Description and outcomes of children requiring long term domiciliary oxygen therapy at Chris Hani Baragwanath Academic Hospital from January 2011 to December 2015.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the Branch of Paediatrics

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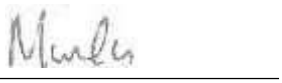
DECLARATION

I, Wendy Kelebogile Maimela, declare that this is all my own work. This work has not been submitted for examination at any other institution or for publication. The research report is submitted for the Degree Master of Medicine in Paediatrics at the University of the Witwatersrand.



Dr. Wendy Kelebogile Maimela

Date: 25 June 2021

DEDICATION

In loving memory of my father

Andrew Mocca Maimela

1948-2008

ABSTRACT

Background: A significant number of paediatric patients are discharged from hospital on long-term domiciliary oxygen therapy (LTDOT). There is, insufficient research investigating the indications and outcomes of the use of LTDOT in low and middle-income countries with a high prevalence of Human Immunodeficiency Virus (HIV) such as South Africa.

Objectives: To describe the diagnosis, clinical characteristics, and the outcomes of children requiring LTDOT at Chris Hani Baragwanath Academic Hospital (CHBAH) in South Africa.

Methods: A retrospective descriptive study on hospital records of children on LTDOT between January 2011 and December 2015. The population included children aged16 years and younger who received LTDOT from the paediatric pulmonology department at CHBAH.

Results: The study included 390 participants (57.5 % males n=172). The median age at initiation was 4.8 (2.1-25.2) months with a median duration of 6.5 (3.2-14.0) months. The prevalence of HIV exposure was 51.3 % n= 116 and 60.3 % n=70 were HIV infected. The majority (89.6 % n= 343) of the participants required full time (24 hours/day) LTDOT, at oxygen flow rates commonly set between 1-2 L/min. Most, 80.3 % n= 248, had a respiratory diagnosis with 67.3 % n=167 being due to neonatal lung disease and 25 % n= 62 being due to an infectious or post-infectious cause. At the six month time point, 20.3 % n=79 of the participants had been weaned off LTDOT and 35.4 % n=138 were weaned off by 12 months. HIV infected participants were found to start LTDOT at ages older than one year 2.28(0.55-9.33) years, when compared to HIV uninfected participants 0.46 (0.21-2.23), p <0.0005 and were 2-fold (OR 2.08, 95% CI 1.07-4.11) more likely to be weaned off LTDOT by 12 months. They also had a high prevalence of infectious or post-infectious respiratory diagnoses OR 5.89, 95 % CI 2.97-11.84 . We found significant differences in duration on oxygen between HIV infected 1.06 (0.33- 4.81) compared to 0.54 (0.04-3.29) years in HIV uninfected participants; p=0.034.

Conclusion: The majority of patients requiring LTDOT at CHBAH do so for respiratory causes, especially those acquired in the neonatal period. Two thirds of patients are weaned off oxygen therapy within 12 months of commencing LTDOT. HIV infected participants were on LTDOT for longer durations than uninfected participants but had a higher prevalence of post infectious bronchiolitis.

ACKNOWLEDGMENTS

Dr Charl Verwey as my supervisor.

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List of Abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
AVSD	Atrio-ventricular septal defect
BO	Bronchiolitis obliterans
BPD	Bronchopulmonary dysplasia
CHBAH	Chris Hani Baragwanath Academic Hospital
CLD	Chronic lung disease
COAD	Chronic obstructive airways disease
CT	Computed tomography
CXR	Chest radiograph
DCMO	Dilated cardiomyopathy
DMD	Duchene muscular dystrophy
ECG	Electrocardiograph
ECHO	Echocardiograph
ELISA	Enzyme-linked immunosorbent assay
ESRD	End stage renal disease
GIT	Gastrointestinal tract
GORD	Gastroesophageal reflux disease
HIV	Human immunodeficiency virus
HREC	Health Research Ethics Committee
ID	Identification number
IQR	Interquartile range
LIP	Lymphocytic interstitial pneumonitis
LMIC	Low- and middle-income countries
L/min	Litres per minute
LTDOT	Long-term domiciliary oxygen therapy
mmHg	Millimeters of mercury
NICU	Neonatal intensive care unit
NIV	Non-invasive ventilation
NHLS	National Health Laboratory Service
OSAS	Obstructive sleep apnoea syndrome
PCR	Polymerase chain reaction
PIBO	Post infectious bronchiolitis obliterans
PMTCT	Prevention of mother-to-child transmission
PDA	Patent ductus arteriosus
SMA	Spinal muscular atrophy
SPO2	Oxygen saturation
UK	United Kingdom
UNAIDS	The Joint United Nations Program on HIV/AIDS
VSD	Ventricular septal defect
WHO	World Health Organization

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Description and outcomes of children requiring long term domiciliary oxygen therapy at Chris Hani Baragwanath Academic Hospital from January 2011 to December 2015.

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CHAPTER 1

1. INTRODUCTION

The medicinal use of oxygen was initially popularised at the end of the 18th century supported by work done at the "Pneumatic Institution" in Bristol (1). The use of oxygen was revolutionised after a Scottish physician published a seminal paper on the proposed therapeutic administration of oxygen in 1917 (2). In child healthcare, oxygen therapy has been used for over 80 years (3). The aim of oxygen therapy is to supply the human body with adequate amounts of oxygen to prevent tissue hypoxia and oxygen therapy can be delivered using oxygen face masks, nasal cannulae (low and high flow devices), headbox and through invasive or non-invasive ventilation strategies (4). Post inhalation, oxygen diffuses across the alveolar-epithelial membrane and enters the blood stream where it is mainly transported to tissues chemically bound to the haemoglobin molecule in red blood cells (4). Delivery of oxygen to tissues, is dependent on the concentration of haemoglobin in the blood, haemoglobin oxygen saturation, the rate of blood circulation and the efficacy with which oxygen is unloaded from the haemoglobin molecule to the tissues (4).

Oxygen saturation (SpO2) can be measured by assessing arterial blood samples through calibrated blood gas machines or estimated by using pulse oximetry devices (5,6). The partial pressure of arterial blood oxygen in healthy individuals breathing in room air (21 % oxygen) at sea level ranges between 75-100 mmHg corresponding with oxygen saturation levels of 94–100 % (5). An estimated reduction in oxygen saturation of 5 % per 1000 m altitude is expected in those living above sea level (5). Hypoxaemia refers to low oxygen levels in the blood, while hypoxia is defined as a deficit of oxygen at a cellular level (4, 6). Organ dysfunction and cell death occur in unrecognised or poorly managed periods of hypoxia (6).

In children living at sea level, for those younger than one year, hypoxaemia is defined as spending 5 % or more of the time with a SpO2 less than or equal to 90 % or, if measurements are taken intermittently, obtaining three independent measurements of SpO2 less than or equal to 90 % (7).

In children older than one year, who live at sea level, hypoxaemia is defined as spending 5 % or more of the time with a SpO2 less than or equal to 93 % or, if measurements are taken intermittently, obtaining three independent measurements of SpO2 less than or equal to 93 % (7). Chronic hypoxaemia leads to pulmonary hypertension by causing pulmonary vasoconstriction in unventilated localized areas of the lungs resulting in right ventricular pressure overload and ultimately cor pulmonale (8). Polycythaemia can also occur in this situation, exacerbating pulmonary hypertension (8). Other systemic effects of chronic hypoxaemia include detrimental effects on growth, retardation in neurological and psychomotor development (cognition and behaviour are affected in later life) and poor quality of sleep (8, 9). Adverse effects on cognition and behaviour have been described at prolonged oxygen saturations less than 85 % but long-term outcomes of prolonged milder levels of hypoxia (85-89 %) are not clear (10). Balfour-Lynn et al suggest that there may also be sequelae from milder or recurrent intermittent forms of hypoxaemia (10).

Oxygen supplementation is required in acute and chronic states of hypoxaemia. When supplemental oxygen is required for more than two weeks to maintain SpO2 at or greater than 92 % or at a PaO2 greater than 60 mmHg in a health facility, long term domiciliary oxygen therapy (LTDOT) becomes a life saving option by addressing physiologic and metabolic demands of the cells (4, 7, 8). The term LTDOT includes chronic continuous oxygen usage (24 hours/day), sleep related oxygen usage (nocturnal or day time) and chronic intermittent oxygen usage (continuous LTDOT in an episodic manner guided by clinical symptoms or pulse oximetry readings) (10). LTDOT is commonly supplied through stationary oxygen concentrators (which require reliable and constant electricity supply), portable oxygen concentrators, cylinders with attached regulators or in liquid form (8).

Clinical and physiological benefits of LTDOT include reduction in length of and number of hospitalizations (8), optimization of physical growth (11,12), improvement of exercise tolerance/quality of life and sleep (13), prevention of pulmonary hypertension and development of cor pulmonale (10,12), reduced nosocomial infections (14, 15) and improved survival (13,14). LTDOT offers patients and their families psychological comfort maintaining normal development and normal bonding between parents and their children (15).

