UiT

THE ARCTIC UNIVERSITY OF NORWAY

Faculty of Health Sciences

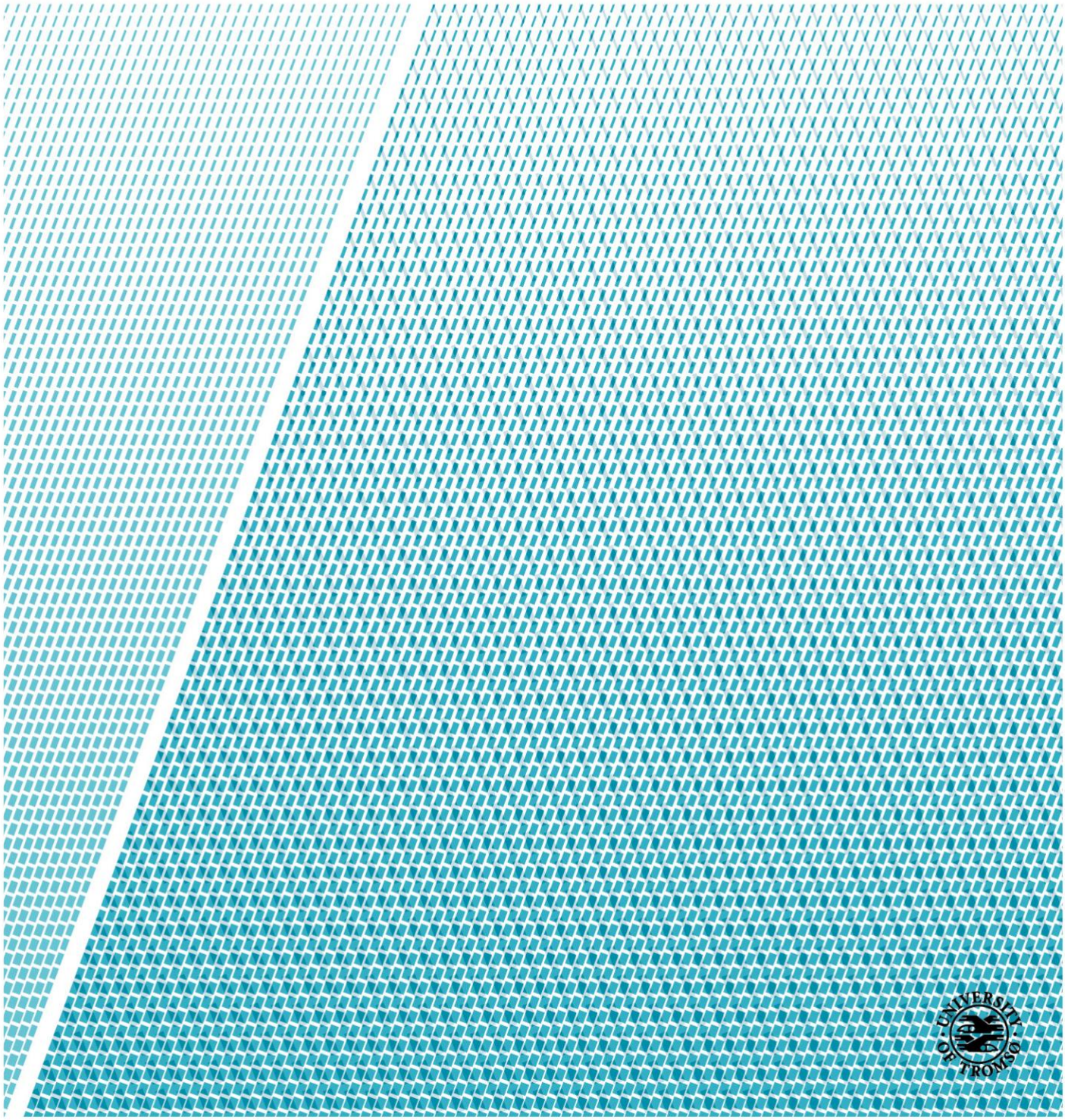
The role of tuberculosis coinfection on lung function of HIV infected children and adolescents in Africa

A systematic review

—

Trym Thune Flygel

MED-3950 Masteroppgave / MK-14
Tromsø: Medisin profesjonsstudium, June 2019
Supervisor: Trond Flægstad, Professor – IKM/UiT



Foreword

When choosing a subject for my master's thesis, I contacted my supervisor from previous work as a medical research student, professor Trond Flægstad at Institute of Clinical Medicine, Department of Paediatrics. Together with Ph.D.-scholar Evgeniya Sovershaeva we discussed issues that could be of interest for the thesis. HIV and tuberculosis coinfection is a huge challenge among children and adolescents in high burden areas, especially in Sub-Saharan Africa, and a major cause of mortality and morbidity among this group. Adolescents have often lived with HIV for a long time, and new information regarding chronic HIV complications are being recognized as the use of ART is increasing and more people are growing up with HIV.

Our first plan was to exchange data on HIV and tuberculosis coinfection in children from our collaborators at University of Cape Town. Unfortunately, this was not possible at the time I started on my thesis, and we had to explore other options. Due to my previous work on microbiota of HIV infected children with chronic lung disease in Zimbabwe, we found it interesting to review existing literature on the impact of tuberculosis on lung function and development of chronic lung disease in HIV infected children and adolescents in Africa. A brief summary of the work timeline is found in Table 1.

I want to thank my supervisors, professor Trond Flægstad, and Ph.D.-scholar Evgeniya Sovershaeva for help throughout the process of writing up this master thesis. I would also like to thank Grete Overvåg at the university library for invaluable help with conducting the systematic searches.

Trym Thune Flygel

Tromsø, June 2019

Table of Contents

List of Tables

List of Figures

Summary

Objectives: To systematically review existing literature on what role history of tuberculosis (TB) plays in lung function abnormalities and the development of chronic lung disease of HIV infected children and adolescents in Africa, as the burden of paediatric HIV and TB coinfection is the highest in this region.

Methods: Systematic searches were performed in PubMed and EMBASE databases using PICO model. Other relevant studies were found through reading reviews and other articles. All included studies were evaluated for quality of evidence using GRADE.

Results: Of 119 unique articles found through searches, 110 were excluded based on title and abstract, 3 additional studies were added, ending up with 12 studies in the review. 10 of the studies were cross-sectional, one was a prospective cohort and one was a randomized controlled trial. All studies reported spirometry as a measure of lung function. Four reported CT scans, three reported chest x-rays. HIV infected children and adolescents with a previous history of TB have a higher prevalence of reduced lung function measured by spirometry compared to HIV uninfected children and adolescents and HIV infected children and adolescents without prior TB. The main abnormality by spirometry reported was obstruction, and was associated with a previous history of TB. HIV infected children and adolescents also have higher prevalence of abnormalities on radiographical examinations, including findings suggestive of bronchiolitis and obliterative bronchiolitis (OB), irrespective of TB exposure.

Conclusion: Recent research on issues of HIV-related comorbidities in children and adolescents has increased. However, most of the studies done to this date are of low or very low quality of evidence. Further studies of higher quality on HIV and TB coinfection and the long-term effects of disease and treatment are needed to better understand the pathogenesis, clinical recognition and to asses treatment options.

Abbreviations

Abbreviation	Full name/text/description
Adolescents	WHO: 10-19 years of age.
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ATS	American Thoracic Society
Children	WHO: 0-14 years of age. Convention of the Rights of Children 0-18 years of age
CLD	Chronic lung disease
COPD	Chronic obstructive pulmonary disease
CT	Computed Tomography
DLCO	Diffusion capacity
Emtree	Embase Subject Headings
eNO	Exhaled Nitric Oxide
ERS	European Respiratory Society
FEV_1	Forced respiratory volume in one second
FEF_{25-75}	Flow between 25 and 75% of FVC
FRC	Functional residual capacity
FVC	Forced vital capacity
GLI	Global Lung Initiative
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	Human Immunodeficiency Virus
IGRA	Interferon gamma release assay
IRIS	Immune Reconstitution Inflammatory Syndrome
LIP	Lymphocytic Interstitial Pneumonia
LRTI	Lower respiratory tract infection
LTBI	Latent Tuberculosis Infection
MDR-TB	Multi-Drug Resistant Tuberculosis
MeSH	Medical Subject Headings
MSM	Men who have sex with men
OB	Obliterative bronchiolitis
PEFR	Peak expiratory flow rate
PCP	Pneumocystis Jiroveci pneumonia
PMTCT	Prevention of mother to child transmission (of HIV)
PTB	Pulmonary Tuberculosis
RCT	Randomized Controlled Trial
SIV	Simian Immunodeficiency Virus
TB	Tuberculosis
TST	Tuberculin skin test
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization
Xpert MTB/RIF	Real-time DNA test that detects TB and rifampicin resistance

1 Introduction

1.1 Human immunodeficiency virus (HIV)

Human immunodeficiency virus (HIV) is a virus grouped in the genus Lentivirus, in the family Retroviridae (1). Its genome consists of two identical single-stranded RNA molecules, that are found in the core of the virus together with two of the three main enzymes; reverse transcriptase and integrase, whereas the third enzyme; protease is situated between the core and the envelope that surrounds the virus. The envelope contains several glycoprotein complexes that are essential for the virus ability to attach to host $CD4^+$ T-cells (2). HIV spreads through three routes of transmission; blood, from mother to child and sexual transmission. It causes severe depletion of $CD4^+$ T-cells, which in turn leads to a compromised immunoreaction and thereby immunodeficiency and makes the host susceptible to opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PCP), Kaposi's sarcoma and more (3).

The first cases of what later became known as HIV infection were described by Gottlieb *et al.* among men who have sex with men (MSM) in United States of America in 1981 (4). In 1983, French clinicians had identified a new human retrovirus (5) and by 1984 a serologic test to identify HIV as the cause of acquired immunodeficiency syndrome (AIDS) was developed (6). Research on the field of HIV grew rapidly, and in 1989 HIV antibodies were discovered in African monkeys, proving that HIV was a result of transmission across species of the simian immunodeficiency virus (SIV) (7). Further, the discovery of $CD4^+$ T-cells as the main target of the virus (8, 9) and the discovery of coreceptors CXR4 and CCR5 in 1996 (10) made the introduction of combination antiretroviral therapy (ART) to prevent the development and spread of disease possible (11).

1.1.1 Epidemiology

As already mentioned, the global HIV/AIDS pandemic started with the discovery of immunodeficiency in previously healthy MSM in USA in the early 1980´s (4). AIDS rapidly spread across the world within the next decade, not only striking the gay population, but people of all genders, sexuality and races around the entire globe, making it a global pandemic (12, 13). By the middle of 1990´s, more than 20 million people were living with

HIV, most of whom in Africa, south of the Sahara (13). This number has continued to increase, and by 2017 an estimated 36,9 million people were living with HIV worldwide, 19,6 million of which in eastern and southern Africa (14, 15).

With new information and due to introduction of ART, people with HIV live longer. We now see that the number of people living with HIV is increasing, but the number of newly infected individuals are on a trend towards declining worldwide. In 2010 2,2 million people were newly infected by HIV, and in 2017 this number was at 1,8 million (14, 15). The biggest decline in new infections happen in the high burden regions, such as eastern and southern Africa, where the reduction in new HIV infections from 2010 to 2017 was at 30%, and the reduction of AIDS-related deaths was at 42% in the same period (Figure 1) (15). This reduction is mainly because of the scale up of national programs for ART, towards the UNAIDS 90-90-90 agenda (90% of people with HIV knowing their status, 90% who know their status are receiving ART and 90% on ART are virally supressed) (16). By 2017 approximately 66% of the population living with HIV in eastern and southern Africa were receiving ART and 52% were virally supressed (15).

1.1.2 HIV in children

By 2017 an estimated 3 million children and adolescents aged 0-19 years were living with HIV (1,2 million children 0-9 years, 1,8 million adolescents 10-19 years), with 87% of cases being in sub-Saharan Africa (14, 17). Treatment programs for prevention of mother to child transmission of HIV (PMTCT) are well established, covering an estimated 77% of pregnant or breastfeeding woman with HIV worldwide. In eastern and southern Africa, this number is a remarkable 93%, making the transmission rate under 10% in 2017 (15). Still, there are children vertically transmitted by HIV, especially in rural areas of low- and middle-income countries. As more people living with HIV are receiving treatment, a growing problem is that a large number of HIV-infected children are now growing up to adolescence, leading to an increase in adolescents living with HIV in high burden regions. There has currently been done few studies on this group, but newer publications implicate that growing up with HIV is an increasing threat to the health of children and adolescents, and several complications due to growing up with HIV are emerging (18, 19). World Health Organization (WHO) alarms that the number of AIDS-related deaths among adolescents are increasing, especially in the

African region, making it the number 2 cause of death in adolescents. At the same time AIDS-related deaths are declining in all other age groups (20).

1.2 Tuberculosis (TB)

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* complex, which consists of the bacilli *Mycobacterium bovis*, *-tuberculosis*, *-africanum* and *-microti*. *M. tuberculosis* is an obligate intracellular pathogen, with humans being it´s primary host (21, 22). The bacteria is not classified as Gram negative or Gram positive, but acid-fast, as it does not decolorize by acidified organic solvents (21). It has a slow rate of mutation, and culturing can take more than six weeks. The disease is transmitted by cough aerosols from an individual with active TB in the lungs, which then are inhaled to the alveoli of the new individual. TB is considered most contagious when a person has active lung TB with findings of acid-fast bacilli by Ziehl-Neelsen staining, yet smear negative patients cannot be considered non-contagious (23). The dominant site of TB infection is in the lungs (pulmonary TB), but the bacilli can cause disease in any organ, often with diffuse symptoms, making diagnostics of the disease challenging (21).

M. tuberculosis was first described by Robert Koch in 1882 in Germany (24), although the disease had been described for thousands of years prior (22). In 1907 the paediatrician von Pirquet from Vienna developed what we today know as the intracutaneous tuberculin skin test (TST) for latent tuberculosis infection (LTBI) (22). In 1921 the first version of the Bacillus Calmette-Guérin (BCG) vaccine was tried in human subjects with subsequent promising results, but it was first in 1973 that WHO recommended widely BCG vaccination (25). From the 1940's the development of effective anti-tuberculosis drugs begun, and led to the discovery of the chemotherapeutic drugs that are essential in treatment of TB also today (22, 26). In 1943 Streptomycin was discovered, followed by Isoniazid in 1952 and Rifampicin in 1963 (22).

1.2.1 Epidemiology

Tuberculosis is among the top 10 causes of mortality worldwide, and is the number one cause of death by a single infectious agent, now causing more annual deaths than HIV/AIDS and

malaria (27). It is estimated that 1,7 billion people are infected by TB worldwide, but only 5-10% are thought to develop active TB disease in their lifetime. In 2017 an estimated 10 million people developed TB disease, of whom 1 million (10%) children aged 0-14 years. Further, 9% of people with TB disease were among HIV infected individuals, of whom 72% live in Africa. The 20 countries with the highest incidence of TB accounted for 84% of the global burden of TB in 2017. 1,6 million people died of TB in 2017, 300.000 of which were HIV infected and 230.000 were children (27).

