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Chronic lung disease in children and adolescents with HIV: a case-control study

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Abstract

Objective: To describe the features of HIV-associated chronic lung disease (CLD) in older children and adolescents living with HIV and to examine the clinical factors associated with CLD. This is a post-hoc analysis of baseline data from the BREATHE clinical trial (ClinicalTrials.gov, NCT02426112).

Methods: Children and adolescents aged 6-19 years were screened for CLD (defined as a FEV1 z-score <-1 with no reversibility post-bronchodilation with salbutamol) at two HIV clinics in Harare, Zimbabwe and Blantyre, Malawi. Eligible participants with CLD (cases) were enrolled, together with a control group without CLD (frequency-matched by age group and duration on ART) in a 4:1 allocation ratio. A clinical history and examination was undertaken. The association between CLD and *a priori*-defined demographic and clinical covariates was investigated using multivariable logistic regression.

Results: Of the 1,585 participants screened, 419 (32%) had a FEV_1 z- score <-1, of whom 347 were enrolled as cases (median age 15.3 years [IQR 12.7 -17.7]; 48.9% female), and 74 with FEV1 z-score>0 as controls (median age 15.6 years [IQR 12.1 -18.2]; 62.2% female). Amongst cases, current respiratory symptoms including cough and shortness of breath were reported infrequently (9.3% and 1.8%, respectively). However, 152 (43.8%) of cases had a respiratory rate above the 90th centile for their age. Wasting and

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taking second-line antiretroviral treatment (ART) were independently associated with CLD.
Conclusions: The presence of CLD indicates the need to address additional treatment support for youth living with HIV, alongside ART provision, to ensure a healthier adulthood.

Keywords: HIV, Adolescents, Chronic Lung Disease, Africa

Introduction

In 2017, an estimated three million children and adolescents were living with HIV worldwide, 90% in Sub-Saharan Africa (1). The incidence of HIV infection acquired through mother-to-child transmission has declined dramatically in recent years due to the scale-up of prevention of mother-to-child HIV transmission programmes as one component of global efforts to eliminate HIV (2,3). At the same time, however, increasing numbers of African children who were perinatally-infected with HIV during peak years of 1995 to 2002 are now reaching adolescence and adulthood, having been diagnosed and treated by national HIV programmes (4). As this large paediatric antiretroviral therapy (ART) clinic cohort reaches adulthood, common comorbidities that result from growing up with perinatally acquired HIV differ from comorbidities seen in adults living with behaviourally acquired HIV. The clinical outcomes for adolescents living with HIV since birth are becoming better described: these include growth failure, cardiac and neurological conditions and notably chronic lung disease (CLD) (5,6).

The main focus of paediatric HIV programmes has been on strengthening the HIV care cascade: ensuring early HIV diagnosis, prompt ART initiation, and retention in care with sustained viral load suppression with relatively little attention paid to defining, diagnosing and managing novel co-morbidities (7,8).

Several studies in sub-Saharan Africa have reported high prevalence of chronic respiratory symptoms among older children and adolescents living with HIV, including both those with delayed HIV diagnosis and treatment, and those already established on ART (9–12). Prevalence can be as high as 25% to 37.5%, with the typical clinical picture being a history of chronic cough with reduced exercise tolerance, and an obstructive defect on spirometry with no response to bronchodilators (9–12). High resolution computed tomography (HRCT) suggests constrictive obliterative bronchiolitis (COB) with or without accompanying bronchiectasis as the underlying cause in most cases (referred to hereafter as presumptive HIV-related COB: PH-COB) (13). Chest radiographic findings are subtle and patients look well at rest, meaning that PH-COB goes undiagnosed in busy African HIV clinics.

The pathogenesis of PH-COB is poorly defined, with no histopathological studies to date, but we and others have postulated that repeated respiratory tract infections in the context of longstanding systemic

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immune activation and dysregulated inflammation are the most likely cause (14). We are evaluating the potential role of azithromycin, which has antibacterial and immunomodulatory properties and effectiveness in bronchiectasis and cystic fibrosis (15,16), using a multi-site, individually randomised, double-blinded, placebo-controlled trial of weekly azithromycin for 48 weeks in children and adolescents meeting case-definitions for chronic lung disease: the BREATHE trial (17).

