

A cross sectional analysis of perinatally HIV-infected (PHIV) adolescents in a paediatric infectious diseases clinic in the Western Cape, South Africa.

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Abstract:

Background

Approximately 1.8 million adolescents were living globally with HIV in 2015. HIV is the leading cause of death in adolescents in Africa and the second leading cause of death in adolescence worldwide. Perinatally HIV-infected (PHIV) adolescents often have chronic complications due to late access to antiretroviral therapy (ART) and ART side effects. There is relatively little information on their psychosocial outcomes although poor adherence has been described. The aim of this study was to describe a cohort of perinatally HIV infected adolescents (PHIVA) attending Tygerberg Hospital, a tertiary hospital in the Western Cape in 2015.

Material and Methods

A retrospective descriptive study (folder review) describing all HIV- infected adolescents between the ages of 10 and 19 years attending the Infectious Diseases Clinic (IDC) during a 12 month period in 2015 was performed.

Results

Ninety-eight of approximately 400 (25%) patients attending the Tygerberg Paediatric IDC were adolescents. Of these, 55 (56%) were female. Median age at first clinic visit was 4.9 years (IQR 1.5-9.4). Median age at most recent clinic visit was 14 years (IQR: 10-19). The majority were WHO clinical stage 3 and 4 at diagnosis (74%).

Twenty-eight (28%) adolescents were on their original ART regimen with no change in drug for side effects, failure or intolerance. Sixty-seven (68%) remained on their first regimen with a single drug switch due to side effects. Fifty of sixty-one adolescents (82%) starting on Efavirenz remained on it. Of 94 adolescents with a viral load available at last clinic visit, 71 (81%) were virologically suppressed. Viral genotyping was done in 7 of the 17 adolescents (41%) with viral loads above 1000 copies/ml. Only 3 (3%) were on third line drugs.

Few adolescents had chronic medical complications: 23/98 adolescents (23%) were documented to have chronic lung disease (CLD) with 58 (59%) previously having Pulmonary Tuberculosis (PTB), 2 (2%) having had multidrug resistant (MDR) Tuberculosis and 1 (1%) having had Extremely Drug Resistant (XDR) Tuberculosis. Four (4%) had cardiac disease, 1 (1%) had HIV related renal disease, 80 (80%) had documented dermatological complications. Forty-one (42%) had central nervous system complications such as seizures and neurodevelopmental delay. The median number of documented hospitalizations since diagnosis was 3 (IQR: 1-4) with no deaths in 2015.

Sixty-eight percent (68%) of adolescents knew their HIV status. There was no documentation in 20 (20%), while 11 (11 %) were not disclosed to. For the latter, 7 had severe neurological disease. Forty-five (55%) attended mainstream school and 34 (34%) a special school/care centre. Forty-six (47%) had failed a grade and 33 (33%) failed more than one grade. Five (5%) were on antidepressants. Fifty-six (57%) had been referred to a social worker for complex psychosocial issues.

When comparing those diagnosed at an age less than 10 years to those diagnosed older than 10 years the only statistic significant difference was a lower baseline absolute CD4 count in those diagnosed after ten years of age (265 vs 554, $p = 0,003$). There was no difference in WHO staging at diagnosis, chronic complications or social issues.

Conclusions

Despite relatively late access to ART, adolescents had good virological outcomes that compare with international cohorts. There are fewer chronic medical complications than noted in other African

cohorts. However, there are significant psychosocial and educational issues and more focused interventions are needed to address these.

Opsomming

Agtergrond

Ongeveer 1.8 miljoen adolessente wêreldwyd het in 2015 met MIV geleef.

MIV is die grootste oorsaak van sterfte by adolessente in Afrika, en die tweede grootste doodsoorsaak by adolessente wêreldwyd. Perinataal MIV-geïnfekteerde adolessente (PMIV's) ervaar dikwels chroniese komplikasies weens vertraagde toegang tot antiretrovirale behandeling (ARV's) sowel as die nuwe-effekte daarvan. Tog is daar betreklik min inligting beskikbaar oor hulle psigososiale uitkomst, hoewel adolessensie 'n risikofaktor vir ARV-versuim kan wees. Die doel van hierdie studie is om die uitkomst van 'n kohort PMIV-adolessente te beskryf wat in 2015 by Tygerberghospitaal, 'n tersiêre hospitaal in die Wes-Kaap, behandel is.