Increased focus on prevention and treatment of TB has led to the incidence rates of disease to be declining, at approximately 2% per year worldwide. The largest decline has been observed in Europe and Africa at 5% and 4 % respectively (27). 16% of people with TB disease died from it in 2017, a decline of 7% from 23% in year 2000. Among HIV infected individuals the decline in TB deaths in the same time period was at 44% (27). Although the numbers are decreasing, this is not enough to reach the WHO goals of the End TB Strategy. To reach this, worldwide decline in incidence needs to be at 4-5% annually and deaths by TB need to drop below 10% (28).

1.2.2 Tuberculosis in children

As previously mentioned children account for a large part of the global TB burden, and suffer grave mortality and morbidity in high endemic areas. Unfortunately, children with TB has been neglected as adult standards of diagnosis of TB often is not suitable for detecting disease in children, leading to underreporting and underdiagnoses in children (29). Some of the differences in adult and paediatric TB is that children often have a more paucibacillary disease, and have therefore not been considered at high risk for contamination or to the public health (29). Despite having more frequent paucibacillary disease, especially young children are at higher risk of developing active disease, and are more likely to develop severe or disseminated and extrapulmonary TB (30).

Due to the nature of paediatric TB disease, diagnostics are challenging, as it can mimic other common childhood diseases, including HIV infection. In many resource-limited settings the

only diagnostic tools are bacterial confirmation through sputum smear microscopy. Children produce less sputum, and only a small percentage are microscopy positive to acid-fast bacilli. Approximately 70% of children remain culture negative where TB is the most probable cause of disease (30). WHO has outlined the key risk factors for paediatric TB to be household or close contacts with confirmed TB, age less than 5 years, HIV infection and severe malnutrition (31).

1.2.3 Diagnostic tools for paediatric TB

Bacteriological confirmation (culture) of acid-fast bacilli from the location of suspected TB disease is considered the golden standard of diagnostics (30, 31). As mentioned, this can be complicated to obtain in children, and other diagnostic tools are necessary. Today's diagnostics is mainly based on clinical manifestations, history of TB exposure, chest x-rays for suspected pulmonary TB (PTB) and the TST. Other diagnostic tools include interferon gamma release assay (IGRA) and real-time PCR test Xpert MTB/RIF. However, access to such tests, including TST, are limited in many high burden areas of TB (30, 31).

TST is an intracutaneous test where different mycobacterial antigens are injected to the skin, where they cause an immune response within 48-72 hours, and the induration of the skin can be measured in mm. When interpreting the size of the induration, one must consider the patients risks of having TB disease as well as the diameter of the induration. In HIV infected or severely malnourished children a cut-off is set at 5 mm, whereas 10 mm is used for all other children regardless of prior BCG vaccination (31). The IGRA test is a blood test that measures the levels of released interferon gamma by T-cells after stimulation from *M. tuberculosis*. It has shown similar accuracy as the TST in children, but cannot be used to differentiate latent from active disease (30). Neither of the test can be used to exclude TB in children, and limited data is available on IGRA in populations with diagnostic difficulties, such as HIV infected children. IGRA is therefore not recommended to replace the TST (31).

Xpert MTB/RIF is an automated real-time PCR DNA-test that can rapidly detect TB infection and resistance towards rifampicin. The accuracy of the Xpert MTB/RIF has been shown to be

very high in adults, with high specificity and sensitivity, yet lower in HIV infected adults (32). The evidence in children is less evident, but WHO has endorsed the use of Xpert MTB/RIF to be used over conventional microscopy and culturing for detecting TB and rifampicin resistance in children, both for pulmonary and extrapulmonary TB. However, the test is still largely unavailable in resource-limited settings due to its costs and complexity (31).

1.2.4 Multidrug-resistant TB (MDR-TB)

MDR-TB is defined as TB disease caused by *M. tuberculosis* that is resistant to at least rifampicin and isoniazid. Extensively drug-resistant TB (XDR-TB) is MDR-TB with additional resistance towards at least one fluoroquinolone or second-line injectable (27). A study by Zignol *et al.* that looked at data reported to WHO from 35 countries, including Namibia and South Africa, with at least one paediatric case of TB, showed that overall children are as likely as adults to have MDR-TB. However, in both countries mentioned, together with UK, Germany and USA, children had higher odds ratio of MDR-TB than adults (33). Further, there is a great overlap between the high burden countries of HIV and TB coinfection and MDR-TB, and there has been shown an association between HIV infection and MDR-TB (27, 34). The paucibacillary nature of paediatric TB disease together with the challenges of diagnosis may therefore be a cause of underdiagnoses and underreporting of MDR-TB in children, especially in HIV infected (33).

1.3 HIV and TB coinfection in children

1.3.1 Epidemiology

HIV increases the risk of developing active TB disease. It is estimated a 20-30-fold increase in the risk of developing active TB in HIV infected, ART naïve individuals compared to HIV uninfected with LTBI. HIV is considered the single strongest risk factor of developing active TB (27, 35). It is reported that a third of all people living with HIV die of TB disease (27). However, data are limited with regards to HIV and TB coinfection in children, and prevalence estimates vary. In a review by Venturini *et al.* from 2014, the prevalence of HIV among children with TB varied from 5.8% to 56% in 8 different studies. In the 4 studies included from Sub-Saharan Africa, the prevalence varied from 37% to 56% (36). With the increased

coverage of ART, also in HIV infected children, there has been a great reduction in new TB cases. However, the incidence of TB is still remarkably higher in HIV infected children compared to healthy children (37).

1.3.2 Pathophysiology

It is known that the interplay between HIV and TB infection cause alterations in the pathogenesis of the two diseases. This interplay is complex and is caused by multiple factors (35). There are several mechanisms which can explain why HIV infected individuals are more prone to develop active TB disease.

$CD4^+$ T-cells are the main point of attack of HIV infection, and in early HIV infection, before decrease of $CD4^+$ T-cell counts in peripheral blood can be detected, the cells are functionally impaired. This impairment includes a poorer opportunity to recognize antigens, and progresses as depletion of $CD4^+$ T-cells increases. The recognition of antigens is also thought to be further impaired by inhibition of cytokine responses that together can cause failure in activation of MTB specific $CD4^+$ T-cells at the site of TB disease. This may explain the increased risk of developing TB when an individual is HIV infected, but still has preserved levels of $CD4^+$ T-cells (35). This may also be part of why the risk of containing TB disease remain a 5-10-fold increased in HIV infected individuals, even after initiation of ART and in individuals with high $CD4^+$ T-cell counts (35, 36). Although the risk of developing TB disease remains higher even after initiation of ART, which restores the $CD4^+$ T-cells in HIV infected individuals, the decrease in risk in the first years of ART is at 80-90% and mortality of TB in HIV infected individuals is reduced greatly. However, this reduction of HIV´s effect on TB is only partial (35).

Further, macrophages play an important role in both diseases. In TB, macrophages are the principal effector cells in the immune responses, but they may also contribute to an environment that is favourable for both mycobacterial growth and replication of HIV (35). TB also causes accelerated decrease of immune function in HIV infected patients, by increasing HIV replication, due to intercellular reactions between immunological cells at the site of TB

disease. An increase in HIV viral load has been shown in plasma of patients with active TB disease, whereas LTBI does not increase viral load (35).

1.3.3 Clinical features

HIV and TB have similar clinical manifestations in children, making diagnosis of TB more difficult among this patient group. The clinical manifestation of both TB and HIV in children include fever, weight loss and lymphadenopathy. These symptoms together with long lasting cough can lead to missed and/or delayed diagnosis of TB in HIV infected children, making long term complications such as chronic lung disease more prominent in these children. However, TB infection in HIV infected children are often more clinically severe than in uninfected (36). WHO recommends HIV testing to all patients, including children with suspected or confirmed diagnosis of TB, and TB screening to all HIV infected children (31). In adults, there has been reported a higher prevalence of extrapulmonary manifestations of TB in HIV infected individuals (38). However, in children studies have been varying, but a higher risk of combination of PTB and extrapulmonary disease has been shown (39). What is agreed upon is that TB in HIV infected individuals, including children, more often have a disseminated form of disease, and depends on the immune status of the individual (36).

1.3.4 Treatment

WHO guidelines recommend immediate start of a two month, four-drug regimen (rifampicin, isoniazid, pyrazinamide and ethambutol), followed by a 4 month, two-drug regimen (rifampicin and isoniazid) in HIV infected children found to have active TB. HIV infected children should not receive intermittent treatment and after successful treatment they should take isoniazid as preventive prophylaxis for another 6 months. ART should be initiated after TB treatment as soon as tolerated and, no later than 8 weeks after initiation of TB treatment (31). This is to reduce risk of developing immune reconstitution inflammatory syndrome (IRIS). HIV infected infants and children should not receive BCG vaccination due to increased risk of disseminated BCG disease (31).

1.3.5 Immune reconstitution inflammatory syndrome (IRIS)

When ART is initiated in HIV infected individuals a paradoxical immune reaction, IRIS, can occur. This is a temporary exacerbation of disease that usually occurs in severely immunocompromised patients within the first 3-6 months of taking ART. The pathogenesis of IRIS is incompletely understood, but is thought to be a consequence of a dysregulated response to a pathogen, *M. tuberculosis* being one of the most common (40). It is often associated with a rapid decrease in VL and increase of CD4 T-cells, and can also be a clinical manifestation of undiagnosed TB in HIV infected individuals, but is also shown in those already on anti-TB treatment (36). Clinical manifestations include worsening of the previous mentioned symptoms of TB with fever, increased size of lymph nodes and increased pulmonary symptoms and respiratory failure (31, 41). IRIS in children is thought to have many of the same causes, risk factors and course of disease as in adults, however, data on paediatric IRIS in TB coinfected children are scarce. Treatment include continuation of ART and anti-TB drugs with addition of non-steroid anti-inflammatory drugs or corticosteroids (41).

1.4 Lung function tests

Currently a number of tests are used to assess lung function. I will briefly describe three of the most commonly used tests by American Thoracis society and European Respiratory society guidelines (42), as well as exhaled nitric oxide.

1.4.1 Spirometry

Spirometry is the most widely used test for lung function in both children and adults. It is a measurement of volume and flow of inhaled and/or exhaled air as a function of time. Spirometry has a wide range of indications including screening individuals at risk of pulmonary disease, to assess lung function or prognosis of pulmonary disease and to assess therapeutic interventions and more (43). A spirometry test requires cooperation between the clinician and a patient, and depend on both personal and technical factors. Hence, the need of a suitable reference group is needed, as lung function depends on an individual's sex, age, height and weight as well as race/ethnicity (44). For optimal interpretation of spirometry results, the test should be repeated at least three times, using the best results from these combined (43).

The main measurements from a spirometry test include forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), the rate between the two measurements; FEV_1/FVC, peak expiratory flow rate (PEFR) and forced expiratory flow between 25 and 75% of vital capacity (FEF_{25-75}). FEV_1, FVC and PEFR are also subject to interpretation when doing bronchodilator reversibility testing to see if the limitations in lung function are reversible. Spirometry is then performed before and after administering bronchodilator drugs, usually a β-agonist such as salbutamol (43). When interpreting results, one must use a suitable reference population to calculate percentage of predicted values for each of the measures mentioned above. Further a lower limit of normal (LLN) cut-off value is set to define pathologic measures of airflow limitation (42).

1.4.2 Diffusion capacity (DLCO)

Another test for lung function is the single-breath carbon monoxide (CO) uptake in the lungs, a measure of diffusing capacity of carbon monoxide in the lungs. Simplified, this can be explained by two properties; 1. membrane conductivity, explaining diffusion properties of the alveolar capillary membrane and 2. binding of CO to haemoglobin (45). The test individual inhales a mixture of gas, including CO, where almost 100% of the inhaled CO will diffuse and bind to haemoglobin. After holding their breath for approximately 10 seconds, the concentration of CO in exhaled air is measured. The difference in concentration between inhaled and exhaled CO will then give information about the diffusing capacity of the lungs, and can be used to calculate the alveolar volume. Values need to be adjusted to confounding factors such as haemoglobin level and obesity (45).

1.4.3 6-minute walk test/shuttle walk test

The 6-minute walk test (6MWT) and shuttle walk test are objective evaluations of exercise capacity. It is often used to evaluate the function of therapy on moderate to severe heart or lung disease, as well as a screening tool for functional status or as a predictor of morbidity (46, 47). The 6MWT is a walking test where the subjects of interest choose their own pace and walks as far as possible along a flat corridor or on a treadmill within 6 minutes, primary outcome is walking distance. It is recommended to measure heart rate, respiratory rate, blood

pressure and saturation (SpO_2) before, during and after the test (46). The shuttle walk test is a test where the subjects walk in the same conditions as 6MWT, measuring walked distance, at an externally controlled pace. Walking speed is controlled by pre-recorded signals that increases in pace until the subject no longer can continue, until a maximum of 20 minutes (47).

1.4.4 Exhaled nitric oxide (eNO)

Nitric oxide (NO) is produced by a variety of cells in the lungs. Under normal circumstances the NO-production is constant, and helps regulate various functions of the airways, including bronchodilation, inflammatory response and secretion of mucus (48). Exhaled NO (eNO) can be used as a marker for airway inflammation and measurements of eNO is an affordable, easy and non-invasive method. However, the clinical use of this test is scarce, but the test may be a supplement to other standardized lung function tests (49). Increased levels of eNO are associated with systemic and lung inflammation, and is shown in e.g. asthma. Reduced levels are seen in active PTB disease and cystic fibrosis, which may be caused by inhibition of enzymes required to produce NO or reduced diffusion due to excessive mucus production (50).

1.4.5 Disease patterns

An obstructive pattern is recognized by a reduction in FEV_1, FEV_1/FVC and PEFR by spirometry. Usually a cut of at 70% predicted FEV_1/FVC, or the use of lower 5^{th} percentile LLN is set to define obstructive lung disease. This shows as an concave flow-volume curve on spirometry (44). Restrictive pattern is recognized by reduction in predicted FVC and normal or increased FEV_1/FVC values. In severe restrictive lung diseases, the FVC can be decreased to a level where FEV_1 also declines, making the FEV_1/FVC unchanged. A restrictive pattern is seen as a convex flow-volume curve on spirometry (44). Mixed pattern spirometry includes a combination of obstructive and restrictive features, with both FEV_1/FVC and FVC being in the low 5^{th} percentile of predicted (44).

DLCO measures are also compared to reference populations and often needs to be evaluated together with spirometry results. Increased DLCO values with normal spirometry can be seen

in e.g. asthma and mild left heart failure, whereas low DLCO values with normal spirometry can be seen in pulmonary vascular disease and early interstitial lung disease. Low DLCO with restrictive spirometry is seen in interstitial lung disease and pneumonitis and low DLCO with obstructive spirometry pattern is seen in bronchiolitis, cystic fibrosis and emphysema/chronic obstructive pulmonary disease (COPD) (45, 51).