The main aim of the (post-hoc) analysis presented here as a case-control study was to use baseline data from trial participants and controls to investigate potential risk-factors for CLD and to describe the clinical features.

Methods

Study Setting and Population

From June 2016 until August 2018, children and adolescents meeting definitions of perinatal HIV infection (defined as self-report of no sexual debut or blood transfusions, a history of orphanhood due to maternal HIV disease and/or of a sibling death due to HIV, guardian report as perinatal acquisition being the known mode of acquisition and characteristic clinical features (≥1 of stunting, history of recurrent minor infections (skin, upper respiratory tract) in childhood, and/or planar warts) were recruited from HIV clinics at Harare Children's Hospital, Harare, Zimbabwe and the Queen Elizabeth Central Hospital, Blantyre, Malawi, using a multistep screening procedure, as detailed in the published protocol [clinicaltrials.gov NCT02426112](17).

Case selection: HIV clinic attendees aged (6-19 years old), taking ART for ≥6 months, and z-score of below -1 for Forced Expiratory Volume at one second (FEV1), with no reversibility met our case definition of chronic lung disease (12,18). Forced Expiratory Volume at one second (FEV1) z-score <-1 with no reversibility was the case definition of CLD in the trial. This definition was chosen as the most objective definition for lung disease; FEV1 z-score has been shown to be strongly correlated with the most common abnormalities observed in high resolution computed tomography, and we anticipate that the effectiveness of azithromycin would be limited in those with advanced disease.

Control selection: HIV clinic attendees with FEV1 z-score > 0 and no chronic cough in the past 3 months were enrolled as controls, using frequency-matching for age (6-12 years and 13-19 years) and duration on ART (6 months to <2 years and 2 or more years).

Study procedures

A standardized questionnaire was administered to participants and their guardians. Height and weight, and respiratory rate at rest were recorded, with heart rate and oxygen saturation were measured using

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pulse oximetry (OxyWatch, Beiijing Choice Electronic Technology Co. Ltd).

Spirometry adhered to American Thoracic Society (ATS) standards, and used EasyOne World spirometers (ndd Medical Technologies, Inc., Andover, Massachusetts, USA). Spirometric indices were expressed as z-scores using GLI2012 reference ranges (19). Participants with a FEV_1 z- score below -1 underwent repeat spirometry 15 minutes after administration of 200µcg inhaled salbutamol via spacer. A high-quality spirometry trace was selected for each participant and the best test performed was defined as the largest sum of FEV_1 and FVC.

An incremental shuttle walk test (ISWT) was performed to measure cardiorespiratory fitness in all cases (20,21). Cases did not undergo shuttle walk test if, at rest, SpO2 was less than 88%, heart rate was more than 120 beats/min and respiratory rate was more than 30 breaths/min or the participant had a physical impediment to optimal exercise e.g. a physical disability.

All participants were tested for tuberculosis with a sputum sample for Xpert™ MTB/RIF (Cepheid, Sunnyvale, CA, USA). CD4 count measurements used PIMA™ Analyser (Alere, Orlando, FL, USA) and HIV viral load used Xpert™ HIV-1 Viral Load (Cepheid, Sunnyvale, CA, USA), lower limit of detection 40 copies/ml .

Data Management and Analysis

Electronic data capture used clinical record forms (Google Nexus™ tablets, Google, Mountain View, CA, USA) and OpenDataKit software, uploaded, into Microsoft Access databases (Microsoft, Redmond, WA, USA). Analysis used Stata version 15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC)

Z-scores for height-for-age and weight-for-age used 1990 British growth reference curves (22). Heart rates and respiratory rates were compared to age-specific centiles developed by O'Leary et al (23).

Comparison between groups used t-test or Mann–Whitney U test for continuous data, and chi-squared test for categorical data. Complete case multivariable logistic regression adjusting for matching variables age, duration of ART, and for other clinically important variables site, sex, weight-for-age, height-for-age, viral suppression, CD4 cell count, history of TB and ART regimen was used to investigate risk factors for CLD. BMI was co-linear with weight-for-age and height-for-age so was not included in the adjusted model.