Materiaal en metodes

'n Retrospektiewe beskrywende studie (pasiëntelêrstudie) is uitgevoer om alle MIV-geïnfekteerde adolessente tussen 10- en 19-jarige ouderdom te beskryf wat in 2015 oor 'n tydperk van 12 maande by die Infeksiesiektekliek van Tygerberghospitaal behandel is.

Resultate

Van die sowat 400 pasiënte wat by Tygerberghospitaal se Pediatriese Infeksiesiektekliek behandel is, was 98 (25%) adolessente. Van hierdie 98 adolessente was 55 (56%) vroue. Die mediaanouderdom van die adolessente met hulle eerste kliniekbesoek was 4,9 jaar (interkwartielafwyking 1,5-9,4), en 14 jaar (interkwartielafwyking 10-19) met hulle mees onlangse besoek. Met diagnose was die meeste adolessente (74%) in fase 3 en 4 van die Wêreldgesondheidsorganisasie se MIV-klassifikasiesistelsel.

Agt-en-twintig (28%) was ten tyde van die studie steeds op hulle aanvanklike ARV-regime, sonder enige middelveranderinge weens nuwe-effekte, ondoeltreffendheid of intoleransie. Sewe-en-sestig (68%) was steeds op hulle eerste regime met 'n enkele middelverandering weens nuwe-effekte. Sewe uit die 17 adolessente (41%) met virale ladings meer as 1000 kopieë/ml het gekwalifiseer vir virale genotipering, die res was waarskynlik as gevolg van swak nakoming. Slegs drie (3%) was op derdeliniemiddels. Vyftig van 61 (82%) adolessente wat efavirens begin gebruik het, het daarmee voortgegaan. Van die 94 vir wie daar met die mees onlangse kliniekbesoek 'n virustelling beskikbaar was, was 71 (81%) virologies onderdruk.

Min adolessente het chroniese mediese toestande ontwikkel: Drie-en-twintig uit 98 (23%) het volgens hulle lêers aan chroniese longsiekte gely. Voorheen het 58 (59%) pulmonêre tuberkulose (PTB), twee (2%) multimiddelweerstandige tuberkulose, en een (1%) uiters middelweerstandige tuberkulose gehad.

Vier (4%) het aan hartsiekte gely, een (1%) het MIV-nefropatie gehad, 80 (80%) gedokumenteerde dermatologiese komplikasies, en 41(42%) komplikasies van die sentrale sensusstelsel, soos toevale en vertraagde neuro-ontwikkeling. Die mediaangetal hospitalisasies sedert diagnose was drie (1-4), en geen adolessent het in 2015 gesterf nie.

Wat onthulling betref, was daar volle onthulling teenoor 67 (68%) adolessente; vir 20 (20%) was daar geen dokumente nie, terwyl daar teenoor 11 (14%) geen onthulling was nie. Sewe van die 11 teenoor wie daar geen onthulling was nie, het aan ernstige neurologiese siekte gely. Vyf-en-veertig (55%) het na hoofstroomskole gegaan en 34 (34%) na spesiale skole/sorgsentrums. Ses-en-veertig (47%) het een graad en 33 (33%) meer as een graad gedruip. So ver vasgestel kon word, was vyf (5%) op antidepressante. Ses-en-vyftig (57%) is vir psigososiale kwessies na 'n maatskaplike werker verwys.

“n Vergelyking is getref tussen die adolessente wat voor die ouderdom van 10 jaar gediagnoseer is teenoor diegene wat na die ouderdom van 10 jaar gediagnoseer is en die enigste statisties betekenisvolle verskil was ‘n laer basislyn absolute CD4 telling in diegene ouer as 10 jaar (265 vs 554, $p = 0,003$). Daar was geen verskil in Wereldgesondheidsorganisasie Klassifikasie stelsel, chroniese komplikasies en sosiale probleme nie.

Gevolgtrekkings

Ondanks vertraagde toegang tot ARV’s toon die adolessente betreklik goeie uitkomst wat ooreenstem met internasionale kohorte. Daar is minder chroniese mediese komplikasies as in ander Afrikakohorte. Tog beleef dié kohort beduidende psigososiale en opvoedkundige kwessies, wat slegs deur meer toegespitste intervensies die hoof gebied kan word.