A significant cost reduction when using LTDOT has been shown as compared to the cost of prolonged or multiple hospitalizations (8, 15). In an American study conducted by DeMauro et al on preterm infants born at less than 27 weeks and requiring LTDOT with a diagnosis of bronchopulmonary dysplasia (BPD), no statistically significant improvement was shown for neurodevelopmental outcomes at corrected ages between 18 and 26 months (16). More research is needed to assess the effects of LTDOT on neurodevelopmental and behavioural outcomes in children where LTDOT has been prescribed for diagnoses other than BPD.

Chronic neonatal lung disease, mostly attributed to BPD, has been identified as the leading indication for LTDOT in infancy in developed countries (7,8,12). In these countries, older children on LTDOT most commonly had a diagnosis of post infectious bronchiolitis obliterans (PIBO) followed by neurological disorders, congenital malformations and cardiovascular disease (10,12). Other common indications for LTDOT were cystic fibrosis, non-cystic fibrosis bronchiectasis, obstructive sleep apnoea syndrome (OSAS), sickle cell anaemia complicated by chronic hypoxia and interstitial lung disease (8,9,10). Data from the United Kingdom in 2008 reported chronic neonatal lung disease (60 %) as the leading diagnosis for LTDOT in their population, followed by neuro disability (7 %), cardiac disease (5 %), neuromuscular disease (3 %) and interstitial lung disease (2 %) (10).

There are very few studies on the use of LTDOT in children residing in low- and middle-income countries (LMIC) like South Africa. In 2001, Norzila et al found that for Malaysian infants (with a median age at initiation of LTDOT of 5 months) the most common indication for LTDOT was BPD (45 %) and PIBO was the second most common diagnosis (23.9 %) with a median age at initiation of LTDOT of 17 months (9). Congenital abnormalities (15.5 %), cardiac disease (7 %) and interstitial lung disease (5.6 %) contributed the least respectively (9). These findings are similar to results reported from other developed countries (9,10). A 2011 Brazilian study by Muhnoz et al showed that BPD was the second most common diagnosis for commencing LTDOT 19 %, cystic fibrosis was the leading diagnosis for commencing LTDOT (22 %) and PIBO (15 %) was third most common diagnosis (14).

The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2013 global report identified that approximately 90 % (2.9 million) of children infected with the human immunodeficiency virus (HIV) live in sub-Saharan Africa (17, 18). The National Antenatal Sentinel HIV and Syphilis prevalence survey (2011) estimated that 5.6 million South Africans were infected with HIV (19). The survey found that the prevalence of HIV amongst women attending public healthcare antenatal facilities was 29.5 % with 28.7 % of these women residing in Gauteng where our study site is situated at Chris Hani Baragwanath Academic Hospital (CHBAH) (19). Results from the survey indicated that approximately 460 000 children (<15 years) were HIV infected and that 260 000 (2200000-2400000) children would require antiretroviral therapy (ART) (19). A 2009 study conducted in South Africa and Zimbabwe estimated that without ART, in South Africa, the prevalence of HIV in 10 year olds was 2.1 % in 2008 and that this would increase to 3.3 % in 2020 (20).

Improved access to ART and co-trimoxazole prophylaxis in sub- Saharan Africa contributed to a reduction in acute respiratory infections and mortality (17,8,21,22). However, despite the introduction of ART, HIV associated cardiopulmonary disease remains highly prevalent among children with perinatally acquired HIV infection in sub-Saharan Africa, although it is now a clinical entity distinct from that in the pre-ART era (23,24). A Zimbabwean study by Rylance et al in 2016 found that chronic respiratory symptoms were rare in HIV uninfected children (0.7 %) but common (25 %) in HIV infected children who had virological suppression on ART (25). HIV infected children are prone to more frequent and severe forms of lower respiratory tract infections compared to HIV uninfected children (17).

In the pre-ART era 30-40 % of HIV infected children developed CLD primarily secondary to LIP (25). Similarly, in established ART usage, 30 % of HIV infected children have CLD commonly secondary to PIBO, tuberculosis, bronchiectasis and interstitial lung disease (17,18,22,25,26). Two studies conducted in Zimbabwe found that obliterative bronchiolitis was the leading cause of CLD which, once established, seemed to have little reversibility with ART (17, 26).

Medical advancements have made the use of LTDOT accessible. However, there is paucity of research on the use of LTDOT in children in LMIC.The objective of this study was to describe the diagnosis, clinical characteristics, and the outcomes of children requiring LTDOT at CHBAH, a tertiary level and academic public healthcare facility in Soweto South Africa.

CHAPTER 2

2. MATERIALS AND METHODS

2.1 Objectives

The objective of this study was to describe the diagnosis, clinical characteristics and outcomes of children younger than 16 years requiring LTDOT at CHBAH, Soweto, South Africa.

2.2 Study design

This retrospective descriptive study included children less than 16 years of age who received LTDOT through the Paediatric Pulmonology Department at CHBAH. A review of hospital records was conducted on children that were treated using LTDOT from 1 January 2011 to 31 December 2015. Inclusion criteria were as follows:

1. Children less than 16 years of age on LTDOT.
2. LTDOT was considered if continuous, sleep time related, or intermittent oxygen delivery was indicated in the outpatient management of the children included in the study.

2.3 Study setting

The study was conducted through the Paediatric Pulmonology Department, a sub-specialist service offered at CHBAH which is a tertiary level academic institution. The institution is affiliated to the University of the Witwatersrand, Johannesburg, South Africa and is a referral center for lower level healthcare facilities that mainly serve the southern parts of Johannesburg.

2.4 Study population

The study population consisted of children 16 years and younger on LTDOT who had been referred to the Paediatric Pulmonology Department at CHBAH. The department accepts referrals from the paediatric and outpatient departments including referrals from other institutions in Johannesburg and the surrounding areas. The need for LTDOT was at the discretion of the treating paediatric pulmonologist. The guidelines for initiating LTDOT includes:

1. Prolonged requirement of hospital based oxygen (>28 days) include an acute illness, with oxygen saturations < 92 % when awake or < 90 % when asleep or feeding.
2. The presence of pulmonary hypertension secondary to hypoxia, as assessed by echocardiogram (ECHO) by the cardiologist.
3. The presence of a chronic pulmonary disease, for example HIV-associated bronchiectasis, with no prospect of weaning off oxygen therapy in the foreseeable future.

When the LTDOT prescription was finalized, a requisition was sent to Vitalaire South Africa, a company contracted by the government to supply LTDOT in Gauteng. Vitalaire would then provide a contract to the caretakers, supply and install the LTDOT equipment at the residence of the child. The type of equipment supplied depended on the availability of electricity at the residence of the child. If electricity was available, an oxygen compressor was installed and if electricity was not available the oxygen was supplied by means of oxygen cylinders. Oxygen therapy was delivered to the child through a low-flow nasal cannula interface as no other interfaces are available to children dependent on government supplied LTDOT. Face mask, high-flow nasal cannula, tracheostomy interfaces and ventilation devices were not supported and any child requiring more oxygen than that deliverable by the low-flow nasal cannula interface would be managed in the hospital. No saturation monitoring devices were supplied to the patients on LTDOT. A community nurse performed a monthly visit to the home and measured oxygen saturations using a pulse oximetry device.

Weaning of the LTDOT was performed by the paediatric pulmonologist at the routine clinic follow up appointments as well as by the community nurse during her home visits.

2.5 Data collection

In order for LTDOT to be considered and prescribed for a child, an LTDOT requisition form was completed by the requesting clinicians and forwarded to the Pulmonology department at CHBAH. The information from the form, was entered into an electronic data base for children who had successfully been prescribed LTDOT. In as far as possible, we supplemented the data base information with information retrieved from the Paediatric Pulmonology clinic file records. Attempts were also made to collect missing data telephonically from caretakers using telephone numbers supplied during patient hospital visits. This was done during routine updates of the LTDOT database and was standard practice. No attempts were made to contact caretakers of the patients on LTDOT after this study had commenced as this was a retrospective database review.

The original LTDOT data base was collected and managed using the Research Electronic Data Capture (REDCap) tool which is hosted by the University of the Witwatersrand, Johannesburg (27, 28). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

The following variables were analysed (see data capture sheet: Appendix A):

1. Sex
2. Age at onset of LTDOT
3. Prescribed oxygen flow rate
4. Type of prescription (full time, sleep related or intermittent use)
5. Diagnosis prior to commencing LTDOT
6. HIV status of the participants .

7. The duration of LTDOT was assessed at two time points: six and twelve months after initial LTDOT prescription, and the assessment was whether or not a child was still utilizing LTDOT at that time point. We analyzed data for participants that had been weaned off LTDOT at six months since initiation and those that weaned off at the twelve month period.

2.6 Data analysis

All available patient data were included in the analysis. Data were exported from the REDCap database onto an Excel spreadsheet version 2016 (Microsoft, USA). Statistical analysis was performed using STATA version 13.0 (StataCorp LLC, Texas USA). Basic description of the data was summarized using mean and standard deviation. Continuous variables that were not normally distributed were reported as median, interquartile range (IQR). Categorical variables were reported as percentages.