Ethical Considerations

Written informed consent was obtained from participants aged ≥18 years and from caregivers of younger participants with written participants assent. Ethical approval for the study was obtained from the

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Medical Research Council of Zimbabwe, the Harare Hospital Ethics Committee, the Biomedical Research and Training Institute Institutional Review Board, Malawi-Liverpool Wellcome Trust Clinical Research Unit in Malawi, the London School of Hygiene and Tropical Medicine Ethics Committee and Regional Committee for Medical and Health Research Ethics in Norway.

Results

During the study period, 1,585 children and adolescents aged 6-19 years, taking ART for more than six months, attending for HIV care and residing within the study catchment area were sequentially screened (Figure 1). Spirometry was performed 1,603 times with 1,305 (81.4%) providing a spirometric trace of high quality. Overall, 419 (32.0%) participants had a FEV1 z-score <-1 with no reversibility post-bronchodilatation, i.e. meeting the trial definition for CLD. Of these eligible participants, 347 (82.8%) were analysed for the main trial ("CLD group", or cases in this paper) (Figure 1). The median age was 15.3 years [IQR 12.7-17.7] and 48.9% were female. A further 74 eligible participants with FEV1 z-score >0 were analysed for the control group, frequency matched by age and duration on ART (median age 15.6 years [IQR 12.1-18.2]; 62.2% female). The median FEV1 z-score was -1.91 [IQR -2.43 - -1.43] for the cases and 0.52 [IQR 0.24-0.79] for the controls (Table 1).

Among the cases, current respiratory symptoms including cough and shortness of breath were reported infrequently (9.0% and 1.7%, respectively). At rest, however, 152 (43.8%) had a respiratory rate and 14 (4.0%) had oxygen saturation below 90%. The mean duration of shuttle walk was 10 minutes 38 seconds (SD 2:00) with the mean difference in heart rate one-minute post shuttle walk in comparison to resting heart rate being 30.3 beats (SD 17.0) (Table 1). Thirteen cases did not undertake shuttle walk due to clinical findings. Hospital admissions in the previous year for chest-related problems were infrequent in both groups.

A greater proportion of cases were taking second-line ART than controls (25.6% vs. 11.0%, p-value=0.005) implying previous treatment failure. Similarly, 44.1% of cases had detectable viral load (>1000 copies/ml) at the time of enrolment, vs. 34.3% of controls. 27% of cases had a viral load <40 copies/ml vs. 36% of controls. The majority of both cases and controls were receiving cotrimoxazole prophylaxis, which is standard of care for children and adolescents in this setting regardless of CD4 count.

Over half (61.1%) of cases were stunted or underweight compared to 32.4% of controls. The prevalence of stunting, underweight and low BMI was higher in cases than controls (Table 1, p=0.001). Overall, 97 (28.0%) cases reported having received treatment for TB in the past at least once, vs. 9 (12.2%) controls (p=0.002).

Cases had higher odds than controls of being male, underweight, stunted, having a low BMI, a past

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history of TB and receiving a second-line ART regimen (Table 2). There was no evidence of an association of CLD with CD4 count or HIV viral load. In the multivariable logistic regression there was strong evidence of an association between being a case and being underweight and weaker evidence that being a case was associated with a past history of TB and with being on second-line ART (Table 2).

Discussion

This study highlights the substantial burden of CLD among treatment-experienced children and adolescents living with perinatally acquired HIV. Over one-third of participants who had a high-quality spirometry performed had an FEV1 z-score below -1 with no reversibility with bronchodilation. The median FEV1 z-score among the CLD group (-1.91) demonstrates the presence of obstructive disease. Symptoms such as cough and breathlessness were infrequently reported. The chronicity of the symptoms may lead to individuals "normalising" symptoms particularly in the context of perinatally-acquired HIV infection, where respiratory tract infections are common. However, almost half of cases had a high respiratory rate (above the 90th centile for age), implying significant respiratory compromise, despite exclusion of individuals with acute respiratory illness and those with active tuberculosis. These findings are consistent with studies reporting a high prevalence of CLD among children attending HIV care in Sub-Saharan Africa (12,24–27).