The results of both 6MWT and shuttle walk test are unspecific, but gives an indication of the subjects´ functional capacity as well as level of morbidity. Both tests have good retest reproducibility, given that testing procedures are consistent. If using a reference population for calculating predicted measures, these should take into considerations the same features as with spirometry (47).

1.5 Pulmonary comorbidities

Lung impairment is common in HIV infected children and adolescents. There is a wide spectrum of HIV-associated lung diseases occurring. I will briefly describe some of the most common pulmonary comorbidities, besides TB, reported in HIV infected children, that may contribute to the higher levels of poor lung function in HIV infected children and adolescents.

1.5.1 Lymphocytic interstitial pneumonia (LIP)

LIP was a common disease among perinatally HIV infected children prior to the introduction of ART (52). The pathogenesis of the disease is not completely understood, but it is found to be related to Epstein-Barr virus and HIV infection, and is characterized with lymphocytic infiltration of the lungs (53, 54). The clinical presentation of LIP is most common at ages 2-3 years, and involves respiratory symptom such as cough, mild tachypnoea and presence of digital clubbing. Extrapulmonary manifestations such as generalized lymphadenopathy and hepato- or splenomegaly may occur. Hypoxemia is rare (54). On chest X-ray one can see a central diffuse reticulonodular pattern, that can be difficult to differentiate from miliary TB (55). Spirometry often show a restrictive pattern; however, obstruction can be present due to overlapping disease. Treatment is symptomatic, including oral corticosteroids, and LIP has been shown to respond well to ART. The prevalence of the disease has decreased drastically

after introduction of ART (56). LIP can lead to chronic lung disease with bronchiectasis and cystic changes with increased risk of recurrent respiratory infections (56).

1.5.2 *Pneumocystis jiroveci* pneumonia (PCP)

PCP was earlier a common opportunistic pathogen causing infection in HIV infected children. Clinically it presents as a severe, rapidly progressing pneumonia, and despite rapid access to antibiotics the mortality rates are high (57). Common X-ray findings are increased lung volumes and diffuse parenchymal opacification (58). After introduction of ART and prophylactic treatment using trimethoprim-sulphamethoxazole the rates of children getting infected with PCP has declined tremendously, along with the mortality (54). However, in developing countries it remains a significant part of the disease burden of HIV infected children (54).

1.5.3 Obliterative bronchiolitis (OB)

OB is a rare, but severe lung disease with poor treatment options to date. The pathogenesis of the disease is unknown, but OB can be caused by a variety of exposures and underlying illnesses. The most frequently reported causes of OB are after allogenic haematopoietic stem-cell transplantation and lung transplantation, but there has also been reported cases due to inhalation of toxins and it has been reported in association with other autoimmune diseases such as rheumatoid arthritis (59-62). In children, post infectious OB has been described, mainly after respiratory tract infections such as adenovirus and Mycoplasma pneumoniae (63). OB is a small airway disease of the bronchioles, where injury and inflammation of airway epithelium and sub-epithelial structures can cause excessive fibroproliferation. A poor repair response, including inadequate epithelial regrowth, can in turn lead to narrowing of the bronchioles and ultimately airflow limitation. The damages are permanent and the clinical features include chronic cough, hypoxemia and reduced lung function. An obstructive pattern spirometry is indicative, with reduced FEV_1 and FEV_1/FVC, and poor response to bronchodilator drugs and ART (61, 64). Radiological findings in OB often include normal conventional chest x-ray, whereas computed tomography (CT) scans can show areas with decreased density of lung tissue and reduced vascular calibre. This patchy pattern is usually referred to as decreased mosaic attenuation (61). Dilatation and thickening of larger airways, as seen in bronchiectasis can occur with advanced disease (61).

1.5.4 Bronchiectasis

Bronchiectasis is a chronic, irreversible lung disease, and is recognized as one of the main causes of lung impairment in HIV infected children, and may be associated with poor immune function in HIV infected children with low $CD4^+$ T-cell counts (54). Bronchiectasis is characterized by permanent changes of the bronchial tree with dilation of airways. The clinical pattern is dominated by productive cough and the dilation of airways causes a less effective clearance of secretions that in turn leads to recurrent and chronic respiratory infections (65). Other signs are digital clubbing, wheezing, dyspnoea and haemoptysis. Radiological findings include ring and/or tramline opacities on chest x-ray (66). Bronchiectasis can be caused by several underlying conditions with recurrent and chronic respiratory infections being most common, including PTB, PCP and LIP (54). HIV infection is, as mentioned, a risk factor for both developing TB and recurrent respiratory tract infections, which may therefore be one of the reasons why HIV infected children have a higher prevalence of bronchiectasis. However, it can be possible that HIV infection itself predisposes to the development of bronchiectasis, even without prior history of respiratory tract infections (67). The cause seems to be multifactorial, but a key factor for development of HIV-associated bronchiectasis is the over-activation of the innate immune system in HIV infection. Further, high levels of neutrophilic inflammation of airways shown in HIV infected individuals may cause excessive destruction of lung tissue, leading to development of bronchiectasis (68, 69).

1.6 Impact of treated TB on lung function

Drug susceptible TB is considered highly curable using todays recommended treatment programme by WHO, with 82% successful treatment rate globally in 2016 (27). Despite curing pulmonary TB disease, up to 50% of microbiologically cured patients are reported to have some kind of pulmonary impairment, that can range from minor abnormalities to severe pulmonary dysfunction (70). The features of post TB lung impairment are reported to be highly heterogenous with reports of both bronchiectasis, pulmonary cavitation, fibrosis or even combinations of these pathologies. By spirometry measures both obstructive, restrictive and mixed patterns are reported, airflow obstruction being the most common (70). HIV coinfection seems to be an additional risk factor, with HIV and TB coinfected patients

showing higher levels of pulmonary dysfunction including airflow obstruction, although data on this patient group is poor (70). However, in addition to extent of disease and length of treatment, there has been shown a correlation between $CD4^+$ T-cell counts and extent of lung damage, with low $CD4^+$ T-cell counts being a risk factor for more severe lung impairment by chest x-ray and spirometry (71). Most studies are performed in adults, and data of lung impairment post TB treatment in children are scarce.

Radiological findings of both active TB disease and post treatment sequela can be of great variety. There are limited studies on post TB treatment radiologic lesions and results are conflicting. By CT scans the most common manifestation post TB treatment is bronchiectasis, which has been shown in 30% - 60% with active recurrent TB disease and in up to 86% in patients with inactive disease (72). However, by conventional chest x-ray, the most common manifestation has been shown to be fibrosis, affecting up to 40%, with bronchiectasis only proven in small percentages of patients (73).

2 Methods

2.1 Objectives

The objectives of this study were to systematically review existing literature on how tuberculosis plays a role in lung function impairment and chronic lung disease of HIV infected children and adolescents in Africa. HIV and TB coinfection is a huge challenge among children and adolescents in high burden areas, especially in Sub-Saharan Africa, and a major cause of mortality and morbidity among this patient group (20).

2.2 Search methods

After consulting with a librarian, a paediatrician and a Ph.D.-scholar in paediatrics we decided on the search strategy, using the PICO framework (Table 2) (74). The search was conducted on April 8th 2019 using a combination of MeSH terms and keywords in PubMed database/search tool. I also conducted a search in EMBASE database, using Ovid search tool, and the same strategy, only by Emtree subject headings. This combination was used to include most relevant papers and to catch the newly published papers, not yet mapped with

MeSH or Emtree terms. Search details can be seen in Figure 2. The search using Emtree and MeSH terms were conducted using the "explode" function to include all relevant mappings, not to lose important studies. Search words were combined using "AND" and "OR" according to the PICO framework (Figure 2).

2.3 Data collection

I chose to include only articles on African individuals, as this is the part of the world where the burden of HIV and TB in children is the highest. Only studies involving child and adolescent populations were considered, and those not involving both HIV, TB or prior history of TB and assessment of lung function were excluded. Other studies excluded were case reports, case series of less than 10 individuals, commentaries, conference- or meeting abstracts only, reviews and meta-analysis or studies not published in English. Reviews and meta-analysis were read through and checked for relevant references.

All studies included in the review was assessed for quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (75). The GRADE guidelines include assessment of quality of the study, consistency, directness, precision and risk of bias. The studies are then graded by four levels of quality ranging from very low quality of evidence (⊕◯◯◯) to high quality of evidence (⊕⊕⊕⊕).

The included studies had a high heterogenicity in what they reported, and we found it most expedient to narratively compose the results. A summary of the studies is found in Table 3, and all GRADE evaluations are found in the appendix.

3 Results

The searches gave me 45 articles in PubMed, and 81 in EMBASE, which results in a total of 126 articles. 7 duplicates were identified and removed, resulting in 119 unique articles. 110 articles were excluded by abstract review using the already explained criteria, resulting in 9

articles included in the review. In addition to the systematic search, I added two articles found through reading reviews and from the references of already included studies. One final study that is accepted in AIDS, and published by manuscript online only, was also included. The process is shown in Figure 3, a modified flow chart from the PRISMA statement (76).

Of the 12 studies included in this review, 10 were cross-sectional, one was a prospective cohort study and one was a randomized controlled trial (RCT). Five of the studies were conducted in Zimbabwe, five in South Africa, one in Malawi and one in Kenya. 10 of 12 studies were of low or very low quality of evidence as per GRADE guidelines, two were of moderate quality of evidence (75). There was only one randomised controlled trial included (77). Although its main objective was not directly related to TB, I chose to include it due to the information it provides on testing of the antibiotic erythromycin on lung function in HIV infected children with likely recurrent respiratory tract infection or TB-related bronchiectasis. A summary of all included studies with main findings on lung function and TB as well as quality assessment by GRADE is found in Table 3.

A total of 1774 HIV infected children were included in the studies. Only four studies included an HIV negative control group of children, with a total of 257 participants (50, 78-80). Four of the studies used the same populations (77, 80-82), and all studies were performed after 2010. 11 of the 12 studies focused on older children and adolescents aged 6-19 years, with mean age ranging from 6.9 to 14.6 years. The one study in younger children had a median age of 5 years (83). One study also had an adult population in addition to adolescents (84). The most likely route of transmission for all studies were from mother-to-child, with a few cases as an exception.

HIV infected participants were on ART in eight of the 12 studies. One study included children at the time of HIV diagnosis, offering HIV counselling and initiation of ART according to guidelines at the time of enrolment (85). In the three remaining studies ART coverage varied from 69% to 94% (64, 84, 86). All studies of HIV infected participants on ART reported duration of ART, ranging from a median of 9.8 months to a mean of 9.8 years.

All studies but one (77) reported previous history of TB diagnosis or treatment. Seven of the studies reported history of TB based on self-reporting or by questionnaires, whereas the other four studies reported it based on review of medical records. The prevalence of a previous history of TB in the different studies varied from 5% to 93% in HIV infected children and adolescents. This big difference in prevalence of prior TB is probably caused by differences in inclusion criteria across studies. In almost all studies, TB or unspecified CLD was the most frequent comorbidity in HIV infected participants. The prevalence of TB was higher in HIV infected participants in all studies.

3.1 Lung function

All studies reported spirometry as a measure of lung function. In addition, three studies reported shuttle walk tests, three studies reported conventional chest x-rays, four studies reported CT scans, one reported DLCO and one study reported exhaled NO. All studies reporting spirometry used American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines for standardized execution (43). In those studies that used reference populations for calculating predicted values Global Lung Initiative (GLI) (87) or other relevant guidelines or reference populations were used.

The most commonly reported spirometry abnormality in HIV infected children and adolescents was obstruction. The definition of obstruction varied across studies, most using a calculated LLN for FEV_1 and/or FEV_1/FVC. The percentages of HIV infected children and adolescents with obstruction as per spirometry varied from 10% to 45% in the five studies that reported it (50, 64, 78, 85, 86). Median FEV_1 values were reported in two studies as 53% and 60% of predicted, however, in the latter study only 48% of participants produced an adequate spirometry (81, 83).

History of TB disease was found to be significantly associated with lower FEV_1 in HIV infected children, indication obstruction, in four of the studies (78, 79, 84, 86). Two reported regression coefficients to be -0.07 (p=0.037) and -0.027 (p=0.024) (78, 79). The remaining

two reported odds ratio (OR) (84, 86). Attia *et al.* reported an OR of 3.15 (95% confidence interval 1.70-5.58), however, this study included adults in the analysis (84). The last study by Mwalukomo *et al.* reported OR of 2.0 (p=0.092) in HIV infected children with previous history of TB (84). In addition, Rylance *et al.* reported an association between history of TB and abnormal spirometry results (OR 1.2), yet it did not reach statistical significance. In the same study restrictive pattern spirometry was the most common in HIV infected participants, however, those with previous history of TB or recurrent respiratory infections had a more obstructive pattern (80). The remaining studies did not report on association between history of TB and spirometry measures.

In the prospective study by Githinji *et al.* HIV infected had significantly lower FEV_1, FVC and FEV_1/FVC at all time points of spirometry performance compared to HIV uninfected. In the same study, history of lower respiratory tract infections (LRTI) and pulmonary TB was associated with lower FEV_1 (p=0.024 for TB and p=0.003 for LRTI) and FVC (p=0.015 for TB and p=0.013 for LRTI) (79). In all studies with HIV uninfected control group, HIV infected participants had higher prevalence of abnormal spirometry (50, 78-80). Attia *et al.* reported of higher levels of abnormal spirometry results in the adolescent group of participants compared to adults, with prior history of TB as the most important cofactor (84).

Sovershaeva *et al.* was the only study to report on eNO, and found that HIV status and previous history of TB in HIV infected participants were both associated with lower levels of eNO, also in the absence of airway obstruction. Further, no association was found between obstruction and eNO. There was no report of association between spirometry and history of TB (50).

Reversibility testing was reported in most studies as >12% improvement in FEV_1 after administration of bronchodilators, Masekela *et al.* (81) used a cut-off of >15% improvement and Attia *et al.* (84) used a cut-off of >10% improvement in adolescents. Most studies used inhalation of 400 μg of salbutamol, however, two studies used 2.5 mg salbutamol on nebulizer (80, 85), and one study used 200 μg of salbutamol (50). All studies showed low

numbers of participants with positive reversibility tests in those with airflow limitation or obstruction as previously described. This makes asthma an unlikely diagnosis.

In two of the three studies that reported exercise testing by shuttle walk- or 6-minute walk test, HIV infected participants had lower exercise capacity compared to HIV uninfected participants or compared to predicted measurements (80, 85). No association between history of TB and exercise capacity was reported. Githinji *et al.* found no difference in distance walked between HIV infected and uninfected (78). Githinji *et al.* was the only study to report on DLCO, showing that HIV infection was associated with low DLCO and FRC. There was no report of associations between DLCO measures and history of TB (78).

3.2 Radiology

Five of 12 studies reported radiological findings. Two reported conventional chest x-ray and CT scans, whereas two reported CT scans only and one reported chest x-ray only (64, 77, 82, 84, 86). Masekela *et al.* used CT scans only to confirm diagnosis of bronchiectasis, other results are not shown (77). The most common finding on chest x-ray was ring and/or tramline opacities, reported in 29% to 56.3% of participants (64, 82, 86).

