HIV associated Chronic Lung Disease in perinatally-infected older children and adolescents: Statistical analysis plan

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1 Study setting

QECH is a tertiary referral teaching hospital for the southern region of Malawi. There are 2 paediatric HIV care clinics i.e. a pre-ART clinic (or paediatric cotrimoxazole (COT) clinic and an ART clinic. The COT clinic runs 5 days per week. Paediatric patients (0-16 years) who test HIV positive are referred to this clinic for HIV staging, CD4 count, cotrimoxazole prophylaxis and for pre ART care. If eligible for ART, they are referred to the ART clinics to initiate ART. The ART clinic for older children and adolescents take place 2 afternoons per week. Although patients are given an appointment date at the ART Clinic, their coming to the clinic depends on availability of transport money and guardian.

2 Type of study

Prospective cohort with open-label response to treatment.

3 Study population

Recruitment started on 8th July 2011. One hundred and eighty participants have been recruited and have completed the first part of a cohort study investigating response to nebulised salbutamol. All are HIV infected older children and adolescents aged 8 to 15 years.

Inclusion criteria

- Documented HIV positive
- Age between 8 to 15 years
- Guardian consent and participant assent
- Able to understand study procedures
- Usual residence within urban Blantyre and intending to continue follow-up in QECH

Exclusion criteria

- Suspected or confirmed pregnancy
- On pulmonary tuberculosis treatment.

- Presence of the following diseases: Kaposi's sarcoma, sickle disease (those with sickle trait are eligible), acute respiratory infection (acute onset [≤ 1 week] of respiratory symptoms including ≥ 1 of the following: fever, purulent sputum, pleuritic chest pain).
- Requiring immediate hospital admission or moribund.

Chronic lung disease is defined as one or more of:

- Hypoxia at rest (oxygen saturation (SaO2) of≤ 92%).
- desaturation (≥ 5% reduction in SaO2 on , or SaO2) on exercise,
- Abnormal spirometry defined as having a forced expiratory volume in one second, forced vital capacity (FEV1/FVC) ratio less than the lower limit of normal (LLN) as predicted by the age and height adjusted Wang reference values for black girls and boys between 6 and 18 years of age. (REF). These reference values were chosen because it is the largest cohort of black children with continuous range from 6 to 18 years, and properly robust sampling with LLN based on the 5th percentile (80).

Objective1: prevalence of HIV associated CLD

1. The overall estimate of the proportion (95% CI) of those who will fulfil the definition of CLD will be calculated.

Participants will be classified as having CLD using the definition above and the estimated proportion of those with CLD, and with each component of the definition of CLD above, will be tabulated.

2. Associations of CLD and some baseline/clinical characteristics

Each pre-specified potential risk factor will be tested for an association with CLD separately (Table 2). Chi-squared tests will be used for categorical variables and chi-squared tests for trend will be used for ordered categorical variables (education and NYHA stage). Logistic regression will be used to calculate odds ratios for univariable analyses and subsequently to build a multivariable logistic regression model which will include any variables which were significantly associated ($p<0.1$) with CLD in the univariable analyses (Table 3).

Table 1: Risk of HIV associated CLD in HIV infected older children and adolescents attending HIV care in Blantyre

Variable		Total with CLD (%)	Unadjusted OR	95% CI	P-value
Sex	male female				
Stunted	No Yes				
Smoker at home	No Yes				
Orphan	No Maternal double Paternal				
Education	None Primary Secondary				
On cotrimoxazole	No Yes				
On ART	No Yes				
Initial (nadir) CD4 (cell/µL)	<50 50-99 100-199 200-299 ≥300				
Current CD4 (cell/µL)	<50 50-99 100-199 200-299 ≥300				
Previous pulmonary Tuberculosis treatment	No Yes				
Breathlessness (current)	No Yes				
Chronic cough	No Yes				
Wheezing	No Yes				
Chest radiograph abnormalities	No Yes				
Clubbing	No Yes				
Hospitalised for LRTI in the past 12 months	No Yes				

>2 courses of antibiotics for LRTI in the past 12 months	No Yes				
NYHA[1] Stage 0 1 2 3/4	0 1 2 3 4				

1 New York Heart Association breathlessness scale

Table 2: Multivariable analysis of factors associated with HIV associated CLD in older children and adolescents attending HIV care in Blantyre

Variable	Unadjusted OR	Adjusted OR	95% CI	P-Value

Objective 2: symptoms, onset and pattern

Amongst those with CLD:

1. Description of onset of symptoms (e.g. n (%) acute or n (%) insidious, n (%) proceeded by chest infection).
2. Median (IQR) age of onset of each symptom: chronic cough (> 6 months), breathlessness and wheezing.
3. Median(IQR) duration of symptoms: chronic cough, breathlessness, wheezing.
4. Description of pattern of symptoms: n (%) episodic (relapsing symptoms with periods of apparent normality);n (%) steady (exacerbations of symptoms without normality inbetween); and n (%) progressive.