Data were stratified by HIV status, duration of LTDOT, and age at commencement of LTDOT to explore for any possible associations. Comparisons were made between the different groups using Student-t test for continuous variables with normal distribution and the Wilcoxon rank sum test for those without normal distribution. The Chi-square was performed for categorical variables. P-values and odds ratios with 95% confidence intervals were reported where appropriate. The differences were considered to be statistically significant when the p-value was less than 0.05. As this was a retrospective chart / database review we were dependent on the quality of the database that we used. Missing data was frequent and we were unable to supplement that data. For analysis, the actual numbers that were available to us were used and described as they were, knowing that the results may be biased due to the missing data. The tables reflect the actual numbers used and all statistics are based upon the actual number of observations that were available and not on the percentage of observations of the full number of patients in the database. The rigour of the study was dependent on the completeness of the database, which unfortunately was not ideal. Due to the retrospective nature of the study and the ethical clearance obtained we could not establish contact with the individual participants to try to obtain more data. Therefore, it is possible that the patients that were lost to follow-up or who had relevant missing data had different characteristics to those included in the study.

2.7 Ethical Considerations

The Paeditric Department's Protocol Review Committee approved the study for conduction at CHBAH. The CHBAH Medical Advisory committee as well as the Human Research Ethics Committee (HREC) of the University of the Witwatersrand approved of the study prior to commencement (ref. No M160768) (see Appendix B).

CHAPTER 3:

3 RESULTS

Three hundred and ninety children were treated with LTDOT by the Paediatric Pulmonology Service at CHBAH during the study period. Eighty-one patients (20.8 %) were lost to follow up, with unknown long-term outcomes. The median age at commencement of LTDOT was 4.8 (2.1-25.2) months. The analyses reported in Table 3.1 are based on available outcomes data numbers for each variable at CHBAH during the study period.

Sex was recorded in 299 children with available outcomes data, and most (57.5 % n=172) of the participants were male. HIV status was recorded in 226 of the children with available outcomes data. Of the 226 children with known HIV status, 51.3 % (n=116) were HIV exposed and 70 (60.3 %) of the exposed participants were HIV infected (Table 3.1). The HIV test conducted was the polymerase chain reaction (PCR) tests in children younger than 18 months and the enzyme-linked immunosorbent assay (ELISA) test in children older than 18 months. The majority of patients were referred from departments within the CHBAH n=357 (93.4 %) and the number of referrals were similar between the general wards and the neonatal unit n=173 (47.6 %) and n=166 (45.7 %) respectively. More than half of the children referred for LTDOT were between the ages of 1-6 months n=162 (52.9 %).

Table 3. 1 Demographic and Clinical characteristics of children referred for LTDOT

Sex (N=299) - Male (N/%)	 172 (57.5)
HIV status (N=226) - Unexposed uninfected (N/%) - Exposed - Uninfected (N/%) - Infected (N/%)	 110 (48.7) 116 (51.3) 46 (39.7) 70 (60.3)
Age at start of LTDOT (N=306) - 1-28 days (N/%) - 1 – 6 months (N/%) - 6 months – 1 year (N/%) - 1 – 5 years (N/%) - 5 – 10 years (N/%) - 10 years + (N/%)	 24 (7.9) 162 (52.9) 22 (7.2) 50 (16.3) 20 (6.5) 28 (9.2)
Age at start of LTDOT (months): Median (IQR) (N=306)	4.8 (2.1-25.2)
Electricity available (N=332) (N/%)	323 (97.3)
Referrals (N=382) - CHBAH (N/%) - District or Provincial Hospitals (N/%) - Private (N/%)	 357 (93.4) 24 (6.3) 1 (0.3)
CHBAH referrals (N=363) - General wards (N/%) - Neonatal unit (N/%) - Subspecialties (N/%)	 173 (47.6) 166 (45.7) 24 (6.7)

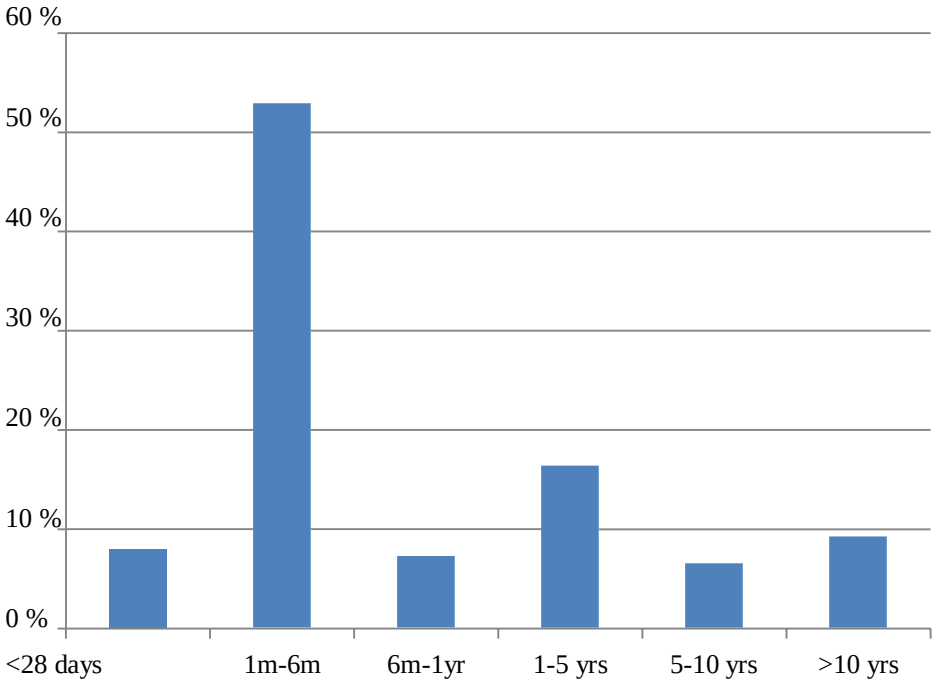

Figure 3.1: Age at start of LTDOT

Illustrated in figure 3.1 is the distribution of the age categories at initiation of LTDOT in our cohort.

The majority of patients n=343 (89.6 %) required full-time (24 hours/day) LTDOT at initiation. Initial oxygen flow rates commonly prescribed at 1 l/min (53.8 %) and 2 l/min (40.9 %) (Table 3.2). Out of the 309 participants who had outcomes for "Duration of LTDOT", 35.4 % (n=138) participants were weaned off oxygen within 12 months of initiating LTDODT. Of these children, 79 (57.2 %) were off oxygen by six months of commencing LTDOT, a further 59 (42.7 %) were weaned of LTDOT within twelve months and at the end of 12 months, 171 (55.3 %) were still requiring oxygen (Table 3.2). Ninety children had outcomes for the reasons LTDOT had been discontinued at the twelve month period. Duration of oxygen usage outcomes were available for 87 children and the median duration was 6.5 (3.2-140) months (Table 3.2).

Table 3.2 LTDOT prescription type, oxygen flow rates and outcomes at 6 months and 12 months time points

Initial prescription (N=383)	
- 24 hours a day (N/%)	343 (89.6)
- Nocturnal only (N/%)	40 (10.4)
Required initial oxygen flow (l/min) (N=364)	
- 0.5 (N/%)	18 (5.0)
- 1 (N/%)	196 (53.8)
- 2 (N/%)	149 (40.9)
- 3 (N/%)	1 (0.3)
Duration of LTDOT (N=309)	
- Off oxygen at 6 month time point (N/%)	79 (20.3)
- Off oxygen at 12 month time point (N/%)	138 (35.4)
- Still requiring oxygen after 12 month time point (N/%)	171(55.3)
Reason for discontinuation of oxygen by 12 month time point (N=90)	
- No longer requiring oxygen (N/%)	48 (53.3)
- Death (N/%)	40 (44.4)
- Relocation (N/%)	2 (2.2)
Duration of oxygen usage in those weaned off (months): Median (IQR), (N=87)	6.5 (3.2-14.0)

We found that the majority (80.3 % n=248) of participants had a pulmonary diagnosis, and neonatal lung disease (67.3 % n=167) was the leading diagnosis, followed by infectious/post-infectious lung disease (25.0 % n=62) (Table 3.3). The infectious/post-infectious category included Tuberculosis (TB), non-TB related infections, PIBO, and chronic suppurative lung disorders. In our data capturing sheet, these categories were not adequately separated so that we could get a clear indication of the numbers each variable contributed individually. In the cardiology category, the number of patients who required LTDOT were similar for congenital 54.9%(n=67) and acquired (54.1 % n=66) cardiac disease (Table 3.3).

Nineteen participants (6.1 %) had a neurological diagnosis. Over-all, 47 (15.2 %) were diagnosed with a congenital syndrome. Down syndrome was identified as the most common diagnosis in syndromic children requiring LTDOT (66.0 %).