CT scans showed high number of patients with one or more abnormalities, with up to 83% of HIV infected children and adolescents having findings on CT, many of which had normal chest x-rays (82). Mosaic attenuation was the most common finding, found in up to 48% of participants who underwent CT scanning (64, 82, 84). Two studies had bronchiectasis as the second most common finding in up to 33% of participants (64, 82), whereas the las study found 9% bronchiectasis (84).

All three studies that reported high levels of mosaic attenuation in HIV infected children and adolescents found there to be an association between decreased attenuation and reduced lung function by spirometry (64, 82, 84). Desai *et al.* found the extent of bronchiectasis and decreased attenuation to strongly correlate with reduced lung function measures FEV_1

($p<0.001$ for both), FVC ($p=0.002$, $p<0.001$, respectively) and FEF_{25-75} ($p<0.001$ for both), without reversibility (82). Ferrand *et al.* found there to be low prevalence of post TB disease on conventional chest x-ray, and the correlation between CT findings and reduced lung function and bronchiectasis suggests most likely diagnosis to be OB, affecting up to 30% of the studied cohort (64). Desai *et al.* also found diagnosis of OB to be the most likely cause of reduced lung function in HIV infected children and adolescents (82). There were no studies that reported on association between radiological findings and history of TB.

4 Discussion

There were few studies that investigated the impact of prior TB on spirometry parameters in HIV-infected children. However, all but one reported significant association between previous history of TB and reduced lung function, mainly obstruction. No studies reported association between radiological findings and history of TB. Main findings in studies reporting radiological findings were mosaic attenuation of small airways by CT, that together with obstruction measured by spirometry are suggestive of OB. The second most reported radiologic abnormality was bronchiectasis, which is associated with both HIV infection itself and a previous history of TB.

An interesting finding was by McHugh *et al.* who reported only 5% previous history of TB among HIV infected. However, 40% of included participants screened positive for TB using WHO guidelines, but only 1 participant had a confirmed positive sample for TB using the GeneXpert (85). This confirms previously reported difficulties in diagnosing TB in children, especially in resource-limited settings where diagnosis is primarily based on X-ray findings (27). This may further explain, together with inclusion criteria, why some studies have very high numbers of previously TB treated individuals.

In the one RCT included it was reported no differences in pulmonary exacerbations between erythromycin and placebo group of the study, both groups being HIV infected with most likely TB-related bronchiectasis. However, there was observed an improvement in FEV_1 and FVC from the beginning to the end of trial in both groups (77). This may suggest that age or

time since TB infection can be of importance for abnormal lung function in HIV infected individuals. Attia *et al.* supports this finding with concluding adolescent age being an independent risk factor of abnormal spirometry in HIV infected individuals (84). However, this may also be due to the increase in HIV infected children growing up to adolescence with HIV.

There are limited data available on prior TB and lung abnormalities in HIV infected children and adolescents in Africa. To the best of my knowledge, no systematic reviews on this topic has been reported to date. The studies included in the review had high heterogenicity, and there were several differences in statistical methods across studies, as well as differences in how results were reported. This makes the studies difficult to compare, and is a limitation of this review. However, results in studies that are comparable do show similar findings. Most studies were cross-sectional and of low or very low quality of evidence, more high-quality studies are needed. Reporting of history of TB disease was mainly self-reported diagnosis or previous treatment, which make up a risk of reporting bias.

5 Conclusion

This literature review has found that HIV infected children and adolescents with a previous history of TB have a higher prevalence of reduced lung function measured by spirometry compared to HIV infected children and adolescents without prior TB as well as HIV uninfected children and adolescents. HIV infected children and adolescents also have higher prevalence of abnormalities on radiographical examinations, including findings suggestive of bronchiolitis and OB, irrespective of TB exposure.

The evidence existing today show an increase in studies on long-term HIV infected children and adolescents. Although ART has reduced the incidence of HIV and TB coinfection, it remains a great public health problem, as well as a significant cause of mortality and morbidity in this patient group. Chronic lung disease has been shown to be one of the major manifestations of long-term HIV infection, and may be explained by the high prevalence of TB coinfection and recurrent respiratory tract infections among this patient group.

Even though recent research has enlightened the issues of HIV-related comorbidities in children and adolescents, further research on these comorbidities and consequences of growing up with HIV and the impact of TB coinfection is strongly needed. Most of the studies done to this date are of low quality, and mostly cross-sectional design. Hence, higher quality studies on HIV and TB coinfection and the long-term effects of disease and treatment are needed to better understand the pathogenesis, clinical recognition and to asses treatment options.

Figures and Tables

Table 1 – Timeline

August 2018	Outlining the paper with my supervisors, deciding on research questions. Finding relevant background literature.
September 2018 – March 2019	Writing up background and finding relevant literature.
March - April 2019	Performing systematic searches using PubMed and EMBASE databases. Started writing up the thesis.
May 2019	Finishing 1st draft of thesis, going through results and writing with supervisors before final draft was ready to be submitted 01.06.19

Table 2 – PICO table

(P) Patient	HIV infected children and adolescents
(I) Intervention	TB coinfection or previous history of TB
(C) Comparison	Healthy children, if possible, or HIV no TB
(O) Outcome	Lung function assessed by spirometry, CT or X-ray, eNO

Table 3 – Summary of included studies with quality assessment

Author(s), *journal*	Location and study design	Participants	Lung function measurement	Summary of findings	GRADE
Attia E. F. *et al.* 2018 **(84)** *AIDS*	Nairobi, Kenya Cross-sectional	n = 52 adolescents (median age 13) n = 375 adults All HIV infected in routine care.	Spirometry Reversibility testing. CT	27% of adolescents had a prior history of TB. TB was associated with FEV_1 < LLN. Adolescents had higher prevalence of abnormal spirometry and was an independent risk factor for abnormal lung function. 80% of adolescents had one or more CT abnormalities. 48% had mosaic attenuation, 9% bronchiectasis. Mosaic attenuation correlated with airflow limitation.	⊕◯◯◯[1]
Ferrand R. A. *et al.* 2012 **(64)** *Clin Infect Dis*	Harare, Zimbabwe Cross-sectional	n = 116 adolescents (10-19 years, mean 14.6) All HIV infected with respiratory symptoms enrolled from 2 HIV outpatient clinics.	Spirometry Chest X-ray CT	36% prior TB treatment. No reporting of TB association to lung function. 45 % had abnormal lung function (FEV_1 < 80%). 47% had chest x-ray abnormalities. Ring and tramline opacities most commonly. Low prevalence of post-TB disease on x-ray. CT scans showed	⊕⊕◯◯

				small airway disease and bronchiectasis, suggestive of obliterative bronchiolitis. Decreased attenuation on CT was associated with low FEV_1 and bronchiectasis.	
Githinji L. N. *et al.* 2017 **(78)** *Ann Am Thorac Soc*	Cape Town, South Africa Cross-sectional	n = 515 HIV infected adolescents (9-14 years, mean 12). n = 110 HIV uninfected All HIV infected enrolled to the Cape Town antiretroviral cohort.	Spirometry Reversibility testing DLCO 6-minute walk test	37% prior TB treatment among HIV infected participants. History of LRTI or TB associated with lower FEV_1. 27% of HIV infected had FEV_1 < LLN, 12 % of uninfected ($p<0.001$). 15% HIV infected had positive reversibility test. HIV infection associated with low DLCO and low FRC.	⊕⊕◯◯
Githinji L. N. *et al.* 2019 **(79)** *Clin Infect Dis*	Cape Town, South Africa Prospective Cohort study	n = 515 HIV infected adolescents (9-14 years, mean 12) n = 110 HIV uninfected adolescents (mean age 11.8)	Spirometry Reversibility testing	HIV infected had lower FEV_1, FVC and FEV_1/FVC at all time points ($p<0.001$). 65% of HIV infected had normal spirometry. History of LRTI and PTB at enrolment associated with lower FEV_1 and FVC	⊕⊕⊕◯[2]

				adjusted for time, smoke and HIV status. 60.2% had prior history of TB at baseline and 3.1% of HIV infected had culture positive TB during follow-up. These had lower FEV_1 (p=0.174).	
Masekela R. *et al.* 2011 **(81)** *Int J Tuberc Lung Dis*	Pretoria, South Africa Cross-sectional	n = 35 children (6-18 years, mean 6.9) All HIV infected with bronchiectasis	Spirometry Reversibility testing	75% prior TB diagnosis, almost 25% had two courses of treatment. No reports of association between TB and lung function. Median FEV_1 53% predicted. Median FEF_{25-75} 52% predicted. 8 participants had positive reversibility testing.	⊕◯◯◯ [3]
Masekela R. *et al.* 2013 **(77)** *J Antivir Antiretrovir*	Pretoria, South Africa RCT	n = 31 HIV infected children with bronchiectasis. n = 17 intervention (mean age 9.1) n = 14 placebo	Spirometry CT	History of TB was not reported. There were no differences in exacerbations between intervention and placebo arm. When pooling results FEV_1% and FVC% were sign. improved at end of trial in both groups.	⊕⊕⊕◯ [4]

		(mean age 8.4)		One participant got culture-positive TB during follow-up. CT scans were performed to confirm bronchiectasis, other results not shown.	
Mwalukomo T. *et al.* 2016 **(86)** *J Pediatric Infect Dis Soc*	Blantyre, Malawi Cross-sectional	n = 160 children (8-16 years, mean 11.1) All HIV infected in HIV outpatient clinics	Spirometry Reversibility testing Chest x-ray	18.8% previously treated for TB. 14.5% had obstructive defects on spirometry. 17.9% had reduced FVC. Lung function abnormalities was not associated with clinical findings, including prior TB. Chest x-ray showed ring or tramline pattern in 56.3%, together with obstruction this is suggestive of bronchiectasis.	⊕⊕◯◯
Rylance J. *et al.* 2016 **(80)** *AIDS*	Harare, Zimbabwe Cross-sectional	n = 202 HIV infected n = 150 HIV uninfected (median age 11.1 in both groups) Recruited from primary health care clinics.	Spirometry Reversibility testing Shuttle walk test	38% of HIV infected was previously treated for TB, only 0.7% of uninfected ($p<0.001$). HIV infected had lower exercise capacity on shuttle walk test and more frequently abnormal spirometry (24.3% vs 11.5% in uninfected) ($p<0.001$).	⊕⊕◯◯

				HIV status, older age and older age at HIV diagnosis was associated with lung function abnormality (p=0.025). Most had restrictive pattern spirometry, but those with prior infections (including TB) had more obstructive pattern.	
Weber H. C. *et al.* 2015 **(83)** *South African Journal of Child Health*	Cape Town, South Africa Cross-sectional	n = 56 children (median age 5) of whom n = 27 had adequate lung function tests	Spirometry Reversibility testing	93% had previously been treated for TB. 64% had had hospitalization requiring pneumonia. Only 48% had adequate lung function tests. Median FEV_1% was 60% with only 5 participants having positive reversibility testing. PTB was most common comorbidity, but unable to establish temporal relationship to CLD. Hyperinflation of the lungs and respiratory rate had clinical association with poor lung function.	⊕◯◯◯ 5

Desai S. R. *et al.* 2018 **(82)** *Clin Infect Dis*	Harare, Zimbabwe Cross-sectional	n = 193 HIV infected children on ART (6-16 years, median 11.2). Of whom n = 84 underwent CT scan	Spirometry Chest x-ray CT	38% of HIV infected was previously treated for TB. No reports of association between TB and lung function. 29% had ring/tramline opacities on chest x-ray. 83% of participants doing CT had abnormalities. 43% had decreased attenuation as part of mosaic pattern. 33% had bronchiectasis. Decreased attenuation and extent of bronchiectasis strongly correlated with reduced FEV_1, FVC and FEF_{25-75} without reversibility. Findings suggest most likely diagnosis of OB.	⊕⊕◯◯
McHugh G. *et al.* 2016 **(85)** *J Acquir Immune Defic Syndr*	Harare, Zimbabwe Cross-sectional	n = 385 HIV infected children (6-15 years, mean 11) enrolled at time of HIV diagnosis	Spirometry Shuttle walk test	5% had previous history of TB. No reports of association between TB and lung function. 54% reported cough for > 1 month, 16% had dyspnoea. 12% had O2 saturation <88% at rest, 10% more <88% after exercise. 10% had obstructive pattern on spirometry, only 0.13% had positive	⊕⊕◯◯

				reversibility testing. 18% had reduced FVC. 40% of participants screened positive for TB using WHO guidelines, only 1 participant had positive GeneXpert.	
Sovershaeva E. *et al.* 2019 (Accepted) **(50)** *AIDS*	Harare, Zimbabwe Cross-sectional	n = 222 HIV infected children and adolescents (6-19 years, median 15) n = 97 HIV uninfected (6-16 years, median 10)	Spirometry Exhaled NO	25.7% of HIV infected had a previous history of TB. 25.2% had airway obstruction, but no history of TB. HIV status was associated with lower levels of eNO (p=0.03). History of TB in HIV infected participants was associated with lower levels of eNO, even if no airway obstruction or abnormality was present (p=0.007). There was no association between airway obstruction and levels of eNO,	⊕⊕◯◯

[1]Downgraded due to skewed population sizes
[2]Upgraded due to good sample size, longitudinal study, objective measurements
[3]Downgraded due to small sample size, poor statistical power and high risk of selection bias
[4]Downgraded due to small sample size and high rate of lost to follow-up
[5]Downgraded due to poor response rate and high risk of selection bias

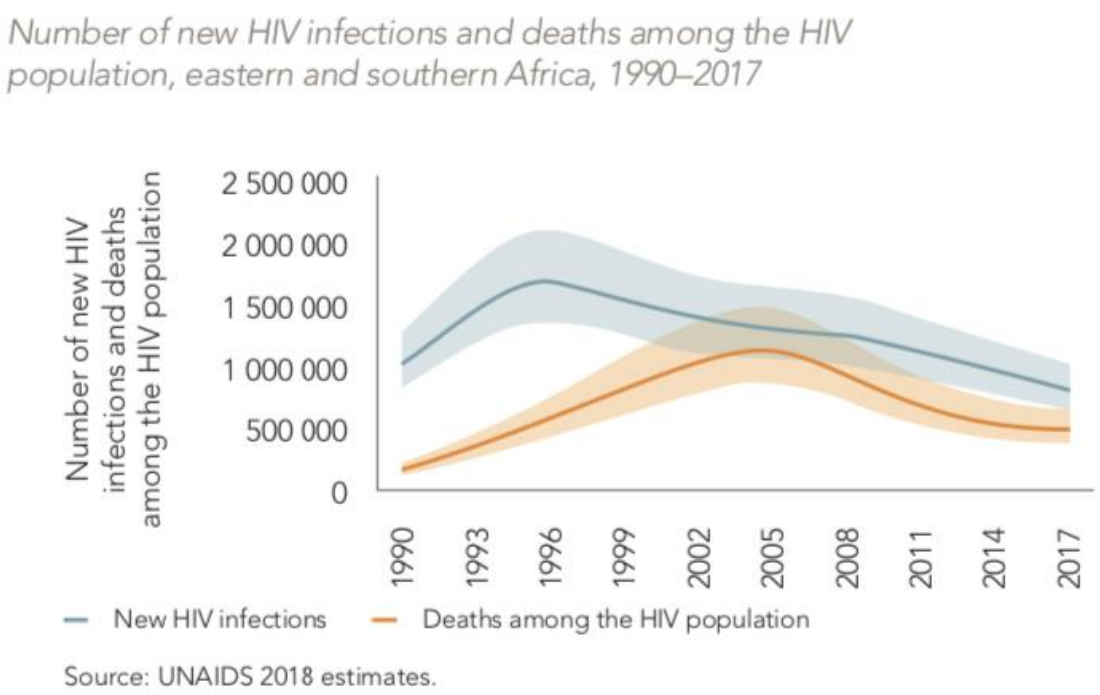


Figure 1 – New HIV infections and AIDS-related deaths (15).