Objective 3:Spirometry

Definitions:

Obstructive lung abnormality: Abnormal spirometry with FEV1/FVC ratio less than LLN.

Other lung abnormality: Abnormal spirometry with FEV1/FVC greater than LLN and FVC less than LLN.

Complete reversibility: reversibility with FEV1 or FVC returning into the normal range.

Partial reversibility: reversibility with FEV1 or FVC not returning into the normal range.

1. The distributions of the measured FEV1, FVC, and PEFR values will be plotted. The mean (SD) FEV1, FVC, and PEFR of the 180 HIV infected older children and adolescents at QECH, Blantyre and their predicted values using the Wang reference values for black girls and boys between 6 and 18 years of age and Malawian reference values will be calculated. For each lung function measure i.e. FEV1, FVC and PEFR, a paired t test will be used to test the difference between the measured values and the predicted values (Table 4).

Table 3: Summary of differences between measured and predicted values of FEV1, FVC and PEFR of HIV infected older children and adolescents attending HIV care in Blantyre

Variable	Measured mean (SD)	Predicted mean (SD) WANG	p-Value [1]	Predicted mean (SD) Malawians	p-Value [1]
FEV1					
FVC					
PEFR					

FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, PEFR: peak expiratory flow rate, SD: standard deviation,
[1]from paired t-test

2. Participants will then be classified as having abnormal spirometry using the previously mentioned definition and the estimated proportion of those with abnormal spirometry will be tabulated.
3. The proportion of participants with reversible lung abnormality will be calculated and tabulated by type of abnormal spirometry. The difference in proportions will be compared by type of lung abnormality using a chi-squared test (Table 5).

Table 4: Abnormal spirometry with reversibility in HIV infected older children and adolescents attending HIV care in Blantyre

	Any Reversibility (%)	Complete	Partial	p-value
Obstructive				
Other lung abnormalities				
Total				

4. The mean change (SD) in FEV1 and FVC before and after inhaled salbutamol will be calculated and tabulated by type of abnormal spirometry. An unpaired t-test will be used to compare the mean change between the two lung abnormality groups (first assessing whether the data are approximately normally distributed).

5. Each variable will be tested for an association with abnormal spirometry separately (Table 6). Chi-squared test will be used for categorical variables and chi-squared tests for trend will be used for ordered categorical variables (education and NYHA stage). Logistic regression will be used to calculate odds ratios for univariable analyses and subsequently to build a multivariable logistic regression model which will include any variables which were significantly associated ($p<0.05$) with abnormal spirometry in the univariable analyses (Table 7).

Table 5: risk factors of abnormal spirometry in HIV infected older children and adolescents attending HIV care in Blantyre

Variable		Total with abnormal spirometry (%)	Unadjusted OR	95% CI	P-value
Sex	male female				
Stunted	No Yes				
Smoker at home	No Yes				
Orphan	No Maternal double Paternal				
Education	None Primary Secondary				
On cotrimoxazole	No Yes				
On ART	No Yes				
Initial CD4 (cell/µL)	<50 50-99 100-199 200-299 ≥300				
Current CD4 (cell/µL)	<50 50-99 100-199 200-299 ≥300				
Previous pulmonary tuberculosis	No Yes				
Breathlessness (current)	No Yes				
Chronic cough	No Yes				
Wheezing	No Yes				
Chest radiograph abnormalities	No Yes				
Clubbing	No Yes				
Hospitalised for LRTI in the past 12 months	No Yes				

>2 courses of antibiotics for LRTI in the past 12 months	No Yes				
NYHA[1] Stage 0 1 2 3/4	0 1 2 3 4				
Abnormal oxygenation (resting)	No Yes				
Abnormal oxygenation (after exercise)	No Yes				

1 New York Heart Association breathlessness scale

Table 6: Multivariable analysis of risk factors associated with abnormal spirometry