In the pre-ART era, the most common cause of CLD in children was lymphoid interstitial pneumonitis (LIP), a lymphoproliferative disorder associated with interstitial accumulation of lymphocytes and plasma cells. The condition responds to ART and the incidence has declined and is seldom reported in the ART era (28,29). The typical findings of LIP on HRCT are ground-glass shadowing, nodules and cysts. In recent HRCT studies of children taking ART, the most common pattern was suggestive of constrictive obliterative bronchiolitis with LIP being an exceptional finding (13).

A higher proportion of cases had an unsuppressed HIV viral load (>1000 copies/ml) than the control group, but this was not associated with low FEV1 z-score. It is important to note that the HIV viral load measurement was done at enrolment and is not a marker of long-term virological control; given that one-quarter of cases are taking second-line therapy it is probable they have had a period of viremia post initial ART regimen. A key finding, however, was that a higher proportion of the cases were on second-line ART (i.e. taking a protease inhibitor-based regimen) than the controls. This is an indication of poorer HIV virological control in the past, possibly caused by suboptimal adherence. It is recognised that HIV infection not only causes immunosuppression resulting in an increased risk of infections, but also promotes dysregulated systemic immune activation and inflammation, which has been implicated in the pathogenesis of chronic comorbidities including cardiovascular and respiratory disease in adults (30,31).

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Therefore, HIV viral replication and poor virological control may promote the development and/or progression of CLD.

Notably, despite the controls being matched for age and duration of ART, cases had a significantly higher prevalence of wasting, stunting and a lower BMI than controls, which are also consequences of poorly controlled HIV infection (5,32). We have recently shown high levels of cytomegalovirus (CMV) viraemia in children and adolescents taking ART, and that viraemia was associated with stunting as well as a low FVC z-score (33). CMV infection is a well-recognised co-factor for HIV disease progression and promotes immune activation, and may play a role in pathogenesis of CLD (34).

A significantly higher proportion of cases than controls had been treated for tuberculosis in the past. There may be two explanations – post-tuberculosis sequelae may be contributing to CLD, but equally clinicians may be more likely to initiate HIV-positive children with CLD on anti-tuberculosis treatment due to their clinical presentation and the high risk of tuberculosis among individuals living with HIV in this setting. Post-tuberculosis lung disease can involve airflow obstruction and/or restrictive ventilatory defects, as well as impairment in gas exchange (35–38). Airflow obstruction is associated with decreased capacity to completely expel air out of the lungs and is probably due to inflammation-induced narrowing of airways (38). Studies in Asia and Africa have consistently reported an association between past pulmonary tuberculosis and decreased FEV1 or chronic obstructive airway disease among adults (39,40). In addition FVC may be affected by pulmonary tuberculosis through lung tissue scarring, bronchial stenosis, bronchiectasis, fibrosis and pleural changes (38,41).

The strengths of this study were that individuals were screened sequentially and an objective case definition was used to recruit participants. Those with acute respiratory illness were excluded and all participants underwent screening for tuberculosis, so the findings are unlikely to be explained by acute infection. Spirometry was performed according to ATS standards and only those with high-quality tracings were enrolled into the study. Limitations of this study include its cross-sectional nature and therefore reverse causality cannot be excluded. The history of TB was obtained by self-report with no microbiological confirmation, and it is possible that those with CLD may have been over-treated for TB in the absence of an alternative diagnosis. In addition, although we postulate that PH-COB is the clinical diagnosis of the cases in this study with CLD, no imaging was performed to confirm this. However, our group has previously performed imaging studies, supporting the finding that adolescents living with perinatally acquired HIV, having a decreased FEV1 z-score have demonstrated radiological appearance of COB on high resolution CT imaging (13). The possibility of residual confounding by other factors such as socioeconomic factors, household smoking and exposure to indoor smoke cannot be excluded. However, both groups were recruited from the catchment area of the hospitals in the two cities, and it is unlikely

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that these would explain the differences observed.

To date, HIV programmes have focused on achieving viral suppression and there has been much less emphasis paid to addressing the long-term consequences of HIV infection. The median age of ART initiation in the current cohort of adolescents in Africa is 8 years (compared to under one year in US cohorts), and the long period of untreated HIV infection may explain the high prevalence of CLD and other chronic comorbidities such as stunting observed in African children (42). Furthermore, adolescence is a particularly high-risk period for poor treatment adherence and rates of viral non-suppression and subsequent virological failure are much higher in adolescents compared to in younger children and adults (43,44). This study highlights the urgent need to focus on addressing chronic comorbidities in addition to provision of ART alongside ensuring sustained viral suppression.