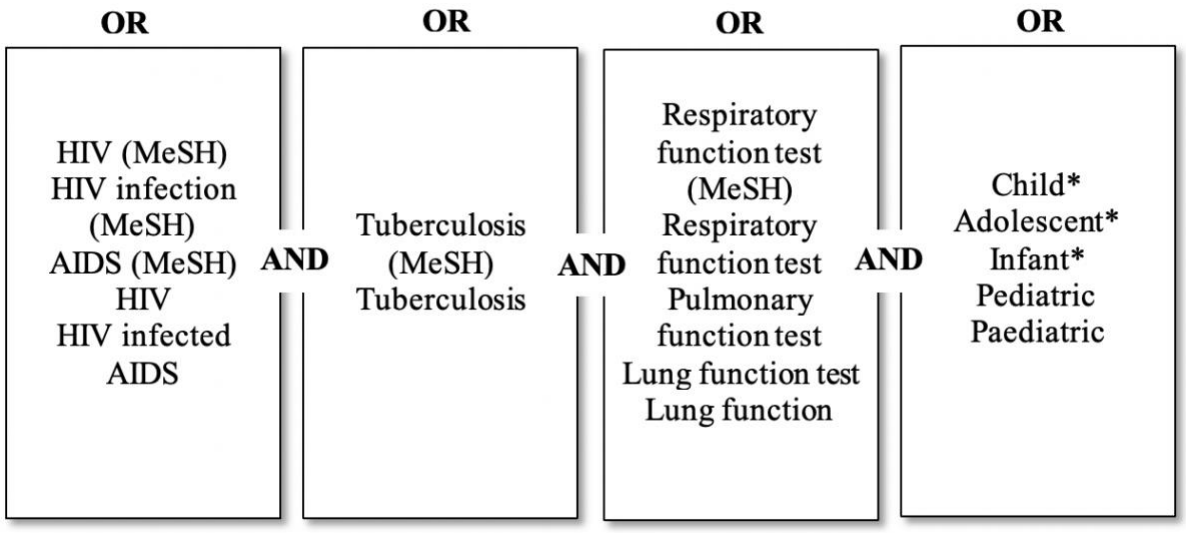


Figure 2 – Composition of the search.

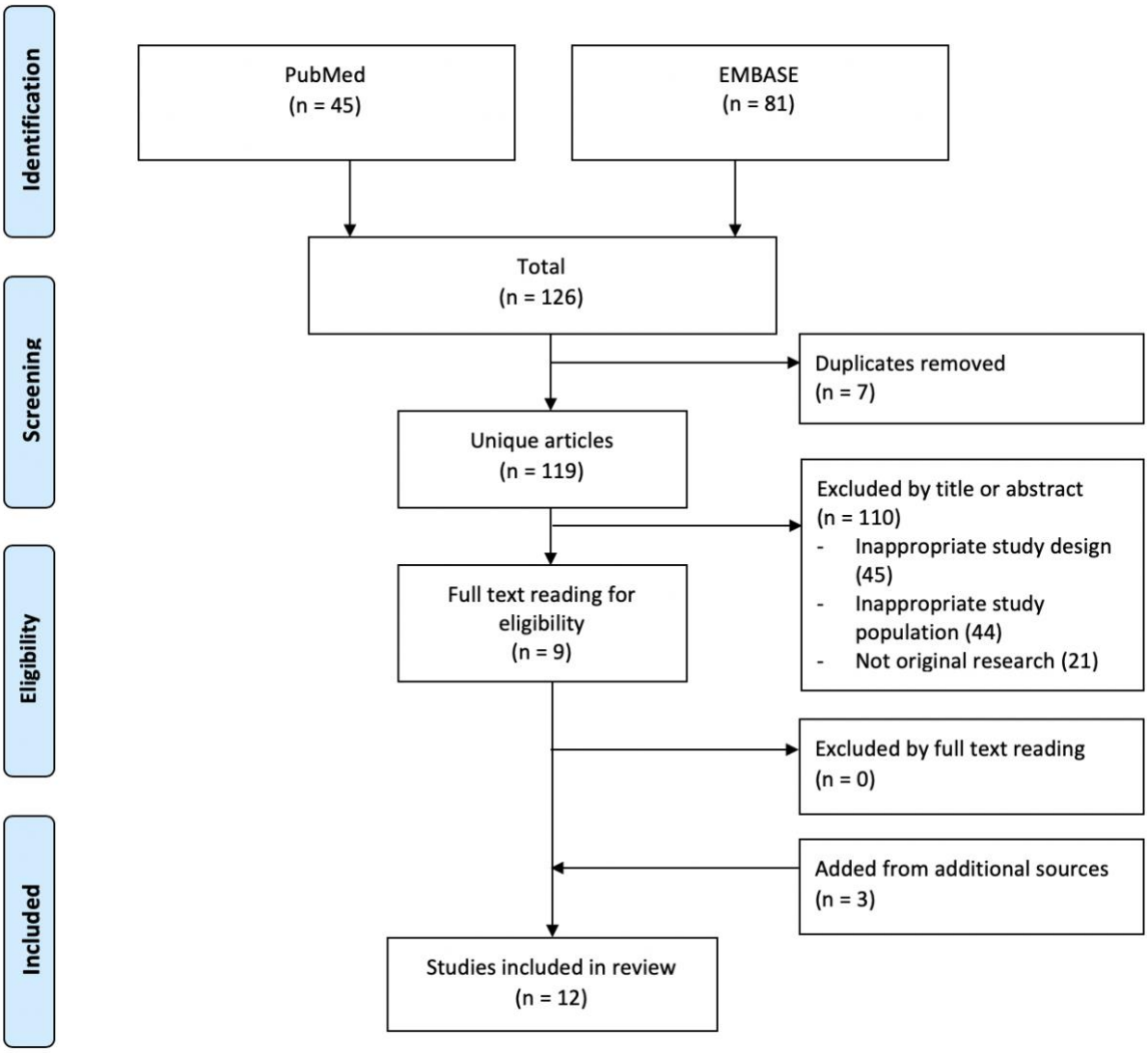


Figure 3 – Flow chart (modified from the PRISMA statement) (76).

Works cited

1. Luciw PA. Human immunodeficiency viruses and their replication. In: Fields BN, editor. Virology, 3rd ed. Philadelphia: Lippincott-Raven; 1996. p. 1881-952.

2. German Advisory Committee Blood (Arbeitskreis Blut), Subgroup ‘Assessment of Pathogens Transmissible by Blood’. Human Immunodeficiency Virus (HIV). Transfus Med Hemother. 2016;43(3):203-22.

3. Whiteside A. HIV/AIDS: A very short introduction. Oxford: Oxford University Press; 2008.

4. Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med. 1981;305(24):1425-31.

5. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983;220(4599):868-71.

6. Schupbach J, Popovic M, Gilden RV, Gonda MA, Sarngadharan MG, Gallo RC. Serological analysis of a subgroup of human T-lymphotropic retroviruses (HTLV-III) associated with AIDS. Science. 1984;224(4648):503-5.

7. Peeters M, Honore C, Huet T, Bedjabaga L, Ossari S, Bussi P, et al. Isolation and partial characterization of an HIV-related virus occurring naturally in chimpanzees in Gabon. Aids. 1989;3(10):625-30.

8. Dalgleish AG, Beverley PC, Clapham PR, Crawford DH, Greaves MF, Weiss RA. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature. 1984;312(5996):763-7.

9. Klatzmann D, Champagne E, Chamaret S, Gruest J, Guetard D, Hercend T, et al. T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. Nature. 1984;312(5996):767-8.

10. Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 Entry Cofactor: Functional cDNA Cloning of a Seven-Transmembrane, G Protein-Coupled Receptor. Science. 1996;272(5263):872-7.

11. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human

immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med. 1997;337(11):725-33.
12. Barré-Sinoussi F, Ross AL, Delfraissy J-F. Past, present and future: 30 years of HIV research. Nature Reviews Microbiology. 2013;11:877.
13. De Cock KM, Jaffe HW, Curran JW. The evolving epidemiology of HIV/AIDS. Aids. 2012;26(10):1205-13.
14. UNAIDS. Global AIDS update 2016. Geneva: Joint United Nations Programme on HIV/AIDS; 2016.
15. UNAIDS. Data 2018. Geneva: Joint United Nations Programme on HIV/AIDS; 2018.
16. UNAIDS. 90-90-90. An ambitious treatment target to help end the AIDS epidemic. Geneva: Joint United Nations Programme on HIV/AIDS; 2014.
17. UNICEF. Children, HIV and AIDS. Global snapshot. New York: United Nations Children's Fund; 2018.
18. Ferrand RA, Corbett EL, Wood R, Hargrove J, Ndhlovu CE, Cowan FM, et al. AIDS among older children and adolescents in Southern Africa: projecting the time course and magnitude of the epidemic. Aids. 2009;23(15):2039-46.
19. Ferrand RA, Bandason T, Musvaire P, Larke N, Nathoo K, Mujuru H, et al. Causes of acute hospitalization in adolescence: burden and spectrum of HIV-related morbidity in a country with an early-onset and severe HIV epidemic: a prospective survey. PLoS Med. 2010;7(2):e1000178.
20. WHO. Health for the World's Adolescents. A second chance in the second decade. Geneva: World Health Organization, Department of Maternal, Newborn, Child and Adolescent Health; 2014.
21. Lawn SD, Zumla AI. Tuberculosis. Lancet. 2011;378(9785):57-72.
22. Daniel TM. The history of tuberculosis: past, present and challenges for the future. In: Schaaf S, Zumla A, editors. Tuberculosis: a comprehensive clinical reference. Philadelphia: Saunders Elsevier; 2009.
23. Behr MA, Warren SA, Salamon H, Hopewell PC, Ponce de Leon A, Daley CL, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. Lancet. 1999;353(9151):444-9.
24. Koch R. Die Äetiologie der Tuberkulose. Berl Klin Wschr. 1882;19:221-30.
25. Luca S, Mihaescu T. History of BCG Vaccine. Maedica (Buchar). 2013;8(1):53-8.
26. WHO. Treatment of tuberculosis: Guidelines - 4th ed. Geneva: World Health Organization, Department ST; 2009.

27. WHO. Global Tuberculosis Report 2018. Geneva: World Health Organization; 2018.
28. WHO. The End TB Strategy. Geneva: World Health Organization; 2015.
29. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. Childhood pulmonary tuberculosis: old wisdom and new challenges. Am J Respir Crit Care Med. 2006;173(10):1078-90.
30. Mandal N, Anand PK, Gautam S, Das S, Hussain T. Diagnosis and treatment of paediatric tuberculosis: An insight review. Crit Rev Microbiol. 2017;43(4):466-80.
31. WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children – 2nd ed. Geneva: World Health Organization; 2014.
32. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database of Systematic Reviews. 2014(1).
33. Zignol M, Sismanidis C, Falzon D, Glaziou P, Dara M, Floyd K. Multidrug-resistant tuberculosis in children: evidence from global surveillance. Eur Respir J. 2013;42(3):701-7.
34. Mesfin YM, Hailemariam D, Biadgilign S, Kibret KT. Association between HIV/AIDS and multi-drug resistance tuberculosis: a systematic review and meta-analysis. PLoS One. 2014;9(1):e82235.
35. Lawn SD, Bekker L-D. Co-pathogenesis of tuberculosis and HIV. In: Schaaf S ZA, editor. Tuberculosis: a comprehensive clinical reference. Philadelphia: Saunders Elsevier; 2009. p. 96-106.
36. Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. BMC Infect Dis. 2014;14 Suppl 1:S5.
37. Jensen J, Alvaro-Meca A, Micheloud D, Diaz A, Resino S. Reduction in mycobacterial disease among HIV-infected children in the highly active antiretroviral therapy era (1997-2008). Pediatr Infect Dis J. 2012;31(3):278-83.
38. Naing C, Mak JW, Maung M, Wong SF, Kassim AI. Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. Lung. 2013;191(1):27-34.
39. Hesseling AC, Westra AE, Werschkull H, Donald PR, Beyers N, Hussey GD, et al. Outcome of HIV infected children with culture confirmed tuberculosis. Arch Dis Child. 2005;90(11):1171-4.
40. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. Aids. 2004;18(12):1615-27.

41. Link-Gelles R, Moultrie H, Sawry S, Murdoch D, Van Rie A. Tuberculosis Immune Reconstitution Inflammatory Syndrome in children initiating Antiretroviral Therapy for HIV infection: A systematic literature review. Pediatr Infect Dis J. 2014;33(5):499-503.
42. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK, et al. Recommendations for a Standardized Pulmonary Function Report. An Official American Thoracic Society Technical Statement. Am J Respir Crit Care Med. 2017;196(11):1463-72.
43. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.
44. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68.
45. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017;49(1).
46. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.
47. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-46.
48. Ricciardolo FL. Multiple roles of nitric oxide in the airways. Thorax. 2003;58(2):175-82.
49. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med. 2005;171(8):912-30.
50. Sovershaeva E, Kranzer K, McHugh G, Bandason T, Majonga ED, Usmani OS, et al. History of tuberculosis is associated with lower exhaled nitric oxide levels in HIV-infected children. AIDS. 2019;forthcoming.
51. McCormack MC. Diffusing capacity for carbon monoxide. In: Stoller JK, Hollingsworth H, editors. UpToDate. UpToDate, Waltham MA. (Accessed May 06, 2019).
52. Andiman WA, Shearer WT. Lymphoid interstitial pneumonitis. In: Pizzo PA, Wilfert CM, editors. Pediatric AIDS: The Challenge of HIV Infection in Infants, Children, and Adolescents, 3rd. Baltimore: Lippincott Williams & Wilkins; 1998. p. 323.