Table 3.3 Underlying diagnoses at initiation of LTDOT

Pulmonary (N/%)
- Neonatal lung disease
  - BPD/CLD
  - MAS
- Infectious / Post-infectious
- UAO / OSAS
- Other
	248/309 (80.3)
	- 167/248 (67.3)
	  - 163/167 (97.6)
	  - 4/167 (2.4)
	- 62/248 (25.0)
	- 5/248 (2.0)
	- 14/248 (5.7)

Cardiac
- Congenital heart disease
  - Acyanotic
  - Patent ductus arteriosus
  - Atrioventricular septal defect
  - Ventricular septal defect
  - Atrial septal defect
  - Valvular lesions
  - Other
  - Cyanotic
  - Pulmonary atresia
  - Tetralogy of Fallot
  - Truncus arteriosus
  - Total anomalous pulmonary venous drainage
  - Other
- Acquired heart disease
  - Eisenmenger syndrome
  - Pulmonary hypertension
  - Other
	122/309 (39.5)
	- 67/122 (54.9)
	  - 54/67(42.9)
	  - 24/54 (44.4)
	  - 18/54 (33.3)
	  - 16/54 (29.6)
	  - 11/54 (20.3)
	  - 4/54 (7.4)
	  - 2/54 (3.7)
	  - 13/67(19.4)
	  - 4/13 (30.8)
	  - 4/13 (30.8)
	  - 1/13 (7.7)
	  - 1/13 (7.7)
	  - 3/13 (23.1)
	- 66/122 (54.1)
	  - 4/66 (6.0)
	  - 59/66 (89.4)
	  - 3/66 (4.5)

Neurological
- Neuromuscular disease
  - Spinal muscular atrophy
  - Duchenne muscular dystrophy
  - Other
- Cerebral palsy
	19/309 (6.1)
	- 9/19 (47.4)
	  - 5/9 (55.6)
	  - 3/9 (33.3)
	  - 1/9 (11.1)
	- 10/19 (52.6)

Genetic syndromes - Down syndrome - Trisomy 18 - Trisomy 13 - Other	47/309(15.2) - 31/47 (66.0) - 3/47 (6.4) - 2/47 (4.3) - 11/47 (23.4)

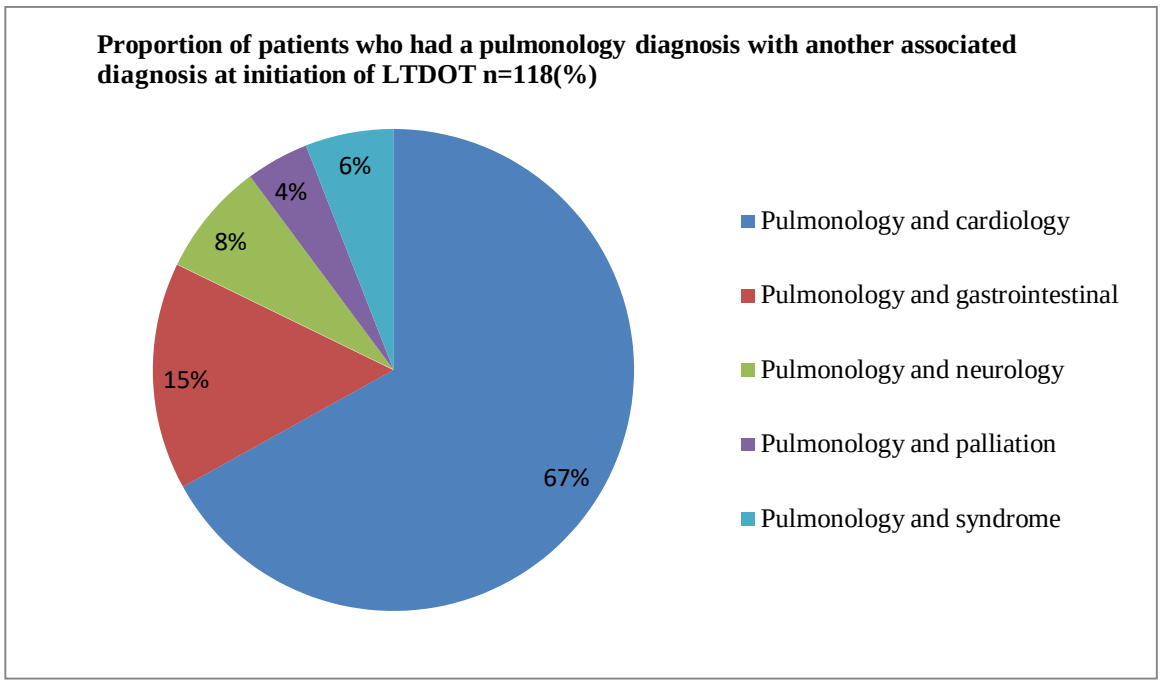

Figure 3.2: Multi-system diagnoses at initiation of LTDOT

Figure 3.2 illustrates the proportion of patients who had multi-system diagnoses (pulmonary diagnosis and another system) at initiation of LTDOT. Two-thirds of the participants had both pulmonary and cardiac disease, 15 % had pulmonary and gastrointestinal disease, and 8 % had pulmonary and a neurological diagnosis. The data collecting tool in REDcap allowed for more than one diagnosis to be captured per patient. All listed diagnoses were included in each participant's profile.

Table 3.4: Comparison of characteristics between HIV infected and HIV uninfected children receiving LTDOT

	HIV uninfected	HIV infected	OR (95% CI)	P-value
Sex - Male (N %) - Female (N %)	 93/159 (58.5) 66/159 (41.5)	 25/55 (45.5) 30/55 (54.5)	 0.59 (0.30-1.15)	 0.094
Age(years) that LTDOT started ((Median (IQR)	0.46 (0.21-2.23), 0.02-17.87	2.28 (0.55-9.33), 0.15-13.46		<0.001
Initial script: - Full-time oxygen (N %) - Nocte oxygen (N %)	 137/165 (83.0) 28/165 (17.0)	 50/61 (82.0) 11/61 (18.0)	 0.93 (0.41-2.23)	 0.851
Duration on oxygen (years) (Median (IQR)	0.54 (0.04-3.29), 0.02-6.35	1.06 (0.50-1.91), 0.33-4.81		0.034
Weaned off Oxygen after 6 months (N %) Weaned off oxygen after 12 months (N %)	49/165 (29.7) 85/165 (51.5)	24/61 (39.3) 42/61 (68.9)	1.54 (0.79-2.95) 2.08 (1.07-4.11)	0.169 0.020
Diagnosis (N %) - Pulmonary - BPD/CLD - Infectious / Post-infectious - Cardiology - Neurology	 127/165 (77.0) 63/165 (38.2) 45/165 (27.3) 58/165 (35.2) 13/165 (7.9)	 60/61 (98.4) 2/61 (3.3) 42/61 (68.9) 28/61 (45.9) 0/165 (0.0)	 17.95(2.86-739.30) 0.05 (0.01-0.22) 5.89 (2.97-11.84) 1.57 (0.82-2.96)	 <0.001 <0.001 <0.001 0.140 <0.001

There were significant differences in age that LTDOT was initiated between participants that were HIV infected 2.28(0.55-9.33) years and those that were not (0.46(0.21-2.23) years (p= <0.001) (Table 3.4). We found significant differences in duration on oxygen between HIV infected 1.06 (0.33- 4.81) years and unifected participants 0.54 (0.04-3.92) p= 0.03 (Table 3.4) When comparing diagnoses at initiation of LTDOT between HIV infected and HIV unifected groups (Table 3.4), we found statistically significant differences for all pulmonary diagnoses and neurological diagnoses (p= <0.001) but no significant differences in cardiology diagnoses (p=0.13) (Table 3.4).

Table 3.5: Comparison between starting LTDOT before 12 months and after 12 months of age

	Start before 1 year of age	Start after 1 year of age	OR (95% CI)	P-value
Sex - Male - Female	 112/183 (61.2) 71/183 (38.2)	 60/116 (51.7) 56/116 (48.3)	 1.47 (0.89-2.42)	 0.106
HIV status - HIV uninfected - HIV infected	 108/129 (83.7) 21/129 (16.3)	 57/97 (58.8) 40/97 (41.2)	 <3.61 (1.877.05)	 <0.001
Initial script: - Full-time - Nocte	 183/209 (87.6) 26/209 (12.4)	 160/181 (88.4) 21/181 (11.6)	 0.92 (0.47-1.78)	 0.801
Duration on oxygen (years) (Median (IQR)	0.54 (0.27-1.16), 0.00-4.81)	0.61 (0.22-1.64), 0.04-6.35		0.806
Weaned off Oxygen after 6 months Weaned off oxygen after 12 months	37/209 (17.7) 60/209 (28.7)	42/181 (23.2) 78/181 (43.1)	0.71 (0.42-1.20) 0.53 (0.34-0.83)	0.178 0.003
Diagnosis - Pulmonary - BPD/CLD - Infectious / Post-infectious - Cardiology - Neurology	 166/209 (79.4) 112/209 (53.6) 29/209 (13.9) 58/209 (27.8) 10/209 (4.8)	 151/181 (83.4) 51/181 (63.0) 75/181 (41.4) 67/181 (37.0) 10/181 (5.5)	 0.770.44-1.32) 2.94 (1.89-4.60) 0.23 (0.13-0.38) 0.65 (0.42-1.03) 00.86 (0.31-2.36)	 0.313 <0.001 <0.001 0.051 0.741)

In this study we found no statistically significant difference between sex for participants who had started LTDOT at age less than 1 year and participants who had started at more than one year (p=0.10) (Table 3.5). HIV infected children were found to have started LTDOT above age one 41.4 % (p= <0.001) and had a median duration on LTDOT of 0.61(0.22- 1.64) months (p=0.80) (Table 3.5). There was a statistically significant difference between participants with pulmonary diagnoses (BPD and infectious/post-infectious categories (p=<0.001) (Table 3.5).