The pathogenesis and natural history of CLD in children is not clear, and longitudinal studies are needed. Several questions remain in addressing CLD in children and adolescents growing up with HIV infection, including the optimum modality and frequency of screening for CLD in low-income settings. Symptoms screening and plain chest radiography are insensitive tools for detecting small airways disease (12). Studies to identify effective therapeutic modalities to prevent the decline of or improve lung function e.g. pulmonary rehabilitation warrant investigation to enable optimal health outcomes for children growing up with HIV.

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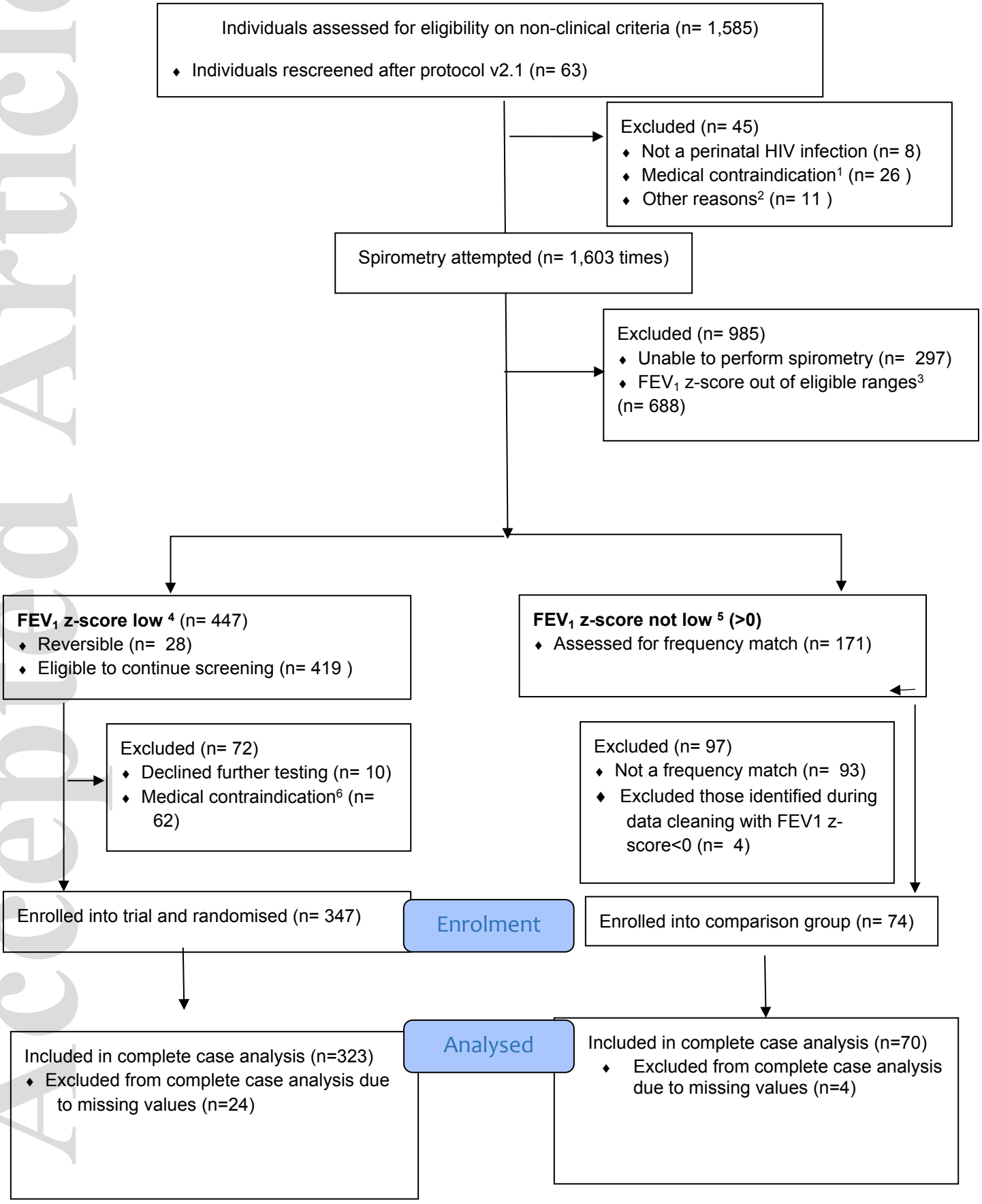
Figure 1. Flow Chart for Eligibility