53. Katz BZ, Berkman AB, Shapiro ED. Serologic evidence of active Epstein-Barr virus infection in Epstein-Barr virus-associated lymphoproliferative disorders of children with acquired immunodeficiency syndrome. J Pediatr. 1992;120(2 Pt 1):228-32.
54. Zar HJ. Chronic lung disease in human immunodeficiency virus (HIV) infected children. Pediatr Pulmonol. 2008;43(1):1-10.
55. Jeena PM, Coovadia HM, Thula SA, Blythe D, Buckels NJ, Chetty R. Persistent and chronic lung disease in HIV-1 infected and uninfected African children. Aids. 1998;12(10):1185-93.
56. Young LR. Lymphocytic interstitial pneumonia in children. In: Mallory GB, Hoppin AG, editors. UpToDate. UpToDate, Waltham MA. (Accessed 06 May 2019).
57. Rabie H, Goussard P. Tuberculosis and pneumonia in HIV-infected children: an overview. Pneumonia (Nathan). 2016;8:19.
58. Pitcher RD, Daya R, Beningfield SJ, Zar HJ. Chest radiographic presenting features and radiographic progression of pneumocystis pneumonia in South African children. Pediatr Pulmonol. 2011;46(10):1015-22.
59. Au BK, Au MA, Chien JW. Bronchiolitis obliterans syndrome epidemiology after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2011;17(7):1072-8.
60. Huang HJ, Yusen RD, Meyers BF, Walter MJ, Mohanakumar T, Patterson GA, et al. Late primary graft dysfunction after lung transplantation and bronchiolitis obliterans syndrome. Am J Transplant. 2008;8(11):2454-62.
61. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. N Engl J Med. 2014;370(19):1820-8.
62. Perez T, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis: clinical, functional, and HRCT findings. Am J Respir Crit Care Med. 1998;157(5 Pt 1):1658-65.
63. Kim CK, Kim SW, Kim JS, Koh YY, Cohen AH, Deterding RR, et al. Bronchiolitis obliterans in the 1990s in Korea and the United States. Chest. 2001;120(4):1101-6.
64. Ferrand RA, Desai SR, Hopkins C, Elston CM, Copley SJ, Nathoo K, et al. Chronic lung disease in adolescents with delayed diagnosis of vertically acquired HIV infection. Clin Infect Dis. 2012;55(1):145-52.
65. Milliron B, Henry TS, Veeraraghavan S, Little BP. Bronchiectasis: Mechanisms and Imaging Clues of Associated Common and Uncommon Diseases. Radiographics. 2015;35(4):1011-30.

66. Chang AB, Bush A, Grimwood K. Bronchiectasis in children: diagnosis and treatment. Lancet. 2018;392(10150):866-79.
67. McGuinness G, Naidich DP. CT of airways disease and bronchiectasis. Radiol Clin North Am. 2002;40(1):1-19.
68. Attia EF, Miller RF, Ferrand RA. Bronchiectasis and other chronic lung diseases in adolescents living with HIV. Curr Opin Infect Dis. 2017;30(1):21-30.
69. Masekela R, Anderson R, de Boeck K, Vreys M, Steel HC, Olurunju S, et al. Expression of soluble triggering receptor expressed on myeloid cells-1 in childhood CF and non-CF bronchiectasis. Pediatr Pulmonol. 2015;50(4):333-9.
70. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: from epidemiology to pathophysiology. Eur Respir Rev. 2018;27(147).
71. Chamie G, Luetkemeyer A, Walusimbi-Nanteza M, Okwera A, Whalen CC, Mugerwa RD, et al. Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata. Int J Tuberc Lung Dis. 2010;14(10):1295-302.
72. Hatipoglu ON, Osma E, Manisali M, Ucan ES, Balci P, Akkoclu A, et al. High resolution computed tomographic findings in pulmonary tuberculosis. Thorax. 1996;51(4):397-402.
73. Menon B, Nima G, Dogra V, Jha S. Evaluation of the radiological sequelae after treatment completion in new cases of pulmonary, pleural, and mediastinal tuberculosis. Lung India. 2015;32(3):241-5.
74. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 1995;123(3):A12-3.
75. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
76. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
77. Masekela R, Anderson R, Gongxeka H, Steel HC, Becker PJ, Green RJ. Lack of efficacy of an immunomodulatory macrolide in childhood HIV related bronchiectasis: A randomised, placebo-controlled trial. Journal of Antivirals and Antiretrovirals. 2013;5(2):044-9.
78. Githinji LN, Gray DM, Hlengwa S, Myer L, Zar HJ. Lung function in South African adolescents infected Perinatally with HIV and treated long-term with antiretroviral therapy. Annals of the American Thoracic Society. 2017;14(5):722-9.

79. Githinji LN, Gray DM, Hlengwa S, Machemedze T, Zar HJ. Longitudinal changes in Spirometry in perinatally HIV-infected South African adolescents on antiretroviral therapy. Clin Infect Dis. 2019.
80. Rylance J, McHugh G, Metcalfe J, Mujuru H, Nathoo K, Wilmore S, et al. Chronic lung disease in HIV-infected children established on antiretroviral therapy. Aids. 2016;30(18):2795-803.
81. Masekela R, Anderson R, Moodley T, Kitchin OP, Risenga SM, Becker PJ, et al. HIV-related bronchiectasis in children: An emerging spectre in high tuberculosis burden areas. International Journal of Tuberculosis and Lung Disease. 2011;16(1):114-9.
82. Desai SR, Nair A, Rylance J, Mujuru H, Nathoo K, McHugh G, et al. Human Immunodeficiency Virus-Associated Chronic Lung Disease in Children and Adolescents in Zimbabwe: Chest Radiographic and High-Resolution Computed Tomographic Findings. Clin Infect Dis. 2018;66(2):274-81.
83. Weber HC, Gie RP, Wills K, Cotton MF. Clinical features and lung function in HIV-infected children with chronic lung disease. SAJCH South African Journal of Child Health. 2015;9(3):72-5.
84. Attia EF, Maleche-Obimbo E, West TE, Ndukwe-Wambutsi L, Kiptinness C, Cagle A, et al. Adolescent age is an independent risk factor for abnormal spirometry among people living with HIV in Kenya. Aids. 2018;32(10):1353-9.
85. McHugh G, Rylance J, Mujuru H, Nathoo K, Chonzi P, Dauya E, et al. Chronic Morbidity Among Older Children and Adolescents at Diagnosis of HIV Infection. J Acquir Immune Defic Syndr. 2016;73(3):275-81.
86. Mwalukomo T, Rylance SJ, Webb EL, Anderson S, O'Hare B, Van Oosterhout JJ, et al. Clinical characteristics and lung function in older children vertically infected with human immunodeficiency virus in malawi. Journal of the Pediatric Infectious Diseases Society. 2016;5(2):162-9.
87. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

Appendix

<table>
<tr><td colspan="3">Reference:
Attia EF, Maleche-Obimbo E, West TE, Ndukwe-Wambutsi L, Kiptinness C, Cagle A, et al. Adolescent age is an independent risk factor for abnormal spirometry among people living with HIV in Kenya. Aids. 2018;32(10):1353-9.</td><td>Design: Cross-sectional study
Level of documentation III
GRADE ⊕◯◯◯[1]</td></tr>
<tr><td>Objective</td><td>Methods</td><td>Results</td><td>Discussion and commentaries</td></tr>
<tr><td>To determine if risk of abnormal spirometry was greater among adolescents with HIV compared to adults with HIV, and to evaluate the role of other cofactors for abnormal spirometry.

Conclusion
Adolescent age is an independent risk factor for abnormal spirometry, particularly airflow limitation among adolescents with HIV. Suggesting that perinatally HIV infected adolescents are at particular risk of chronic lung disease.

Country
Kenya
Year of data collection
2014</td><td>375 adults and 52 adolescents with HIV were enrolled prospectively from routine care at Nairobi Hope Center, Kenya over a time period of 3 months. Participants with acute respiratory infections, recent tuberculosis or pregnancy were excluded. Adolescents with sibling/maternal HIV infection, no sexual debut and no injection of drugs met criteria of perinatal HIV infection.

Standardized questionnaires assessed risk factor and exposure for lung disease. CD4 counts and other HIV-related measurements from last 120 days at the clinic were used. Low BMI was set to under 18.5 kg/m^2. Oxygen saturation was measured at rest and after sub-maximal exercise. Spirometry with FEV_1 and FVC was measured before and after 400 µg of salbutamol. Global Lung Initiative equations were used to calculate predicted measures and lower limits of normal (LLN). Abnormal spirometry was defined if any criteria was less than LLN before bronchodilators. Airflow limitation was defined as FEV_1/FVC less than LLN. High resolution CT scans were obtained in adolescents with abnormal spirometry who consented.

Statistical tests used was chi-squared, Fishers exact for categorical, t-test and Wilcoxon rank sum test for continuous variables. Bivariate logistic regression was used to evaluate association of adolescent age and cofactors thought to be associated with abnormal spirometry.</td><td>Adolescents had a median age of 13 years, 54% were male, 23% had low BMI and 7% had recent measure of CD4 < 200 cells/µl.

Substantially more adolescents than adults had abnormal spirometry (40% vs. 17%, p < 0.001).

More adolescents had airflow limitations than adults, 23% vs. 10% (p=0.008) pre-bronchodilator and 27% vs 7% (p<0.001) post bronchodilator respectively. Adolescents had significantly higher prevalence of FEV_1 less than LLN and FVC less than LLN.

Multivariable analysis showed adolescent age, prior pulmonary tuberculosis and smoking pack-years were associated with abnormal spirometry and airflow limitation.

46 of 52 adolescent underwent chest CT. 80% had at least one CT abnormality: 22(48%) had mosaic attenuation, 10 (22%) groundglass opacities, 9 (295) bronchial wall thickening, 8 (17%) micronodules, 5 (11%) emphysema and 4 (9%) bronchiectasis. Mosaic attenuation correlated with postbronchodilator airflow limitation (r=0.6, p=0.02).</td><td>Checklist:
-Did the study address a clearly focused issue? YES
-Was the study based on random selection of suitable participants? YES
-Were inclusion/exclusion criteria clearly defined? YES
-Were all participants representative of a specified population? YES
-Was the response rate high? YES

-Were objective criteria used to assess/validate outcome measures? YES
-Have authors identified all relevant confounders? UNCLEAR
-Are prognostic/confounding factors considered in the study design and/or analysis? YES

-Do you trust the results? YES
-Can the results be applied to the local population? YES
-Do the results of this study support other available evidence? YES

Strengths:
Statistical analysis included most known cofactors. Standardized tests of lung function.
Limitations:
No HIV uninfected control group. Co-factors/exposures were measured by self-reporting. CT scans were analysed by only one radiologist. Population size differed between groups and may give insufficient statistical power.

[1]Downgraded due to skewed population sizes</td></tr>
</table>

Reference: Ferrand RA, Desai SR, Hopkins C, Elston CM, Copley SJ, Nathoo K, et al. Chronic lung disease in adolescents with delayed diagnosis of vertically acquired HIV infection. Clinical Infectious Diseases. 2012;55(1):145-52.			**Design:** Cross-sectional study **Level of documentation** III **GRADE** ⊕⊕◯◯
Objective	**Methods**	**Results**	**Discussion and commentaries**
Investigate clinical features and morphologic characteristics of CLD in older children with perinatal HIV infection attending HIV outpatient care in 2 public sector hospitals in Harare, Zimbabwe. **Conclusion** 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. Obliterative bronchiolitis (OB) being the most probable cause. Aetiology, prognosis and response to treatment are currently unknown. **Country** Zimbabwe **Year of data collection** 2011	116 adolescents aged 10-19 years were enrolled from 2 HIV care outpatient clinics in Harare, Zimbabwe. Exclusion criteria were horizontally acquired HIV, severe hospitalising illness, living outside Harare, recent tuberculosis, pulmonary Kaposi sarcoma or acute respiratory tract infection. Interview recorded reason for HIV testing, duration of ART, respiratory symptoms and exercise tolerance using NYHA scale. All participants underwent respiratory examination, height, weight and Tanner puberty staging. CD4 counts were measured, spirometry performed, echocardiography and chest X-ray (CXR). Oxygen saturation and respiratory rate were measured at rest and after exercise. Patients suspected of CLD or abnormal CXR were invited to perform high resolution CT scan, were abnormalities were categorized by airway pathology or parenchymal disease. If suspicion of TB, patients were excluded. Z-scores for height and weight were calculated using British ref. curves. Spirometry results calculated using age-, sex- and height- adjusted standards from Malawian school children.	Mean age 14.6 years, 43% male. HIV diagnosis at median 23 months prior to recruitment. 99 (85%) had WHO stage 3/4 disease. 37% underwent HIV testing due to presumed TB or repeated chest infections/coughing. Median CD4 counts was 384 cells/µl. 82 (71%) had a prior diagnosis of CLD, 42 (36%) had been treated for suspected TB. 24 (21%) had reduced exercise tolerance, 41 (35%) were dyspnoeic and/or hypoxic at rest. 52 (45%) had abnormal lung function (FEV_1 < 80%). There was no association between duration of ART or CD4 count and abnormal lung function. Of ART-naïve participants 8 of 18 (44%) had clinical CLD and 5 of 18 (28%) had abnormal CT scans. 16 (14%) had raised mean pulmonary artery pressure on echocardiography. 55 (47%) had abnormalities on CXR, most commonly ring and tramline opacities. 100 (86%) met criteria of suspected CLD, 56 of these underwent CT scan. CT scans showed predominantly small airway disease and bronchiectasis with good interobserver agreement. Decreased attenuation was strongly correlated with extent of bronchiectasis (r=0.80, p<0.001). Mosaic decreased attenuation was significantly associated with FEV_1 and bronchiectasis. And makes diagnosis of OB most likely.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Was the study based on random selection of suitable participants? **YES** -Were inclusion/exclusion criteria clearly defined? **YES** -Were all participants representative of a specified population? **YES** -Was the response rate high? **YES/NO** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **UNCLEAR** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES** -Do you trust the results? **YES** -Can the results be applied to the local population? **YES** -Do the results of this study support other available evidence? **NO** **Strengths:** Use of CT scans that were analysed by 2 independent, blinded radiologists **Limitations:** Low number of patients undergoing CT scan. Lack of histologic confirmation of OB.