Definitions and abbreviations:

WHO: World Health Organization

Adolescence: Defined by WHO as ages ranging between 10 years and 19 years.

HIV: Human immunodeficiency virus

AIDS: Acquired Immune-deficiency syndrome

PHIV: perinatally HIV-infected

PHIVA: perinatally HIV-infected adolescents

PMTCT: Prevention of mother-to-child transmission

SA: South Africa

ARV: antiretroviral

ART: antiretroviral therapy

IDC: Infectious diseases clinic

PJP: Pneumocystis Jiroveci Pneumonia

SA: South Africa

IV: intravenous

UNAIDS: United Nations Programme on HIV/AIDS

CLD: Chronic lung disease

LIP: Lymphocytic Interstitial Pneumonitis

DCMO: dilated cardiomyopathy

HIVAN: HIV associated nephropathy

TB: Tuberculosis

APOL1: Apolipoprotein L1.

CD4: cluster of differentiation 4. This is a glycoprotein found on the surface of immune cells such as T helper cells

*Only absolute CD4 counts were documented at first visit, no percentages available in folders.

Viral Load: the number of copies of HIV RNA per millilitre of blood

LDL: lower than detectable limit.

*For the purpose of this study the definition of LDL was less than 40 copies/ml

D4T: Stavudine

TDF: Tenofovir

LMIC: low-and middle income countries

Introduction:

The definition of adolescence as defined by WHO, includes ages between 10 years and 19 years. This is further divided into younger (10 – 14 years) and older (15 – 19 years) groups.¹

In 2015, there were 1.2 billion adolescents between the ages of 10–19 years globally.² Of these, 1.8 million are living with Human Immunodeficiency virus (HIV), 80% of whom live in sub-Saharan Africa.³ These HIV- infected adolescents are a heterogeneous population of perinatally HIV-infected (PHIV) children that have survived to adolescence and those adolescents who have been infected with HIV between the age of 10-19 years.³

The successful prevention of mother to child transmission (PMTCT) programme in South Africa (SA) has reduced perinatal infections in a significant way from >20% in 2004 to < 2% in 2015.⁴ This decrease along with early initiation of combination antiretroviral therapy (ART) in infants has further reduced the morbidity and mortality of PHIV children. As a result of this, HIV is now evolving into a chronic disease.²

The natural history of untreated vertically transmitted HIV is characterized by progressive immunosuppression. The majority of children infected with HIV show progression of HIV infection to Acquired Immunodeficiency Syndrome (AIDS) and eventually death within first 5 years of age.⁵ In those children who acquire HIV vertically, infection, disease progression and mortality vary significantly in the manifestations. Two basic patterns of disease progression have been identified: rapid disease progression where children reach a severe clinical stage within the first year of life or a more typical, slower progression with deterioration by the age of 5 to 6 years.⁶ Those in the early onset group present with Pneumocystis Jiroveci pneumonia (PJP) infection, encephalopathy and wasting syndrome. This group has a high mortality in comparison to those in the late onset group who present with recurrent bacterial infections, generalized lymphadenopathy and lymphocytic interstitial pneumonitis (LIP).⁶

Up to 36% of perinatally HIV-infected adolescents (PHIVA), may be slow progressors and may have a mean survival of 16 years without ART⁷ however, the majority of PHIVA diagnosed in early adolescence have severe immunosuppression and a heavy burden of chronic complications, the most common being growth failure, lung and cardiac disease.⁸ The magnitude of this morbidity in PHIVA is poorly documented especially in those adolescents living in low and middle income countries (LMIC).