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Notes

1. Medical contraindications were: taking a course of Digoxin, taking a prolonged course (>2 weeks) of fluconazole, past allergic reaction, history of jaundice or liver problems with past use of azithromycin, has worsening cough, breathlessness or sputum in the past 7 days, taking TB treatment
2. Other reasons were out of age range, pregnancy, on ART for <6 months, or no firm home address
3. A buffer zone was allowed between those with low FEV1 z-score and those to be recruited into the comparison group.
4. Protocol v1 dated 15th Dec 2015 FEV1 z-score<-1.64, Protocol v2.1 dated 9th May 2017 in Zimbabwe and 1st June 2017 in Malawi, FEV1 z-score<-1
5. Enrolment of comparison cohort commenced after protocol v2.1 dated 9th May 2017 in Zimbabwe and 1st June 2017 in Malawi
6. Medical contraindications were: Prolonged QTc interval, Unable to produce sputum to discount TB, current TB infection, Creatinine clearance of less than 30mls/minute, or ALT more than 2 times the upper limit of normal

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Table 1. Participant characteristics by FEV1 z-score

Characteristics	**CLD-group n=347**	**Comparison group n=74**	**p-value[1]**
Sociodemographic			
Site, n (%)			0.85
Zimbabwe	241 (69.5%)	55 (74.3%)	
Malawi	106 (30.6%)	19 (25.7%)	
Female, n (%)	170 (48.9%)	46 (62.2%)	0.04
Age, n (%)			0.06
6-9 years	32 (9.2%)	10 (13.5%)	
10-12 years	63 (18.2%)	14 (18.9%)	
13-16 years	149 (42.9%)	20 (27.0%)	
17-19 years	103 (29.7%)	30 (40.5%)	
Attending school currently, n (%)[2]	284 (83.0%)	65 (87.8%)	0.35
Same age as most children in class, n (%)[3]	182 (91.5%)	47 (95.9%)	0.52
Repeated ≥1 school grade, n (%)[2]	197 (58.3%)	28 (37.8%)	0.006
HIV and ART			
Years since HIV diagnosis, median (IQR)	7.4 (IQR 4.9, 9.7)	8.4 (IQR 4.7, 10.0)	0.33
Age at diagnosis (years), median (IQR)	7.6 (IQR 4.2, 10.5)	7.3 (IQR 4.1, 9.9)	0.41
Duration on ART (years), median (IQR)	6.3 (IQR 3.9, 8.5)	6.8 (IQR 3.9, 8.9)	0.48
Duration on ART[2]			
>6 months to <2 years	33 (9.5%)	4 (5.4%)	
2 to <4 years	57 (16.4%)	16 (21.6%)	0.28
4 to <6 years	72 (20.8%)	13 (17.6%)	
6 years or more	174 (50.1%)	41 (55.4%)	
Age at ART initiation (years), median (IQR)	8.4 (IQR 5.7, 11.6)	8.4 (5.1, 10.4)	0.39
Taking cotrimoxazole prophylaxis, n (%)[2]	313 (90.7%)	60 (84.5%)	0.04
ART regimen, n (%)[2]			0.007
NNRTI-based	258 (74.6%)	65 (89.0%)	
PI-based	88 (25.4%)	8 (11.0%)	
HIV VL >1000 copies/ml, n (%)	152 (44.1%)	25 (34.3%)	0.12
CD4 count (cells/mm^3), median (IQR)	571 (IQR 358, 784)	654 (IQR 384, 863)	0.21