Variable	Unadjusted OR	Adjusted OR	95% CI	P-Value

Objective 4: chest radiographic abnormalities

1. Chest radiograph abnormalities will be tabulated (Table 8).

Table 7: Chest radiographic abnormalities

Chest radiograph abnormality	N (%) prevalence of abnormality with CLD in Malawi (8-15 years)
Rings/tramline opacities	
Consolidation	
Volume loss	
Paucity of vascular markings	
Non-cavitating nodules	
Ground-glass Opacification	
Hyperexpansion	
Reticular pattern	

Objective 5: response to treatment

3.1 Response to salbutamol

1. Proportion of participants with improvement (12%) in FEV1/FVC ratio as above.

2. Change in symptoms using the Global rating of change scale.

An estimate proportion (%) of participants with large change.

3. Change in symptoms using CFQ-R respiratory scores.

   An estimated proportion (%) participants with CFR-Q respiratory symptom score improvement after 4 weeks of inhaled salbutamol by≥ 5 scores.

3.2 Response to oral prednisolone

1. Proportion (95% CI) of participants with improvement (12%) in FEV1/FVC ratio.
2. Change in symptoms using the Global rating of change scale (definition as above) Proportion (%) with large change.
3. Change quality of CFQ-R: (respiratory domain score by≥ 5 scores) (as above).
4. Change in exercise tolerance change from desaturation of ≥5 % to desaturation of <5% in oxygen saturation after exercise (as above).

Numbers are unlikely to be sufficient to permit formal comparisons between types of abnormality.

Objective 6: quality of life

1. Comparing baseline median scores between individuals with CLD and those without CLD.

The baseline median (IQR) scores of each domain of the CFQ-R will calculated for participants with CLD and without CLD. For each domain median (IQR), a Wilcoxon rank-sum (Mann-Whitney) test will be used to test the difference between participants with CLD and participants without CLD (Table 9).

Table 8: Quality of life in HIV infected older children and adolescents with and without HIV associated CLD in Blantyre

CFQ-R domain	CLD	No CLD	P value
Physical functioning			
Social Functioning			
Emotional			
Eating			
Body			
Treatment burden			
Respiratory			
Digestion			
Weight			
Vitality			

2. Comparing scores before and after 4 weeks inhaled salbutamol in participants with abnormal spirometry (Table 10).

Table 9: quality of life in HIV infected older children and adolescents with abnormal spirometry, before and after 4 weeks of inhaled salbutamol

CFQ-R domain	Before salbutamol	After salbutamol	P value
Physical functioning			
Social Functioning			
Emotional			
Eating			
Body			
Treatment burden			
Respiratory			
Digestion			

The baseline median (IQR) scores of each domain of the CFQ-R will calculated for participants with abnormal spirometry before and after 4 weeks of salbutamol. The difference between the median scores before and after treatment will be calculated using the Wilcoxon signed rank sum test.

3. Comparing scores before and after 4 weeks oral prednisolone in participants with abnormal spirometry (Table 11).

Table 10: Quality of life in HIV infected older Children and adolescents with abnormal spirometry before and after 4 weeks of oral prednisolone

CFQ-R domain	Before prednisolone	After prednisolone	P value
Physical functioning			
Social Functioning			
Emotional			
Eating			
Body			
Treatment burden			
Respiratory			
digestion			

The baseline median (IQR) scores of each domain of the CFQ-R will calculated for participants with abnormal spirometry before and after 4 weeks of prednisolone. The difference between the median scores before and after treatment will be calculated using the Wilcoxon signed rank sum test.

4. Associations of domain scores with baseline/clinical characteristics and abnormal spirometry.

   The association between baseline/clinical characteristics, abnormal spirometry and domain scores will be calculated using the Wilcoxon rank sum test.

5. Comparing child administered score and parent administered scores.

The median (IQR) scores of each domain of the CFQ-R child administered and parent administered questionnaires will be calculated. The difference between the median (IQR) scores for the child and parent administered questionnaire will be calculated using Wilcoxon signed rank sum test (Table 12).

Table 11: Comparison of participants and their guardians' quality of life score for HIV infected older children and adolescents attending HIV care in Blantyre

CFQ-R domain	Child	Parent	P value
Physical functioning			
Social Functioning			
Emotional			
Eating			
Body			
Treatment burden			
Respiratory			
Digestion			