The second decade of life, is a critical period in life as it represents a time of both vulnerability and potential. This time period is characterized by significant physical, emotional, social and psychological growth in a child's life that is associated with the development of autonomy, increased impulsivity and risk taking. Adolescence is also a high risk period for non-adherence and associated virological failure.⁹ Reasons for poor adherence are thought to be due to lack of knowledge about HIV, delayed disclosure of HIV status to the adolescent, being orphaned and mental health problems.¹⁰

Some PHIVA were started on ART in early childhood and some may already be on second- or third-line ART by the time they reach adolescence. This, in combination with the risk of developing drug resistance due to prior sub optimal regimens is of grave concern in view of the limited availability and cost of alternative regimens in resource constrained settings.¹¹

Retaining adolescents in care may be challenging. The prospect of lifelong treatment is daunting at any time in one's life but for PHIVA this is by far more taxing than their usual challenges of developing maturity. In a recent publication investigating the research priorities for adolescent health in LMIC, HIV featured prominently.¹² The recommended areas of research included how to improve adherence to treatment, identifying barriers to health care for HIV-infected adolescents, describing long term outcome and the prevalence of tuberculosis amongst this vulnerable population.¹²

The aim of this study was to describe the clinical, psychosocial and virological outcomes, complications and ART history of the PHIVA attending a paediatric infectious diseases clinic in a middle income

country with high prevalence of HIV and TB. A secondary outcome was to determine the possible risk factors for non-adherence to treatment and thirdly to compare clinical and virological outcome in those diagnosed below or above 10 years of age.

Literature review

The Joint United Nations Programme on HIV/AIDS (UNAIDS) reports that there are 1.8 million HIV-infected adolescents between 10 and 19 years of age.² Of HIV-infected adolescents 80% are found in Eastern and Southern Africa.² HIV is the leading cause of death in adolescents in Africa and the second leading cause of death for adolescents worldwide.¹² Between 2005 and 2012, adolescents were the only population worldwide that saw an increase in AIDS-related deaths: 50% increase compared to 30% decline seen in general HIV population.¹³ It is estimated that in 2015 approximately 5700 new HIV infections (adults and children) occurred globally every day of which 66% were in Sub-Saharan Africa.¹¹ Of those infected daily, 400 were children less than 15 years of age.¹⁴

There are 15 high burden countries but South Africa is home to 20% of the 1.8 million HIV infected adolescents. This means there are about 250 000-300 000 HIV infected adolescents in South Africa.¹⁵ The population of adolescents living with HIV in SA consist of adolescents with perinatal infection who have survived to adolescence and those who acquired HIV at an older age through sexual activity, IV drug use or other less common modes of transmission.¹ There is limited data on the health of South African adolescents, partly because of the age limits used in the District Health Information System.¹⁶ Global HIV monitoring systems have been aggregating adolescents aged 10 – 14 years with all children less than 15 years and those aged between 15 and 19 years with all children older than 15 years. This has resulted in a challenge to monitor the adolescent HIV population as a unique target population with differences between the younger and older groups.¹⁶

ARV triple therapy became available in South Africa in 2004. In the past ART guidelines for children necessitated clinical or immunological deterioration (CD4 counts less than 350 cells/mm³) to qualify for starting ART. In 2013 new guidelines concluded that all HIV-infected children below the age of 5 years regardless of the WHO clinical stage or if CD4 count equal or less than 500 cells/mm³ should be initiated on treatment.¹⁷

Perinatally HIV-infected adolescents:

Evidence from Zimbabwe suggests that there are increasing numbers of long-term survivors of mother-to-child transmission who are reaching adolescence, the majority of whom are not yet in HIV care suggesting mother-to-child transmission as the predominant source of infection in adolescents presenting to acute primary care services.¹⁸ The average age at diagnosis in these patients is 8 years.¹⁸ The relatively high CD4 cell counts in some of these previously undiagnosed cases raises the possibility that HIV progression may be very slow in some older long-term survivors.¹⁹ Children infected postnatally through breast feeding may be more likely to be slow progressors than those infected in utero or intrapartum.²⁰

PHIVA differ from those behaviourally infected in the fact that they are dealing with a chronic illness from a young age. These adolescents may have multiple chronic medical complications which include stunting, chronic lung disease, cardiac, neurological and dermatological complications.²¹ They have been attending clinic for many years and may have had multiple admissions to hospital. The chronic disease and complications have a great impact on their emotional well-being and can lead to psychiatric illness.²² Due to poor adherence and previous limited ARV regimens many have been exposed to at least 3 ART classes as well as suboptimal regimens and are at risk of having resistant virus. Due to these factors health care services have a great challenge to maintain these adolescents in care.²³

Medical issues

One of the striking features of HIV infection in PHIVA is the high prevalence of chronic complications. Chronic lung disease (CLD), cardiac disease, neurocognitive disorders, skin and renal disease are important complications that have been described.²³