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CD4 count < 200cells/mm^3, n(%)	34 (9.9%)	6 (8.2%)	0.67
Anthropometric			
Weight-for-age z-score, mean (SD)	-2.15 (1.47)	-1.09 (1.24)	<0.001
Underweight (weight- for-age z-score <-2), n (%)	181 (52.2%)	14 (18.9%)	<0.001
Height-for-age z-score, mean (SD)	-2.09 (1.22)	-1.50 (1.00)	<0.001
Stunted (height-for-age z-score <-2), n (%)	172 (50.4%)	22 (29.7%)	0.001
BMI-for-age z-score, mean (SD)	-1.09 (SD 1.17)	-0.21 (SD 1.05)	<0.001
Low BMI (BMI-for-age z-score <-2), n (%)	69 (20.0%)	3 (4.1%)	0.001
Respiratory			
Past history of TB, n (%)[2]	97 (28.0%)	9 (12.2%)	0.002
Number of times previously treated for TB, range	1 to 3	1 to 2	-
Admitted for chest problems in the past one year, n (%)	6 (1.7%)	1 (1.4%)	0.82
Number of times admitted to hospital for chest problems, range	1 to 1	1 to 1	
FEV1 z-score, median (IQR)	-1.91 (IQR -2.43, -1.41)	0.52 (0.24, 0.79)	<0.001

1 p-values for proportions are chi-squared, for medians are Wilcoxon rank sum, and for means are t-test

2 Missing values for: duration on ART, n=11 cases, n=0 controls; attending school currently, n=5 cases, n=0 controls; Repeated ≥1 school grade, n=9 cases, n=1 controls; taking cotrimoxazole prophylaxis, n=2 cases, n=3 controls; ART regimen, n=1 cases, n=1 controls; past history of TB, n=0 cases, n=1 controls;

3 Only asked for those currently attending school. Missing values for: Same age as most children in the class, n=61 cases, n=9 controls

4 Only asked if past history of TB

5 Only asked if admitted for chest problems in the past year

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Table 2: Characteristics associated with chronic lung disease i.e. FEV 1 z-score <-1, complete case analysis n=323 cases and n=70 controls

Characteristic	Level	**N (%) with CLD**	**Crude Odds ratio**	**P-value**	**Minimally adjusted Odds Ratio[1]**	**P-value**	**Adjusted Odds Ratio[2]**	**P-value**
Site	Zimbabwe Malawi	240 (81.6%) 83 (83.8%)	1.0 (ref) 1.17 (0.63, 2.15)	0.62	1.0 (ref) 0.99 (0.52, 1.89)	0.99	1.0 (ref) 0.90 (0.44, 1.83)	0.78
Sex	Male Female	166 (86.5%) 157 (78.1%)	1.0 (ref) 0.56 (0.33, 0.95)	0.03	1.0 (ref) 0.55 (0.32, 0.94)	0.03	1.0 (ref) 0.90 (0.49, 1.65)	0.73
WFA z-score	>= 2 <-2	154 (73.3%) 169 (92.4%)	1.0 (ref) 4.39 (2.35, 8.20)	<0.001	1.0 (ref) 4.47 (2.37, 8.43)	<0.001	1.0 (ref) 3.92 (1.73, 8.87)	0.001
HFA z-score	>=2 <-2	160 (76.6%) 163 (88.6%)	1.0 (ref) 2.38 (1.36, 4.14)	0.002	1.0 (ref) 2.28 (1.30, 4.02)	0.004	1.0 (ref) 1.03 (0.50, 2.12)	0.93
BMI z-score	>=-2 <-2	260 (79.5%) 63 (95.5%)	1.0 (ref) 5.41 (1.65, 17.77)	0.005	1.0 (ref) 5.82 (1.75, 19.32)	0.004	-	-
HIV VL copies/ml	<1000 ≥1000	180 (80.0%) 143 (85.1%)	1.0 (ref) 1.43 (0.84, 2.44)	0.19	1.0 (ref) 1.41 (0.56, 2.58)	0.15	1.0 (ref) 1.43 (0.76, 2.67)	0.27
CD4 cells/mm^3	>=200	289 (81.9%)	1.0 (ref)		1.0 (ref)		1.0 (ref)	0.79

