of HRCT using a standardized comprehensive reporting template by two to three experienced readers, a well phenotyped cohort established on cART and well reporting template by two to three experienced readers, a well quality, interpretation of HRCT using a standardized comprehensive

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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5 CONCLUSION

This study highlights the high prevalence of small airway disease in perinatally HIV-infected adolescents, who were well-controlled on long standing cART. These changes were associated with prior pulmonary TB or severe pneumonia. The cART regime was not associated with airway disease. The importance of early life respiratory infections on long term lung health and the need for strengthened preventative strategies are emphasized. Further longitudinal studies to investigate the evolution of small airway disease and determinants in this population are needed.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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