Table 3.6: Comparison between children on LTDOT for more or less than a year

	Duration of oxygen <1 year	Duration of oxygen >1 year	OR (95% CI)	P-value
Sex				
- Male	39/58 (67.2)	133/241 (55.2)	1.67 (0.88-3.23)	0.095
- Female	19/58 (32.8)	108/241 (44.8)		
HIV status				
- HIV uninfected	37/46 (80.4)	128/180 (71.1)	1.67 (0.72-4.21)	0.204
- HIV infected	9/46 (19.6)	52/180 (28.9)		
Initial script:				
- Full-time	57/59 (96.6)	286/331 (86.4)	4.48 (1.11-39.13)	0.027
- Nocte	2/59 (3.4)	45/331 (13.6)		
Age that LTDOT started (years) (Median (IQR)	0.46 (0.19-1.18), 0.05-13.78	0.40 (0.17-2.49), 0.02-17.87		0.896
Weaned off Oxygen after 6 months	15/59 (25.4)	64/331 (19.3)	1.42 (0.69-2.80)	0.284
Weaned off oxygen after 12 months	16/59 (27.1)	122/331(36.8)	0.64 (0.32-1.22)	0.150
Diagnosis				
- Pulmonary	39/59 (66.1)	278/331 (84.0)	0.37 (0.19-0.73)	0.001
- BPD/CLD	14/59 (23.7)	149/331 (45.0)	0.38 (0.19-0.74)	0.002
- Infectious / Post-infectious	15/59 (25.4)	89/331 (26.9)	0.93 (0.46-1.80)	0.815
- Cardiology	21/59 (35.6)	104/331 (31.4)	1.21 (0.64-2.23)	0.527
- Neurology	6/59 (10.2)	14/331 (4.2)	2.56 (0.77-7.47)	0.057

In the comparison of factors associated with prolonged duration (>1 year) of LTDOT, HIV infection was not significantly associated with prolonged LTDOT use (p=0.204) The age at start of LTDOT and disease profiles were similar for both groups (Table3.6).

CHAPTER 4

4.1 DISCUSSION

The objective of this study was to describe the diagnosis, clinical characteristics and outcomes in a sample (n= 390) of children younger than 16 years requiring LTDOT at CHBAH in Soweto, South Africa. Eighty one (20.8%) of our study population was lost follow up and 40 (44.4%) of the participants died during the study period.

In this study, we found an overall male predominance (57.5%), this did not differ for those that had started prior to the age of one year (61.2 %) or after the age of one year (51.7 %) These findings are similar to findings in other countries Brazil (53 %), Malaysia 70.4 % and another in Portugal (59.3 %) (9,12, 14). The majority (68 %) of our study population were initiated on LTDOT before the age of one year, median age 4.8 (2.1-25.2) months. Similarly, in a group of Portuguese participants (86) in a retrospective and comparative study of clinical records between 2003-2012, Olivera et al found that 75.6 % of their study participants had started LTDOT before the age of one year (12). Furthermore, they identified two age group peaks; those that had started in their first year of life (prematurity related or congenital malformations) and those that had started after 36 months due to PIBO or the progression of other chronic conditions such as cystic fibrosis, sickle cell anaemia or neurological disorders (12) Similarly, in our study, the majority of participants had started LTDOT between 1-6 months (52.9 %), followed by the 1-5 year age category (16.3 %) and then by those older than 10 years (9.2 %). In a Malaysian study conducted over a 7 year period (1992-2000) on 71 participants who had been prescribed LTDOT, Norzila et al reported that for participants with BPD and congenital abnormalities, median age of initiating LTDOT was 5 months and for those with cardiac disease and interstitial lung disease it was 6.5 months (9). Munhoz et al from Brazil conducted a retrospective cohort study between 2002-2009 on 165 participants on LTDOT and found that 28 % of their participants had started LTDOT at ages less than one year but had a much higher median age of commencement of 3.6 years (0.1-21.5 years) (14).

The large percentage (89.6 %) of participants in our study who required full time (24 hours/day) LTDOT is comparable to other studies. Oliveira et al reported that 86.6 % of their study participants required 24 hour/day oxygen and Munhoz et al reported that 65 % of their participants required full time LTDOT (12, 14).

All our patients received oxygen through a low-flow nasal cannula interface (services offering other interphases were not available at CHBAH during our study period) and the majority used 1- 2 l/min flow rates, this was similar to the study by Muhnoz et al (14). In the study by Muhnoz et al, Non-invasive ventilation (NIV), mostly through bi-level pressure masks, was used for 14.0 % of their study participants (12). It was reported that the participants who had required NIV had mostly presented with a neurological disorder (12). A 2016 study by Groenendijk et al, conducted at a tertiary center in Cape Town South Africa on patients in a home ventilation care programme, the most common indications for tracheostomy insertion and long term ventilation at home were upper airway obstruction (secondary to subglottic stenosis following intubation) 21.7 % and bulbar palsy that was associated with neonatal hypoxic ischaemic encephalopathy (HIE) 14.6 % (29).

In our study, 35.4 % of the patients were off LTDOT by 12 months after initiation and within the first six months 20.3 % had weaned off LTDOT. The median duration of usage of those that had been weaned off by 12 months was 6.5 (3.2-14.0) months. There was no statistically significant difference in median duration of LTDOT between participants that had started using LTDOT before the age of one year 0.54 (0.27-1.16) or after 0.61 (0.22-1.64) years p=0.8.Of those that had started before one year of age, 17.7 % weaned at six months and 28.7 % weaned off LTDOT at 12 months. For participants who had started after one year of age, 23.2 % weaned off LTDOT at 6 months and 43.1 % weaned off at 12 months. Due to the format of data set, we were unable to assess duration of LTDOT for each diagnostic category. This is different to the studies conducted in high-income countries. Muhnoz et al found that median duration of LTDOT was 15.0 (3-223) months and that duration on LTDOT was largely dependent on the underlying diagnosis necessitating the prescription of LTDOT(12).

For those with BPD, in the Muhnoz study, the median duration was 3.5 (3-6) months, PIBO 19 (1-48) months, congenital abnormalities 3 (0.75-5.5) months and interstitial lung disease 3 (3-60) months (12). A study conducted at a BPD clinic at Johns Hopkins University between 2008 and 2013 on 420 subjects, found that the median age of weaning off LTDOT was 12.5 (10.9-14.2) months, which varied depending on the oxygen flow rate at the time of discharge from the neonatal intensive care unit (NICU) (30). In that population, the mean duration of LTDOT use was 10.9 (SD 12.7) months (30).

Norzila et al found a median duration of oxygen for BPD to be 3.5 (3-3.6) months, bronchiolitis obliterans 19 (1-48) months, congenital abnormalities 6 (0.75-5.5) months, interstitial lung disease 3 (3-60) months, cardiac disease 9 (IQR not reported) months for bronchiectasis 5 (IQR not reported) (9). In our study, of the participants for whom we had outcomes data for discontinuation of LTDOT, 53.3 % no longer required oxygen, 44.4% had died and 2.2 % had relocated to areas outside of the catchment area for CHBAH.

We found that the majority of participants had a pulmonary diagnosis (80.3 %), of which, neonatal associated conditions were the most common (67.3 %), followed by infectious and post-infectious category(25.0 %). The next most common diagnoses were from cardiac causes (39.5 %) (there were minimal differences between congenital heart defects and acquired cardiac disease 54. 9 % and 54. 1 % respectively), genetic syndromes 15.2 % and neurological disorders 6.1 %. Our findings were similar to the study conducted in Portugal, which also reported that the majority of patients required LTDOT for BPD (53.5 %), followed by PIBO (14.0 %), neurological disorders (10.5 %), Cystic fibrosis (8.1 %), miscellaneous syndromes (5.8 %), sickle-cell disease (3.5%), other neonatal lung diseases (2.3 %) and interstitial lung diseases (2.3 %) (12). The British Thoracic Society, in 2009, concluded that the most common underlying diagnoses for prescribing LTDOT were chronic neonatal lung disease (60 %), neurodisability (7 %), cardiac disease (5 %), neuromuscular disease (3 %) and interstitial lung disease (2 %) (10). Furthermore, the Norzila et al study, reported that the majority of patients requiring LTDOT had BPD (45.1 %) and PIBO (16.9 %), followed by congenital abnormalities (15.5 %), and interstitial lung disease (5.6 %) (9).