Reference: Githinji LN, Gray DM, Hlengwa S, Myer L, Zar HJ. Lung function in South African adolescents infected Perinatally with HIV and treated long-term with antiretroviral therapy. Annals of the American Thoracic Society. 2017;14(5):722-9.			**Design:** Cross-sectional **Level of documentation** III **GRADE** ⊕⊕◯◯
Objective	**Methods**	**Results**	**Discussion and commentaries**
To investigate lung function in HIV infected adolescents on ART in the Cape Town antiretroviral cohort. **Conclusion** Perinatally HIV infected adolescents on ART in South Africa have lower lung function than uninfected adolescents. Prior LRTI or PTB is associated with lower lung function. **Country** South Africa **Year of data collection** 2013-2015	515 HIV infected adolescents aged 9-14 on ART for at least 6 months were enrolled to a prospective cohort study. Comparison group was 110 uninfected demographically matched adolescents. All participants underwent lung function testing at baseline. Exposure data and adherence to ART was collected through self-reporting. Screening for respiratory symptoms was done by validated questionnaire. Lung function was measured by spirometry (FEV_1, FVC and FEV_1/FVC), DLCO, single-breath test for diffusion capacity, multiple-breath nitrogen washout measuring FRC. 6-minute walk test and bronchodilator response with 400 µg of salbutamol. American thoracic society and European respiratory society guidelines were used. Lung function measures were summarized with mean or median. HIV uninfected group was used as reference. Comparisons of lung function made using two-sample t-test and Wilcoxon rank sum test for data not normally distributed. Z-scores were used to compute difference between proportions. Univariable and multivariable linear regression was used to explore lung function and demographic data.	Mean age 12 years, 52% male. Median duration of ART 7.6 years. 37% of HIV infected reported prior PTB, none of uninfected. PCP reports in 1.4%, and pneumonia was more common in HIV infected. 18 (3,5%) HIV infected had digital clubbing, none uninfected. 27% of HIV infected had FEV_1 under LLN, to 12% of uninfected (p=0.001). 15% HIV infected and 8% uninfected had positive bronchodilator response. No difference in distance walked or oxygen saturation in 6-min walk test. HIV infection was associated with lower DLCO, although only 4 had under LLN. (p=0.001) and lower FRC (p=0.004). History of previous LRTI or TB was associated with decreased FEV_1 (p=0.001/p=0.004). Those with digital clubbing had lower FEV_1. Self-reported wheeze or asthma were associated with lower FEV_1.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Was the study based on random selection of suitable participants? **YES** -Were inclusion/exclusion criteria clearly defined? **NO** -Were all participants representative of a specified population? **YES** -Was the response rate high? **YES** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **UNCLEAR** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES** -Do you trust the results? **YES** -Can the results be applied to the local population? **YES/NO** -Do the results of this study support other available evidence? **YES** **Strengths:** Good sample size **Limitations:** Only spirometry. No radiological imaging. Lack of reference values for the group. Healthy HIV-cohort, with close follow-up.

Reference: Githinji LN, Gray DM, Hlengwa S, Machemedze T, Zar HJ. Longitudinal changes in Spirometry in perinatally HIV-infected South African adolescents on antiretroviral therapy. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2019.			**Design:** Prospective cohort study **Level of documentation** IIb-III **GRADE** ⊕⊕⊕◯[1]
Objective	**Methods**	**Results**	**Discussion and commentaries**
To investigate the progression of spirometry findings over 2 years in HIV infected adolescents on ART in Cape Town. **Conclusion** HIV infected adolescents had lower lung function by spirometry at all time points over 2 years than HIV uninfected. Previous TB or LRTI was associated with reduced FEV_1 and FVC. There was a high incidence rate of TB in HIV infected adolescents. **Country** South Africa **Year of data collection** 2013-2017	515 HIV infected adolescents, mean age 12 and 110 HIV uninfected adolescents, mean age 11.8 were recruited from primary care clinics and hospital-based ART-clinics. Inclusion criteria were age 9-14 years on ART for more than 6 months. Comparison group were age, sex and ethnicity matched. No history of pre-existing lung disease. Spirometry with FEV_1 and FVC and bronchodilator testing after 400 µg of salbutamol was done at baseline, 12- and 24-months using guidelines. Global Lung Initiative African-American reference population was used to calculate lower limit of normal (LLN) outcome measures. Obstructive pattern was defined as FEV_1/FVC<LLN, restrictive FVC<LLN and reversibility >12% after salbutamol. Annual measurements of CD4, VL, height, weight, and questionnaire on exposure and symptoms. ART adherence was calculated. Two sample t-test was used to compare lung function between HIV infected and uninfected. Covariates were determined using Directed Acylic Graphs and Mixed-effect modelling to compute longitudinal changes in lung function. After two-year follow-up 473 (92%) HIV infected and 97 (88%) HIV uninfected were tested.	Median duration of ART was 9.8 years, with median age of initiation 4.3. HIV-infected were shorter and had lower BMI than uninfected. Prior TB or hospitalisation for LRTI was more common in HIV infected. 3.2% of HIV infected had intercurrent culture-positive PTB during the study. These had on average 0.23 lower FEV_1 z-score (p=0.174) adj. for time and HIV. Participants had more symptoms of cough and wheezing at enrolment. Among HIV infected 115 (22.9%) were on CTX prophylaxis at enrolment, and 33 (7.6%) at 2 years. HIV infected had lower FEV_1, FVC and FEV_1/FVC z-scores compared to uninfected at all time points (p<0.001). However, the change over the 2 years was similar in both groups. History of PTB or LRTI prior to enrolment were significantly associated with lower FEV_1 and FVC z-score adjusted for smoke, time and HIV. Over 65% of HIV infected had normal spirometry at all timepoints. HIV infected shower more mixed-pattern spirometry. Obstructive pattern increased from 4.8% to 8.1%. Bronchodilator response decreased from 16.1% and 11.4% to 6.2% and 5.7% in HIV infected and uninfected.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Were the groups recruited from the same population groups? **YES** -Were the groups comparable considering background? **YES** -Were inclusion/exclusion criteria clearly defined? **YES** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **UNCLEAR** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES** -Was the follow up rate high enough? **YES** -Was the follow up long enough? **YES** -Do you trust the results? **YES** -Can the results be applied to the local population? **YES/NO** -Do the results of this study support other available evidence? **YES** **Strengths:** Objective, longitudinal measurements of lung function. Good sample size. **Limitations:** Spirometry only, lack of radiological imaging. The close follow-up may improve results on drug adherence and clinical management. [1]Upgraded due to good sample size, longitudinal, objective measurements.

Reference: Masekela R, Anderson R, Moodley T, Kitchin OP, Risenga SM, Becker PJ, et al. HIV-related bronchiectasis in children: An emerging spectre in high tuberculosis burden areas. International Journal of Tuberculosis and Lung Disease. 2011;16(1):114-9.			**Design:** Cross-sectional **Level of documentation** III **GRADE** ⊕○○○[1]
Objective	**Methods**	**Results**	**Discussion and commentaries**
To study predisposing factors for the development of bronchiectasis in a developing world setting. **Conclusion** Children with HIV-related bronchiectasis are diagnosed after the age of 6 years and suffer significant morbidity. Immune stimulation mechanisms in these children are intact despite the level of immunosuppression. **Country** South Africa **Year of data collection** 2009-2010	35 children, aged 6-18 years with HIV-related bronchiectasis attending paediatric clinic in Pretoria were enrolled to perform lung function testing. Included was children with symptoms suggesting bronchiectasis and radiological confirmation. Spirometry with FEV_1, FVC, FEV_1/FVC and FEF_{25-75} were performed. Bronchodilator response was set to 15% increase in FEV_1. Data collected on HIV diagnosis, time on ART. Induced sputum samples for TB, RS-virus, influenzae A and B, parainfluenza 1-3, adenovirus and CMV was collected. Blood samples for HIV staging and food and aeroallergens was collected. Statistical analysis was done using STATA, measures made by Spearman rank correlation and Wilcoxon rank sum test. 7 participants lost to follow-up and excluded from study. 2 patients died during the one-year follow-up. Only induced sputum samples were prospectively collected.	Male 57%, HIV diagnosis at a mean age of 6.9 years. Median CD4 count of 569, 19 subjects were virally supressed (VL<25 copies/ml) and 16 non-supressed. All but one participant on ART for median of 18 months. No significant difference between supressed and non-supressed individuals with FEV_1 or anthropometric measurements. 161 sputum samples were collected, 43.8% had a positive bacterial culture, *H. influenzae* and *parainfluenza* accounted for 49% of all cultures. Median FEV_1 were 53% predicted. Median FEF_{25-75} were 52% predicted. Only 8 participants had positive bronchodilator response. Based on sputum culture, groups did not differ on spirometry, as well as smoke exposure. 75% of the participants had prior diagnosis of TB, and almost a quarter had 2 courses of anti-tuberculosis treatment.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Was the study based on random selection of suitable participants? **YES** -Were inclusion/exclusion criteria clearly defined? **NO** -Were all participants representative of a specified population? **YES** -Was the response rate high? **YES** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **UNCLEAR** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES** -Do you trust the results? **YES** -Can the results be applied to the local population? **NO** -Do the results of this study support other available evidence? **YES** **Strengths:** Multiple collection of sputum samples. Wide range of blood samples. **Limitations:** No comparison group. Low sample size. High risk of selection bias. [1]Downgraded due to low sample size, poor statistical power and high risk of selection bias.

Reference: Masekela R, Anderson R, Gongxeka H, Steel HC, Becker PJ, Green RJ. Lack of efficacy of an immunomodulatory macrolide in childhood HIV related bronchiectasis: A randomised, placebo-controlled trial. Journal of Antivirals and Antiretrovirals. 2013;5(2):044-9.			**Design:** Randomized controlled trial **Level of documentation** Ib **GRADE** ⊕⊕⊕◯[1]
Objective	**Methods**	**Results**	**Discussion and commentaries**
To assess the efficacy of low dose erythromycin in reducing the number of pulmonary exacerbations in HIV infected children with radiologically confirmed bronchiectasis. **Conclusion** Administration of ART and adjunctive care, including airway clearance ant treatment of exacerbations in children with HIV-related bronchiectasis is associated with improvement in pulmonary function tests and IL-8, with no additional benefit from the use of erythromycin. **Country** South Africa **Year of data collection** 2009-2012	43 HIV infected children with bronchiectasis were randomized 1:1 to erythromycin (n=17, 55%) or placebo (n=14, 45%) treatment for 52 weeks. Inclusion criteria was children aged 6-18 with HIV and presence of bronchiectasis on CT scan, and all children had to perform reliable lung function tests. Those with abnormal liver function tests, urea/creatinine or on medication were excluded. Lung function tests included spirometry with FEV_1, FVC and FEF_{25-75}. Data collected on HIV diagnosis, time on ART. Height, weight and BMI z-scores. Sputum samples were collected monthly. High resolution CT scanning was performed and analysed by two independent, blinded radiologists. Statistical power calculations were done, with 20 in each study arm giving 90% power. ANOVA analysis of variance was used to compare groups with mean exacerbations. For comparing variables from the start to the end of the trial, ANCOVA was used. Wilcoxon test and spearman rank correlation test ere used for lung function and cytokine analysis respectively. 2 deaths, 10 lost to follow-up.	31 completed intervention. Intervention mean age 9.1 and placebo mean age 8.4, more males in intervention arm (55%). Higher CD4 counts in placebo arm. All participants on ART prior to enrolment. No difference in number of exacerbations in placebo vs. erythromycin arm. There was improvement in predicted FEV_1 and FVC, but not significant (p=0.31 and p=0.46) in both groups. When pooling the data, FEV_1% predicted and FVC% predicted were significantly improved from start to end of trial (p=0.005 and p=0.001). IL-8 was elevated in sputum samples, and a non-significant decrease was observed in both treatment arms. Pooling of data found a significant decrease of IL-8 from baseline to end of study (p=0.04). TNF-alpha declined in both treatment arms, not attributed to erythromycin. The change was also independent of CD4 counts VL. One participant had culture positive TB during follow-up.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Were inclusion/exclusion criteria clearly defined? **YES** -Were the groups similar from the beginning of the trial? **YES** -Was randomization done adequately? **YES** -Were patients, health workers and study personnel blinded to treatment? **YES** -Were the groups treated equally aside from intervention? **YES, except CD4 counts and gender** -Were participants accounted for at the end of trial? **YES** -Do you trust the results? **YES** -How precise are the results? **Results show no additional effect of erythromycin** -Can the results be applied to the local population? **YES** -Are the benefits worth the harms and costs? **NO** -Do the results of this study support other available evidence? **UNCLEAR** **Strengths:** Double blinded **Limitations:** Small sample size, high rate of lost to follow-up. Short follow-up. [1]Downgraded due to small sample size, and high rate of lost to follow-up.

Reference: Mwalukomo T, Rylance SJ, Webb EL, Anderson S, O'Hare B, Van Oosterhout JJ, et al. Clinical characteristics and lung function in older children vertically infected with human immunodeficiency virus in Malawi Journal of the Pediatric Infectious Diseases Society. 2016;5(2):162-9.			**Design:** Cross sectional **Level of documentation** III **GRADE** ⊕⊕◯◯
Objective	**Methods**	**Results**	**Discussion and commentaries**
To describe the burden of HIV-related CLD in children and assess spirometry, bronchodilator response, quality of life and chest radiography in these children. **Conclusion** Symptoms of CLD was highly present, with 2 phenotypes "cough" and "hypoxia". Lung function abnormalities are common, poor response to bronchodilators were apparent throughout the age range of the cohort. Pathological causes remain to be elucidated. **Country** Malawi **Year of data collection** 2011	Children aged 8-16 years were recruited from HIV outpatient clinics in Blantyre, Malawi. The 3 first eligible patients per day was included. Exclusion criteria included residency outside Blantyre, currently under TB-treatment, Kaposi sarcoma, reported acute respiratory symptoms or acquired emergent hospitalization. All participants were WHO staged of HIV disease, CD4 counts were taken and TB smear and culture were done on those able to expectorate. 200 m submaximal walk test was done unless contraindicated. Spirometry was performed according to ATS/ERS guidelines. With reporting of FEV_1, FVC and FEV_1/FVC. 5th percentile of reference population set as LLN. Reversibility set to >12% improvement of FEV_1 or FVC. Chest X-ray were analysed by 2 independent clinicians. Univariable associations of abnormal lung function assessed by logistic regression. Multivariate analysis to age and sex. Multivariable logistic regression was done to identify independent variables to the two phenotypes of CLD	160 patients, mean age 11.1 years. 50% female. 60 (37.5%) had cough. 55 (34.4%) had moderate or severe hypoxia. 34 (22.1%) had digital clubbing. 33 (20.6%) were hypoxic at rest. 118 (73.8%) were receiving ART. Participants on ART had higher CD4 counts (median 698 vs 406 cells/µl), p<0.001. 30 (18.8%) had previously been treated for TB, 6 (3.8%) had more than 2 courses. 145 (90.6%) had FEV_1 and FVC 1.06 and 0.89 standard deviations below predicted mean, respectively. 21 (14.5%) had obstructive defects and 26 (17.9%) had reduced FVC. "Tramlines" and ring shadows were present in chest X-rays of half of the participants. Lung function abnormalities was not associated with any clinical findings, including ART and prior TB-treatment. There was a high number of participants being previously treated for chest infections. This together with reduced lung function, clubbing and radiological findings are suggestive of bronchiectasis.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Was the study based on random selection of suitable participants? **YES** -Were inclusion/exclusion criteria clearly defined? **YES** -Were all participants representative of a specified population? **YES** -Was the response rate high? **YES** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **UNCLEAR** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES** -Do you trust the results? **YES** -Can the results be applied to the local population? **YES** -Do the results of this study support other available evidence? **YES** **Strengths:** Good sample size. **Limitations:** Not only perinatally infected participants. No control groups. Only conventional chest x-ray.