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	<200	34 (85.0%)	1.25 (0.51, 3.11)	0.62	1.41 (0.56, 3.57)	0.46	0.87 (0.30, 2.48)	
Past history of TB	No Yes	226 (78.8%) 97 (91.5%)	1.0 (ref) 2.91 (1.39, 6.09)	0.005	1.0 (ref) 3.01 (1.43, 6.36)	0.004	1.0 (ref) 2.20 (1.00, 4.87)	0.05
ART regimen	NNRTI PI	235 (79.1%) 88 (91.7%)	1.0 (ref) 2.90 (1.34, 6.31)	0.007	1.0 (ref)3.31 (1.49, 7.34)	0.003	1.0 (ref)2.42 (1.02, 5.71)	0.04

[1] Adjusted for age (6-9 years; 10-12 years; 13-16 years; 17-19 years) and duration of ARV treatment (6 months-2 years; 2-4 years; 4-6 years, more than 6 years)

[2] Adjusted for all covariates except BMI because of collinearity

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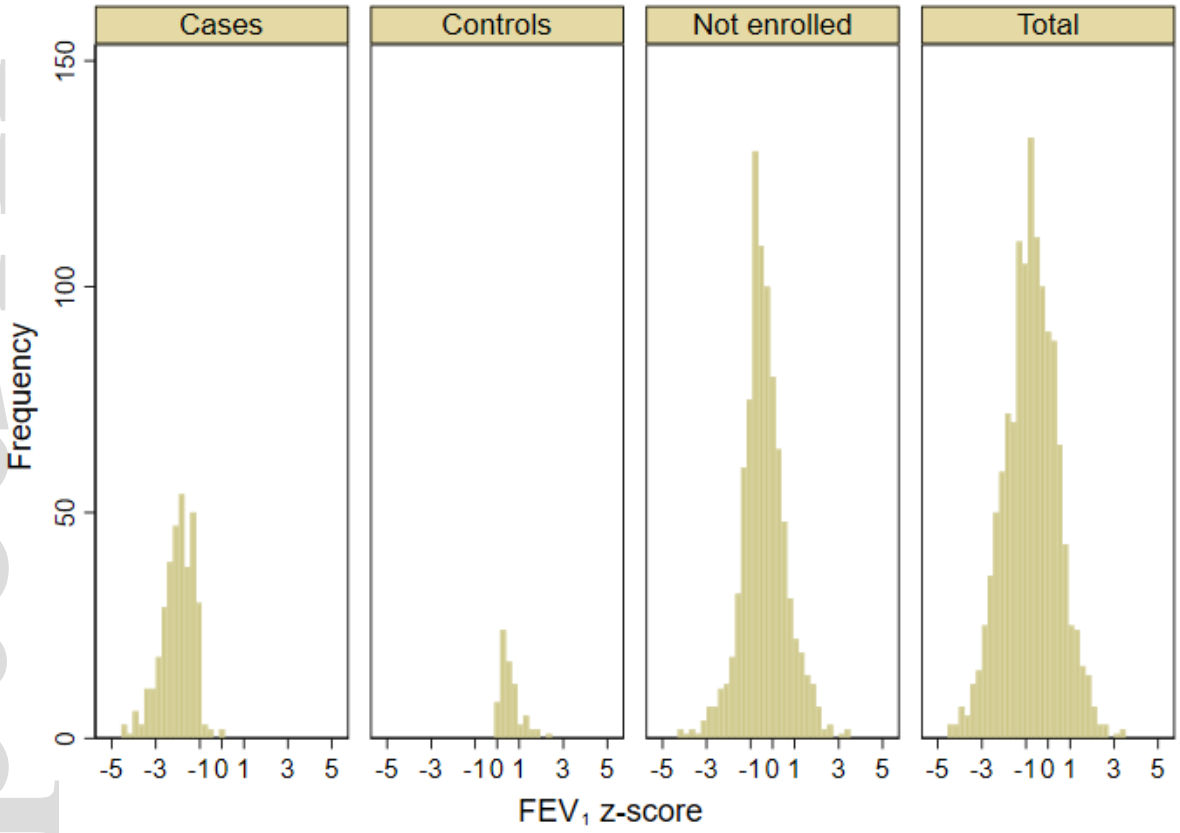
Figure 2. FEV1 distribution



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