The Johns Hopkins University study, found that 36.6 % of the preterm infants with BPD were discharged from the hospital with supplemental oxygen (30).

A significant number of our patients (30.3 %) had more than one diagnosis necessitating LTDOT, with the majority (67 %) having a combination of a pulmonary and a cardiac diagnosis. The second most common combination was a pulmonary and gastrointestinal tract diagnosis (15 %).In the Oliveira et al study, they identified that 25.0 % of their participants had comorbidities, with gastroesophageal reflux reported in 16.2 %, pulmonary hypertension in 4.7 % and obstructive sleep apnoea (3.4 %) (12). From the Malaysian study by Norzila et al they found that 11.3 % of their participants had gastroesophageal reflux disease, 31.0 % had hyper-active airways requiring inhaled corticosteroids and intermittent broncho dilator therapy (9). Furthermore, in 2016 Yeh et al. reported that 24 % of children with BPD also had pulmonary hypertension (30). We were unable to delineate what the primary diagnosis was and which was a comorbid illness in our study due to the nature of the database.

Githinji et al conducted a cross-sectional analysis between 2013 and 2015 in a South African cohort of ages 9 -14 years (24), one group had perinatally acquired HIV infection and had been on ART for at least 6 months and the other group was HIV uninfected (24). They reported that cardiopulmonary dysfunction occurred in 13 % of African adolescents with perinatally acquired HIV despite being on ART and having well-controlled HIV infection while cardiorespiratory dysfunction occurred in 8 % of HIV uninfected adolescents (24). A Zimbabwean study by Ferrand et al conducted on 116 adolescent participants (mean age of 14 years +/- 2.6 years) 69 % of whom were on ART reported that over 40 % of HIV infected survivors met criteria for severe hypoxic CLD, approximately 45 % of their study participants had abnormal pulmonary function tests, 13 % had resting and 29 % had exertional hypoxaemia (17). Furthermore, 66 % had Chronic cough, 21 % had reduced exercise tolerance and 41 % had reported multiple respiratory tract infections in the previous year (17).

To our knowledge none of the studies looking at the use of LTDOT in children had investigated HIV infection prevalence and its contribution in the requirements for LTDOT. In our study HIV infected participants were found to have required LTDOT at older ages with the median age at initiation being 2.28 (0.55-9.33) years in comparison to the HIV uninfected participants, who had a median age of 0.46 (0.21-2.23) years at initiation. Only, 16.3 % had started LTDOT before the age of one year and 41.2 % after the age of one year in the HIV infected group. There were no differences in the type of script required between the two groups and over 80 % in both groups required 24 hours/day LTDOT: HIV infected group 82 % and HIV uninfected group 83 % p=0.8.).

The median duration of LTDOT was longer for those that were HIV infected 1.06 (0.50-1.91) years (p = 0.03). Of interest, we found that more participants in the HIV infected group were weaned off LTDOT earlier than in the HIV uninfected group. At the six month time point 9.6 % more participants had been weaned off LTDOT although this was not statistically significant (p=0.1) and at the 12 month time point 17.4 % more participants (p=0.1) in the HIV infected group versus the HIV uninfected group. Nearly all participants (98.4 %) in the HIV infected group had a pulmonary diagnosis (P < 0.0005) with a predominance of a infectious/post infectious cause 68.9 % (p=<0.0005). Interestingly, 20.4 % of the participants that were HIV exposed but uninfected required LTDOT. We did not explore their characteristics and diagnoses separately although this would have been an interesting group to study further. Gray et al conducted a study in Cape Town South Africa over a three year period on predominantly African children (93 %) to assess the impact of HIV exposure on lung growth and function in the first two years of life (31). They found that exposure to HIV (more-so in situations of high maternal viral loads and delayed ART initiation during pregnancy) were associated with altered lung functions and growth soon after birth and at 2 years of age (31).

Provision of LTDOT in our study was limited to state resources and access to this service is impacted by the socio-economic circumstances of the population that requires this service.

The availability of LTDOT plays a role in decreasing prolonged hospital admission and avails hospital beds which would otherwise be occupied . The CHBAH manages mainly children from poor socio-economic backgrounds. Electricity supply is a pre-requisite in order for oxygen concentrators to be installed for LTDOT use, otherwise oxygen cylinders have to be used instead, 97 % of our participants had electricity. As a LMIC, in 2010, 60 % of the children in South Africa lived in poverty, 38 % of these children lived in Gauteng with 35 % living in a household with no employed adult (32). Poverty was defined as living below R575 per month (32). In 2010, 67.9 % of all children living in South Africa lived in 40 % of the poorest communities in South Africa (33). Poverty influences access to services, health and living conditions (33). Child health is influenced by multiple factors including nutrition, access to clean water, adequate housing and sanitation as well as safe living environments, these in turn are income dependent. As a way of mitigating the effects of childhood poverty, the South African social services introduced the social assistance grants system in 1998 (32).

In July 2012, 11.2 million children aged 0-17 years received the child support grant (R280), 117.256 the care dependency grant (R770) and 572.903 the foster care grant (R1200) (32). Thirty seven percent of children were noted to be living far (30 minutes away, regardless of mode of transport) from the primary health care facilities they use (31). The LTDOT programme is super specialist dependent, which requires tertiary level care (access to these facilities is likely even more difficult to achieve given the socio-economic conditions of the population served by the institution where the study was conducted).

The limitations of our study are many. Of note, this was a retrospective database review and therefore the rigour of the study was highly dependent on the completeness of the database, which unfortunately was not ideal. Files were manually retrieved from the Pulmonology clinic to supplement the information in a pre-existing data base, however, the information in the files was not always sufficient to supplement the data base adequately. A large number of patients (21%) were lost to follow up. In a number of cases, the contact information in the files was outdated making it difficult to trace some of the patient's caretakers in order to supplement the data base prior to commencement of the study. Due to the retrospective nature of the study and the ethical clearance obtained we could not establish contact with the individual patients to try to obtain more data once the study was underway.

A strength was the large database from which we could gather information and HIV related statistics in relation to LTDOT usage.

4.2 CONCLUSION

Due to medical and technological advancement, the provision of LTDOT has improved significantly in children and adolescents. Pulmonary and cardiovascular diagnoses are the most common indications for prescribing LTDOT in HIV infected and uninfected participants. To our knowledge, ours is the only study to describe the demographics of HIV infected children on LTDOT. This study showed that HIV infected participants required LTDOT at older ages but used it for shorter durations compared to HIV uninfected participants. While BPD and PIBO were the leading diagnoses for LTDOT, those who were HIV infected had a higher prevalence of PIBO. More studies are required to further assess the indications for LTDOT, duration for each diagnosis and to further delineate the impact of HIV on the use of LTDOT. We recommend that a well-planned long-term prospective follow up study be conducted to explore this subject in depth. Improved follow up systems should be implemented.

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APPENDIX A: Data collection sheet

Baseline Home Oxygen Database

GT Number

_____

First Name

_____

Last Name

_____

Caretaker MotherFather Grandparent Sibling

Aunt or Uncle Foster Caretaker name

_____

ID number

_____

Address

_____

Phone number

_____

Electricity Yes NoReferred from

_____

Home Ward

_____

Sex Male FemaleDate of Birth

_____

BOC Number

_____

Date Oxygen Ordered

_____

Age at Oxygen start

_____

Date of Last Visit

_____

Confidential

Oxygen script Full-timeNocte

Off OxygenCancelled Removed

Still on Home Oxygen 6 months1 year

Required Oxygen Flow

_____

(l/min)

Date off Oxygen

_____

Duration of oxygen

_____

Date Oxygen Cancelled

Reason for Cancellation No longer requires oxygenDeath

Relocation

Date Oxygen Removed

Diagnosis Pulmonology

Cardiology
Neurology Gastroenterology Stand-alone syndromePalliation

Other

Pulmonology CLDi / BPDMAS

Acute Non-TB InfectiousAcute TB Infectious PIBO / COAD

Suppurative lung diseasechILD

UAO / OSAS

Reflux or Aspiration

Hepato-pulmonary syndromeRecurrent infections Congenital lung lesion

Non TB infectious AdenovirusPCP/CMV

Bacterial Unknown

Cardiology Congenital cyanoticCongenital acyanotic Eisenmengers

Pulmonary hypertensionCongenital heart block Other

Type of Other

Type of Congenital Cyanotic TGVTOF

Truncus ArteriosusTicuspid Atresia TAPVD

Ebsteins Pulmonary atresiaOther

Type of other

_____

Types of Congenital Acyanotic ASD

VSDPDA AVSD
ValvularOther

Type of Other

_____

Types of Valvular ARAS

CoarctationMR

MSPS PRTR TS

Neurology NeuromuscularCerebral Palsy Neuromuscular SMA Congenital myopathy Duchennes

Syndrome Trisomy 21

Trisomy 18Trisomy 13Other
Other Syndrome

_____

Other diagnosis

_____

Retro status Unexposed negativeExposed negative

Exposed positivePending Unknown

APPENDIX B: Ethics clearance certificate

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor.
Medical School Secretariat: PV Tobias Building 3rd Floor.
Private Bag 3, Wits 2050, www.wits.ac.za
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04 August 2016

To Whom It May Concern

SUBJECT: **CONFIRMATION OF STUDY APPROVAL**
Protocol Ref No: M160768
Protocol Title: Description and Outcomes of Children Requiring Long Term Domiciliary Oxygen Therapy (LTDOT) at Chris Hani Baragwanath Academic Hospital
Principal Investigator: Dr Wendy Kelebogile Maimela
Department: Paediatrics

This letter serves to confirm that the Human Research Ethics Committee (Medical) has received an ethics application for the abovementioned study. In order for a clearance certificate to be issued, the researcher is required to submit written approval to conduct the study in your district/institution.