Reference: Rylance J, McHugh G, Metcalfe J, Mujuru H, Nathoo K, Wilmore S, et al. Chronic lung disease in HIV-infected children established on antiretroviral therapy. Aids. 2016;30(18):2795-803.			**Design:** Cross sectional **Level of documentation** III **GRADE** ⊕⊕◯◯
Objective	**Methods**	**Results**	**Discussion and commentaries**
To investigate symptom prevalence, lung function and exercise capacity among older children established on ART and an age-matched HIV uninfected group **Conclusion** In children, despite ART, HIV is associated with significant respiratory symptoms and functional impairment. Understanding pathogenesis is key, as new treatment strategies are urgently required **Country** Zimbabwe **Year of data collection** 2014-2015	202 HIV infected and 150 HIV uninfected children and adolescents (median age 11.1 in both groups) were recruited unselectively from primary health care clinics in Harare, Zimbabwe. Questionnaires on socio-demographic indices, clinical history and symptoms were filled out. Standardized examinations were performed. Spirometry performed using ATS standards, measuring FEV_1, FVC and FEV_1/FVC. Obstruction defined as reduced FEV_1/FVC. Reversibility testing was performed using 2.5 mg salbutamol on nebulizer in participants with spirometry abnormalities. Global lung initiative standards were used to calculate reference values for spirometry. LLN was set to 1,64 SDs below mean expected value Incremental shuttle walk test (SWT) validated for children with CLD was used to assess cardiorespiratory fitness. Respiratory rate, heart rate and oxygen saturation were measured before and immediately after testing. Students t-test was used to compare parametric means between HIV infected and uninfected groups. Mann-Whitney U-test was used for non-parametric variables. Categorical data was compared using Chi-square test and logistic regression to evaluate association of clinical parameters (a priori) and abnormal lung function.	55% female in HIV infected group, 42% in uninfected group. 25% of HIV infected had respiratory symptoms, and only 0.7% of uninfected reported it. 76 (38%) of HIV infected were previously treated for TB, compared to only 1 (0.7%) in HIV uninfected group ($p<0.001$). No TB was found on examination of the participants. 88% of HIV infected and 87% of uninfected produced high-quality spirometry. HIV infected had lower exercise capacity (SWT 771m vs. 889m) ($p<0.001$) and more frequently abnormal spirometry (43 (24.3%) vs. 15 (11.5%)) ($p<0.001$). HIV status and older age was associated with lung function abnormality, as well as older age at HIV diagnosis ($p=0.025$). Those with prior infections (including TB) were more likely to have abnormal lung function ($p<0.05$) The most common lung function abnormality was a restrictive pattern spirometry. However, those with previous history of infection, including TB, had a more obstructive pattern with reduces FEV_1/FVC.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Was the study based on random selection of suitable participants? **YES** -Were inclusion/exclusion criteria clearly defined? **YES** -Were all participants representative of a specified population? **YES** -Was the response rate high? **YES** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **UNCLEAR** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES** -Do you trust the results? **YES** -Can the results be applied to the local population? **YES** -Do the results of this study support other available evidence? **YES/NO** **Strengths:** HIV uninfected control group. Unselective recruitment. **Limitations:** Not available spirometry for all participants. Self-reporting of illness. No radiological tests.

Reference: Weber HC, Gie RP, Wills K, Cotton MF. Clinical features and lung function in HIV-infected children with chronic lung disease. SAJCH South African Journal of Child Health. 2015;9(3):72-5.			**Design:** Cross sectional **Level of documentation** III **GRADE** ⊕◯◯◯[1]
Objective	**Methods**	**Results**	**Discussion and commentaries**
To report the clinical manifestations and lung function tests in children with advanced HIV disease at a tertiary care centre in a region with high HIV and TB burden, and determine clinical predictors of poor lung function. **Conclusion** The authors identified useful clinical signs predictive of poor lung function in HIV infected children with CLD, especially in resource-limited settings. **Country** South Africa **Year of data collection** 2005-2006	56 children with HIV and suspected CLD due to chronic symptoms and/or signs or with previous history of pneumonia were recruited. All participants underwent clinical examination, lung function testing and retrospective chart history was undertaken. Lung function tests were done according to ATS/ERS standards and reference values were calculated. Bronchodilator reversibility testing was done, with cut off at >12% increase in FEV_1%. Spearman's correlation coefficients were used to measure associations between FEV_1% and clinical characteristics measured on continuous scales. T-tests were used for comparing mean FEV_1% to continuous variables. Univariate and multivariable linear regression was used to determine predictors for poor lung function.	Median age was 5 years, 53.6 % male. 93% of participants had been previously treated for PTB. 36 cases had a history of hospitalisation for pneumonia, 27 (74%) had two or more and 13 (37%) had three or more. 27 (48%) had adequate lung function tests. Median FEV_1% was 60% (IQR 45.3 – 86.3) and only 5 (18.5%) had positive bronchodilator responsiveness. There was significant negative association with respiratory rate and lung function in univariate analysis, but not in multivariable. Hyperinflation was associated with lower lung function. PTB was the most frequent comorbidity, but temporal relationship between PTB and CLD could not be established. Over-diagnosing could be an issue. Hyperinflation, respiratory rate and hyperpigmented skin lesions had clinical association with poor lung function.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Was the study based on random selection of suitable participants? **YES** -Were inclusion/exclusion criteria clearly defined? **NO** -Were all participants representative of a specified population? **YES** -Was the response rate high? **NO** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **UNCLEAR** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES** -Do you trust the results? **YES** -Can the results be applied to the local population? **YES** -Do the results of this study support other available evidence? **YES/NO** **Strengths:** Objective measures of lung function **Limitations:** Small sample size. No control groups. No radiological measures. Only 48% had adequate lung function tests. [1]Downgraded due to poor response rate and high risk of selection bias.

Reference: Desai SR, Nair A, Rylance J, Mujuru H, Nathoo K, McHugh G, et al. Human Immunodeficiency Virus-Associated Chronic Lung Disease in Children and Adolescents in Zimbabwe: Chest Radiographic and High-Resolution Computed Tomographic Findings. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2018;66(2):274-81.			**Design:** Cross sectional **Level of documentation** IIb-III **GRADE** ⊕⊕◯◯
Objective To investigate radiologic features of chronic lung disease in HIV infected children aged 6-16 years receiving ART for 6 months or more in Harare, Zimbabwe **Conclusion** The HRCT findings strongly suggest that obliterative bronchiolitis may be the major cause of chronic lung disease in this cohort. Further studies to understand the pathogenesis and natural history are urgently needed. **Country** Zimbabwe **Year of data collection** 2016-2017	**Methods** 202 HIV infected children aged 6-16 years were enrolled at routine HIV care at Harare Central hospital, Zimbabwe. All participants were on ART for at least 6 months. Participants with TB or symptoms and signs of acute respiratory failure were excluded. 193 had chest x-ray available. Questionnaires were used to collect sociodemographic and clinical data, including HIV treatment, history of illness, and current symptoms. Participants underwent standardized clinical examination. All performed shuttle walk testing, spirometry and pulse oximetry. Spirometry was recorded using ATS standards. Normal ranges were defined using GLI standards. LLN was set to 1.64 SDs of the reference population (lower 10th percentile). HRCT was done in those with abnormal chest x-rays and those meeting clinical definitions of CLD. Radiology was examined by 2 independent blinded thoracic radiologists. Severity of chest x-ray and HRCT was assessed using weighted quadratic Cohens kappa. Associations between HRCT patterns and FEV_1 was examined by Spearman rank correlation.	**Results** 193 patients were included in the analysis. 46% female, median age 11.2 years. Median CD4 count was 720 cells/µl. and 79% had viral load <400 copies/ml. 55 (29%) had ring/tramline opacities, 7% had consolidations. 84 participants underwent HRCT, these participants were similar. 70 of 84 (83%) had HRCT abnormalities. 39 (56%) of these had normal chest x-ray. Decreased attenuation as part of mosaic attenuation pattern was present in 43% of scans. 35 of 36 of these has >5% extent of the pattern. 33% had bronchiectasis, 29% lobar volume loss and 26% had large- or small-airway plugging. 7% had emphysema. There was a strong correlation between decreased attenuation and extent of bronchiectasis ($r=0.68$, $p<0.001$) and severity of bronchial wall thickening ($r=0.63$, $p<0.001$). Decreased attenuation ($r=-0.52$, $p<0.001$) and extent of bronchiectasis ($r=-0.50$, $p<0.001$) strongly correlated with reduced FEV_1, FVC, and FEF_{25-75} without reversibility. These findings support OB as most likely cause of CLD in these participants.	**Discussion and commentaries** **Checklist:** -Did the study address a clearly focused issue? **YES** -Was the study based on random selection of suitable participants? **YES** -Were inclusion/exclusion criteria clearly defined? **YES** -Were all participants representative of a specified population? **YES** -Was the response rate high? **YES** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **UNCLEAR** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES** -Do you trust the results? **YES** -Can the results be applied to the local population? **YES** -Do the results of this study support other available evidence? **YES** **Strengths:** Unselected enrolment. 2 individual, blinded radiologists. **Limitations:** CT was only performed only in participants with clinical CLD. Some observer variation in examination of CT scans. No histologic confirmation of OB diagnosis.

Reference: McHugh G, Rylance J, Mujuru H, Nathoo K, Chonzi P, Dauya E, et al. Chronic Morbidity Among Older Children and Adolescents at Diagnosis of HIV Infection. J Acquir Immune Defic Syndr. 2016;73(3):275-81.			**Design:** Cross sectional **Level of documentation** III **GRADE** ⊕⊕◯◯
Objective	**Methods**	**Results**	**Discussion and commentaries**
To investigate the prevalence of chronic morbidity among children aged 6-15 years at diagnosis of HIV infection. **Conclusion** In children with slow-progressing HIV, there is a substantial burden of chronic morbidity even when CD4 count is relatively preserved. Timely HIV testing and prompt ART initiation are urgently needed to prevent development of chronic complications **Country** Zimbabwe **Year of data collection** 2013-2014	385 participants aged 6-15 years were recruited from 449 children that tested positive for HIV at 7 primary health care clinics in Harare, Zimbabwe. Clinical history was undertaken by interview-based questionnaire. HIV staging was done according to WHO guidelines. A standardized physical exam was performed in all participants. Cardiorespiratory function was assessed by shuttle walk test and spirometry. Reversibility testing was done using 2.5 mg salbutamol by nebulizer. By spirometry obstruction was defined as FEV_1/FVC less than 1.64 SD below the mean, and restrictive pattern as FVC < 1.64 SD below mean with normal FEV_1/FVC. Reference values was calculated using GLI standards Participants who screened positive for TB by sputum were examined by microscopy and Xpert TB. Statistical analysis of association between a priori variables and CD4 count was determined using logistic regression, adjusted for age and sex. Missing variables were excluded from regression analysis	Median age at HIV diagnosis was 11 years. 52% female. Most likely route of transmission was mother-to-child. 18 (5%) had previous history of TB. Chronic respiratory symptoms were very common, 54% reporting cough of more than 1-month duration. 16% dyspnoea. 12% had O2 saturation <88% at rest, and additional 10% dropped to <88% after exercise. 238 participants underwent spirometry, of whom 23 (10%) had obstructive pattern, only 3 had positive reversibility test. 43 (18%) had reduces FVC. 155 (40%) of participants screened positive for TB using WHO guidelines, but only 1 had findings of TB on GeneXpert. CD4 count <500 or <350 cells/mm^3 was not associated with WHO stage of disease, reduced FEV_1 or FVC. Cough, hypoxia, reduced exercise tolerance and obstructive lung defects with no reversibility was predominant. This makes asthma unlikely. 119 (31%) had poor spirometry that could not be interpreted.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Was the study based on random selection of suitable participants? **YES** -Were inclusion/exclusion criteria clearly defined? **YES** -Were all participants representative of a specified population? **YES** -Was the response rate high? **YES** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **UNCLEAR** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES** -Do you trust the results? **YES** -Can the results be applied to the local population? **YES** -Do the results of this study support other available evidence? **YES** **Strengths:** Good sample size. Low risk of selection bias. **Limitations:** Newly diagnosed. No control groups. High number of not interpretable spirometry.

Reference: Sovershaeva E, Kranzer K, McHugh G, Bandason T, Majonga ED, Usmani OS, et al. History of tuberculosis is associated with lower exhaled nitric oxide levels in HIV-infected children. AIDS. 2019; forthcoming.			**Design:** Cross sectional **Level of documentation** III **GRADE** ⊕⊕◯◯
Objective	**Methods**	**Results**	**Discussion and commentaries**
To investigate the relationship between exhaled nitric Oxide (eNO), a marker of lung inflammation, HIV status and airway abnormalities in perinatally HIV infected children and adolescents. **Conclusion** HIV infection and history of TB were associated with lower levels of eNO. eNO-levels may be a marker of HIV- and TB-induced alteration in pulmonary physiology: Further studies focused on potential causes for lower eNO in HIV and TB are warranted. **Country** Zimbabwe **Year of data collection** 2017-2018	222 HIV infected children with CLD was recruited as a part of an RCT with azithromycin vs placebo at Harare Central hospital paediatric HIV clinic. 97 HIV uninfected participants were enrolled from the same catchment area. Exclusion criteria included age 6-19 years, no active TB or respiratory tract infection and on ART for > 6 months. The uninfected group was tested at enrolment, were 6-16 years, had no history of heart or lung disease and normal spirometry. Participants filled out a questionnaire on previous medical history and demographic information. All participants had a full blood count done, as well as CD4 and VL counts. eNO and spirometry testing were done according to ATS guidelines. FEV_1 z-scores were calculated using prediction equations from the global lung function initiative. Characteristics between study groups were compared in STATA using Fishers exact test for categorical and Kruskal-Wallis or Wilcoxon rank sum test for continuous variables. eNO values were log transformed and associations with explanatory variables were investigated using linear regression analysis.	Median age of HIV infected 15 years, uninfected median of 10 years. Median time on ART was 6.6 years. HIV infected participants were more likely to be wasted, stunted, have anaemia and exposed to passive smoking. 57 (25.7%) of HIV-infected had a history of TB, and 56 (25.2%) had airway obstruction, but no history of TB. HIV status was associated with lower eNO levels (p=0.03). History of TB in HIV infected was associated with lower levels of eNO, adjusted for age, sex and time of eNO testing (p=0.007), even if no airway obstruction or abnormality was present. There was no association between airway obstruction measured as FEV_1 z-score < -1.64 and eNO levels in HIV infected children, in line with previous studies on adults with COPD.	**Checklist:** -Did the study address a clearly focused issue? **YES** -Was the study based on random selection of suitable participants? **YES** -Were inclusion/exclusion criteria clearly defined? **YES** -Were all participants representative of a specified population? **YES** -Was the response rate high? **YES** -Were objective criteria used to assess/validate outcome measures? **YES** -Have authors identified all relevant confounders? **YES** -Are prognostic/confounding factors considered in the study design and/or analysis? **YES/NO** -Do you trust the results? **YES** -Can the results be applied to the local population? **YES** -Do the results of this study support other available evidence? **YES/NO** **Strengths:** Good sample size. HIV uninfected control group. **Limitations:** Age difference in groups. Self-reporting of TB, no information of pulmonary/extrapulmonary.