The researcher has been informed that this study cannot commence without your approval and receipt of the Clearance certificate from the HREC (Medical).

Should you have any queries, you may contact me at tel: 011 717 1234/2700/2656 or by email Rhulani.Mkansi@wits.ac.za

Yours Faithfully,

.....
Mr Rhulani Mkansi
Administrative Officer
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
04 AUG 2016
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

APPENDIX C: Turnitin Report

ORIGINALITY REPORT

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APPENDIX D: Research Protocol

Description and outcomes of children requiring long-term domiciliary oxygen therapyat Chris Hani Baragwanath Academic Hospital

Investigator: Dr. Wendy.K. Maimela

Student number:1530902

Protocol submission for degree:Mmed (Paed)

Supervisor: Dr. Charl. Verwey

Qualification: MBChB (UP), FCPaed (SA), Mmed (Wits), Cert Paed Pulmonology (SA)

Chris Hani Baragwanath Academic Hospital

Introduction

Aerobic animal life is sustained by the pulmonary transfer of oxygen from the atmosphere into the blood for distribution to all body tissues by the cardiovascular system(1). Many acuteand chronic disease processes may result in impaired oxygen delivery to cells(1). In chronic disease states, impaired oxygen delivery to the body tissues may result in a need for long term oxygen therapy for periods that may extend from months to years(1). Patients requiring long term oxygen therapy may be considered for long term domiciliary oxygen therapy (LTDOT).

Chronic hypoxia has been shown to have an adverse effect on normal growth and neurodevel-opment including cognition and behaviour in later life (3). Adverse events are proven to oc-cur at oxygen saturations equal to or less than 85% (3). Long-term outcomes of children with prolonged milder levels of hypoxia(85-89%) are not clear (3) but studies suggest that there may also be sequelae from milder or recurrent intermittent forms of hypoxia(4).

Sustained or recurrent alveolar hypoxia results in pulmonary hypoxaemia and subsequent pulmonary arterial vaso-constriction (5). This may result in pulmonary arterial hypertension which in turn results in right ventricular hypertrophy and ultimately right heart failure (corpulmonale) (6). Levels and duration of hypoxaemia resulting in pulmonary hypertensionand corpulmonale are unclear and may be related to an individual's genetic susceptibility (5).By decreasing sustained pulmonary vasoconstriction and ultimately pulmonary vaso-re- sistance, early supplemental oxygen therapy may prevent right heart dysfunction and in the long term corpulmonale (5). Other documented adverse outcomes of sustained or recurrent alveolar hypoxia are acute life-threatening events, sudden infant death syndrome, poor growth velocity and poor neurodevel-opment (6).

LTDOT is defined as continuous supplemental oxygen usage outside of the hospital setting (3).It's use in children was first reported in developed countries in 1970(2) and in developing countries such as Malaysia in 1992(3).

LTDOT is used for the optimization of oxygen saturation levels in children who would otherwise be hypoxic outside of hospital (4). The term LTDOT includes chronic continuous oxygen usage, sleep related oxygen usage and chronic intermittent oxygen usage.

Chronic continuous LTDOT is defined as oxygen supplementation used to treat chronic hypoxia for 24 hours a day (4). The aim would be to maintain oxygen saturation (SaO2) at or greater than 92% or a PaO2greater than 60 mmHg, which promotes normal growth and neurodevelopment (5).

Sleep related LTDOT is used to prevent hypoxia during periods of sleep(day or night) (4).It is commonly used for children with obstructive sleep apnoea syndrome (OSAS) secondary to congenital or acquired upper airway obstruction. Congenital causes of OSAS are associated with congenital syndromes with upper airway malformations whereas acquired upper airway obstruction is mostly secondary to long standing adeno-tonsilar hypertrophy (4).

Intermittent LTDOT is used in children with underlying pathology that may result in frequent episodes of acute deterioration requiring oxygen therapy to prevent frequent hospitalisation(4).An example would be children with bronchiectasis who have increased risk for recurrent lower respiratory tract infections resulting in periods of hypoxaemia. Without access to LTDOT these episodes would require hospitalisation.

Medical indications for LTDOT within the paediatric population vary considerably between

developed and developing countries. In developed countries during infancy, the main indica-tion for LTDOT is chronic lung disease of infancy including bronchopulmonary dysplasia (BPD) and congenital malformations, including congenital lung abnormalities, associated with chronic hypoxia. Beyond infancy, in developed countries, LTDOT is used mainly in children with congenital lung abnormalities, cardiac lesions, neuromuscular disorders and OSAS(3).

In developing countries, children requiring LTDOT often have a different set of pathologies. A study conducted in Malaysia showed that the majority of patients who qualified for LTDOT in their low Human Immunodeficiency Virus(HIV) prevalence setting had BPD, post infectious bronchiolitis obliterans, congenital abnormalities, interstitial lung disease, ac-quired cardiac disease, bronchiectasis, obstructive sleep apnoea and spinal injuries(3).In sub-Saharan Africa, a developing country with high HIV prevalence, indications for LTDOT in the infancy is similar to those of other developing countries. Beyond infancy it is mainly re- quired by children with post infectious respiratory insufficiency, a significant proportion be- ing related to respiratory complications of long standing and untreated HIV infection(6).

More than 90% of the estimated 3 million global paediatric HIV infections occur in sub-Sa-haran Africa, predominantly as a result of vertical transmission(7).Untreated survivors of ver-tically acquired HIV infection are reaching adolescence in large numbers in Africa(6) .It is estimated that up to one third of HIV infected children are slow progressors with an esti- mated survival rate of ten to sixteen years (6, 7). Therefore, a large number of paediatric patients are at high risk of chronic complications of untreated HIV infection prior to diagnosis. The respiratory system is most commonly affected (6). From 2009-2011 only 59% of HIV- infected pregnant women were in a prevention of mother to child transmission (PMTCT) pro-gramme. Enrolment in a PMTCT programme has resulted in a 24% drop in vertical HIV transmissions in sub-

Saharan Africa (7). Although this is the case, there are still persistent an-tiretroviral treatment roll-out gaps in the paediatric population with only 34% of paediatric HIV infected patients received Antiretroviral Therapy(ART), which is half of the average coverage of adults at 64 %(8).

In a study conducted in Zimbabwe, it was found that recently diagnosed or undiagnosed ver-tically acquired HIV was the most common cause of in-hospital deaths(6). The study further states that undocumented epidemics of similar magnitude could be inferred to affect neigh-bouring countries such as South Africa.

HIV infected children suffer from more frequent episodes and more severe forms of lower respiratory tract infections, including tuberculosis, than HIV uninfected children (9). Other HIV associated complications affecting the respiratory tract include bronchiectasis, post-in-fectious bronchiolitis obliterans and interstitial lung disease (7). These common complica- tions may result in chronic respiratory insufficiency which may necessitate LTDOT. Study Aims and ObjectivesAims

To determine the indications for the use of LTDOT and to describe the characteristics and outcomes of paediatric patients on LTDOT in a low-to-middle income setting with a highHIV prevalence.

Objectives

1. To describe the diagnosis necessitating LTDOT in children under 16 years of age atChris Hani Baragwanath Academic Hospital (CHBAH).
2. To describe the clinical characteristics of children on LTDOT at CHBAH.
3. To determine the outcomes of children on LTDOT at CHBAH at six month and oneyear after

prescription of the LTDOT.

Methods and MaterialsStudy design

A retrospective descriptive study of all the paediatric patients who have received LTDOT from the paediatric pulmonology clinic at CHBAH since 01 February 2011 until 31 Decem-ber 2015.

Study site

The Department of Paediatrics at CHBAH.

Study population

Paediatric patients (birth until 16 years of age) who have been prescribed LTDOT through the division of paediatric pulmonology at CHBAH residing within the South Western Townships (SOWETO).

Sample size

Approximately 180 paediatric patients.

Inclusion criteria

All paediatric patients (birth to 16 years) attending the paediatric pulmonology clinic at CHBAH and who have been prescribed LTDOT residing within the South Western townships (Soweto).

Limitations

1. The limitations of the study are that it is a retrospective record review. Files might notbe able to be retrieved and records may be incomplete.

Methods

Chris Hani Baragwanath Academic Hospital (CHBAH) is a University of the Witwatersrand affiliated tertiary training centre for medical professionals and a medical referral centre. The

department of Paediatrics at CHBAH serves as one of two tertiary referral centres for paediat-ric patients for the population of Johannesburg in Gauteng, South Africa. The paediatric pul-monology division at CHBAH sees patients mostly from Southern Johannesburg but also from other cities, provinces and surrounding countries.

Referrals to the pulmonology clinic are either received from the in-house pulmonology ser- vice at CHBAH or through direct referrals from referring hospitals to the paediatric pulmo- nology clinic. The in-house pulmonology service at CHBAH covers the general paediatric wards, including four acute general wards and all the subspecialties. There are a number of primary and secondary level hospitals which also refer patients to the pulmonology clinic generally through the in-house twenty four hour general paediatrics clinic, HIV clinic, acute admissions ward and through any of the above mentioned sub-specialties. A large number ofreferrals to the pulmonology clinic are patients who are referred for assessment of eligibility for LTDOT and facilitation in acquiring LTDOT. All patients in the CHBAH referral region who require LTDOT have to be assessed through the paediatric pulmonology division before LTDOT will be supplied. This is to ensure that patients who require LTDOT are correctly in-vestigated by a paediatric pulmonologist before this commitment is made. It also ensures ade-quate follow-up care for those prescribed LTDOT.

Each patient's history, investigations and prognosis is considered prior to initiating LTDOT. There is no specified time frame for the initiation of LTDOT. Generally LTDOT will not be prescribed for a child with an acute infective respiratory disease within the first month of ill-ness. After this period LTDOT will be initiated if there is no ongoing improvement in the pa-tient's condition. LTDOT will be prescribed immediately for patients requiring oxygen for palliation. LTDOT will be prescribed immediately for patients awaiting surgery, for example

cardiac lesion with increased left to right blood flow. For chronic respiratory conditions, for example bronchiectasis, LTDOT will be describe when the patient's disease process is seenas stable and all contributing factors that may worsen the patient's respiratory condition hasbeen rectified.

The paediatric pulmonology clinic at CHBAH was established in February 2011. A database has been kept of all patients (including all those for whom LTDOT was prescribed) who have been to the clinic. Therefore the period assessed will be from 01 February 2011until 31 December 2015.

All patients presenting for assessment at the division of paediatric pulmonology are seen by a member of the division of paediatric pulmonology. The history will be noted, a general examination is done and oxygen saturation levels are measured. Majority of patients have a chest radiograph (chest x-ray) and an electrocardiograph (ECG) as part of the initial workup for LTDOT. Gastro-oesophageal reflux is excluded in most patients through a combination of speech therapy assessment, upper gastro-intestinal swallow and a radio nucleotide labelled milk scan. Further imaging studies such as computed tomography scan (CT scan) of the chestand Echocardiogram (echo) are only acquired on individual basis. Patients sent for chest CT scan are those who are suspected to have congenital malformations or acquired lung or cardiovascular structural pathology. Those sent for echo are those with clinical or radiological features in keeping with pulmonary hypertension.

The prescription of LTDOT is necessary when the oxygen saturation level during awake periods is less than 92% or when the oxygen saturations are higher than this but pulmonary hypertension and corpulmonale is present in the absence of other reversible diseases. In the caseof reversible diseases being present, an attempt would be made to rectify these problems be-fore

LTDOT is prescribed. This however is not always possible, in which case LTDOT willbe prescribed while plans are made to work through the underlying pathologies.
LTDOT is prescribed at the lowest oxygen flow required to keep the saturation above 94% during waking hours.

Once the decision has been made to prescribe LTDOT a paediatric pulmonologist is required to approve the order forms prior to putting them through to the supplying company; Vitalaire.The community clinic nearest to the residential address of the patient is also informed of the process. LTDOT is then supplied to the patient's home and Vitalaire is responsible for educating the patient and/or family on the management of the LTDOT. Community nurses and Vitalaire staff visit the family approximately every month. A paediatric pulmonology follow- up date is given for one month after the patient has been discharged on the LTDOT and if all is well at the first visit, subsequent visits will be made at three monthly intervals. During eachfollow-up visit a general assessment is conducted on the patient and oxygen saturation moni- toring is performed, both on and off oxygen. The LTDOT is weaned according to the oxygen saturation levels and the lowest oxygen flow required to keep the saturation above 94% dur- ing awake hours is prescribed. Weaning is carried out by trained nursing staff from the com- pany that provides home oxygen, vitalaire, in conjunction with the pulmonology team of doc-tors at follow up visits. Attempts to wean are made at each visit by both teams.

Data collection and analysisCollection All patient data will be collected from the CHBAH division of paediatric pulmonology Red-cap (Research Electronic Data Capture) computer database hosted by the University of the

Witwatersrand. The data will be transferred onto an excel spread sheet in preparation for analysis by the researcher.

The data collection sheet will include patient demographics, clinical findings and diagnosis requiring LTDOT, as well as the outcomes on LTDOT (Appendix 1). All data will be supplemented where necessary from the CHBAH division of paediatric pulmonology patient files. All identifying patient characteristics will be kept separate from the database and a study identification number (ID) will be assigned to each patient. Only the researcher will have access to the study ID and patient identifiers. Where supplemental information is required, the information from the data base will be complimented with information from patient hospital records. For those whom hospital records are inadequate, attempts to have telephonic conversations with the primary care-givers will be made. Supplemental information will also be obtained from the Vitalaire records for patients whose hospital records and telephonic conversation information is inadequate.

Analysis

Description of the data will be summarized using the mean and standard deviation for continuous variables with normal distribution, median, interquartile percentiles and ranges for continuous data without normal distribution and proportions for categorical variables. A table will be used to outline the diagnostic indications for initiating LTODOT for paediatric pa- tients at CHBAH. The demographic characteristics of all study patients on LTDOT will also displayed in a table. Comparisons will be made between patients requiring prolonged LTDOT and those weaning off LTDOT, as well as between HIV exposed and HIV unex-posed patients.

Ethical Considerations

Application for approval of the study protocol will made to the Human Research Ethics Committee (HREC) of the University of the Witwatersrand.

As this is a retrospective study, it is anticipated that signed consent from study participants or their guardians will not be required.

As the trial is retrospective there is no direct risk to the participants.

There is also no direct benefit to the participants of the study, although the outcome of the study may influence or change the future management of the participants or of other patientsnewly diagnosed with similar conditions requiring LTDOT.

Timing

	Nov-Dec'15	Jan-May'16	Jun – Jul '16	Aug-Oct '16	Nov'16-Jan'17	Feb – Apr '17	May-Jun "17
Literature review							
Protocol preparation							
Protocol assessment							
Ethics application							
Data collection							
Data analysis							
Writing thesis							
Submit							

Funding

An estimated amount of R1000 will be needed for photocopying and printing and this cost will be borne by the researcher. All additional costs involving telephonic conversations to pri-mary care-givers in order to supplement the data base and patients file information will be funded by the pulmonology department at CHBAH.

References

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Appendices

A: Red Cap data capture sheet from pulmonology division CHBAH

Baseline Home Oxygen Database

GT Number

_____

First Name

_____

Last Name

_____

Caretaker MotherFather

GrandparentSibling

Aunt or Uncle Foster Caretaker name

_____

ID number

_____

Address

_____

Phone number

_____

Electricity Yes NoReferred from

_____

Home Ward

_____

Sex Male FemaleDate of Birth

_____

BOC Number

_____

Date Oxygen Ordered

_____

Age at Oxygen start

_____

Date of Last Visit

_____

Confidential

Page 2

Oxygen script Full-timeNocte

Off OxygenCancelled Removed

Still on Home Oxygen 6 months1 year

Required Oxygen Flow

_____

(l/min)

Date off Oxygen

_____

Duration of oxygen

Date Oxygen Cancelled

_____

Reason for Cancellation No longer requires oxygenDeath

Relocation

Date Oxygen Removed

_____

Diagnosis PulmonologyCardiology

Neurology Gastroenterology Stand-alone syndromePalliation

Other

Pulmonology CLDi / BPDMAS

Acute Non-TB InfectiousAcute TB Infectious PIBO / COAD

Suppurative lung disease

chILDUAO / OSAS

Reflux or Aspiration

Hepato-pulmonary syndromeRecurrent infections Congenital lung lesion

Non TB infectious AdenovirusPCP/CMV

Bacterial Unknown

Cardiology Congenital cyanoticCongenital acyanotic Eisenmengers

Pulmonary hypertensionCongenital heart block Other

Type of Other

_____

Type of Congenital Cyanotic TGV

TOFTruncus ArteriosusTicuspid Atresia TAPVD
Ebsteins Pulmonary atresiaOther

Type of other

_____

Types of Congenital Acyanotic ASDVSD

PDA AVSD

ValvularOther

Type of Other

Types of Valvular ARAS

CoarctationMR

MS

PS PRTRTS
Neurology NeuromuscularCerebral Palsy Neuromuscular SMA Congenital myopathy Duchennes

Syndrome Trisomy 21

Trisomy 18

Trisomy 13Other

Other Syndrome

Other diagnosis

Retro status Unexposed negativeExposed negative

Exposed positive
Pending Unknown