Chronic lung disease:

Few studies have extensively examined the epidemiology of CLD in HIV-infected children and adolescents. Due to limited data, the full impact of HIV-related CLD cannot at present be calculated.²⁴ CLD is a non-specific term that does not define the underlying pathology, but only suggests an underlying chronic lung condition.²⁴

Lymphocytic Interstitial pneumonitis (LIP) was the most common cause of CLD before ART was widely available. LIP responds to ART but if treatment is delayed it leads to long term complications such as bronchiectasis and cor pulmonale. Another more serious complication is obliterative bronchiolitis, which unlike LIP has very little reversibility after starting ART.²⁵

Another important cause for CLD is recurrent pneumonia and tuberculosis (TB).²⁵ TB causes airway destruction and leads to bronchiectasis. In a case study of older children receiving ART complicated by bronchiectasis, 36% were previously treated for TB, with microbiological confirmation in only 11%.²⁴ This highlights the difficulty in confirming the diagnosis of TB in HIV-infected patients. These patients are however frequently treated for TB.²⁵ In a Zimbabwe study of 116 PHIVA, more than 30% of adolescents had severe and disabling chronic respiratory symptoms. High-resolution CT scanning showed predominantly small-airways disease consistent with constrictive obliterative bronchiolitis, with LIP being an exceptional finding.²⁶ According to a Western Cape cohort, lung function impairment is common in PHIVA on ART despite being controlled on treatment.²⁷ The same study also found that previous PTB increases your risk for lung function impairment.²⁷ CLD in HIV-infected children and adolescents requires heightened awareness to clinically identify children and adolescents at an early stage to prevent ongoing lung function loss.²⁶

Cardiac complications:

Complications of cardiac disease include dilated cardiomyopathy (DCMO), pericardial effusion and left ventricular diastolic dysfunction. Few data are available on the burden of HIV associated cardiac pathology, the morbidity it causes and the outcome in HIV-infected adolescents living in Africa.²⁸

Renal complications:

Black people might be at high risk for HIV associated nephropathy (HIVAN) because of the frequency of APOL1 gene variants associated with HIV nephropathy in African cohorts.²⁹ HIV is also associated with decreased bone mineral content and density.²⁹ Adolescence is an important period for bone mineral acquisition, therefore compromised bone mass can lead to premature osteoporosis. Tenofovir has been associated with proximal renal tubular toxic dysfunction.²⁹

Growth and puberty:

Stunting and pubertal delay is the hallmark of pediatric HIV infection and this distinguishes PHIVA from their uninfected peers and those infected during adolescence through sexual activity.³⁰ Catch-up growth can be achieved after ART is initiated, but unfortunately those who begin ART in later childhood are typically unable to regain their height potential.³⁰

Neurological complications:

Progressive encephalopathy is well recognised in children and adolescents with HIV. Data on the effect of ART on neurocognitive outcomes suggest that if ART is started as early as infancy the developmental outcome will be better.³¹ Asymptomatic PHIVA may have deficits that include shortfalls in cognitive and fine motor skills, memory and perceptual performance as well as mental processing and language abilities. These are difficult to identify by routine testing.³¹

Skin complications:

Skin disease is a common and striking clinical feature amongst HIV-infected adolescents. Common manifestations include papular pruritic eruption, angular stomatitis and molluscum contagiosum.³² That which is visible to everyone is of great concern to adolescents because resultant scarring is both disfiguring and stigmatizing.³² Social stigma can have a very negative impact on the well-being of HIV-infected adolescents and is reason for concern, therefore the presence of cutaneous manifestations should be recognized and treated early.³²

Psychiatric complications:

Mental health disorders, including general psychological distress, emotional, and behavioural problems, are a leading cause of health-related disability, affecting 10–20% of children worldwide.³³

A 2013 systematic review on mental health of adolescents living with HIV, found few studies describing the prevalence of psychiatric diagnosis in these adolescents. New studies suggest that psychiatric disease such as depression and anxiety are more prevalent among PHIVA comparing to non-infected adolescents.³⁴ In a 2000 study in United States, 53 % of HIV-infected adolescents had received a psychiatric diagnosis prior to HIV treatment and 44% experienced ongoing depressive disorders.³⁴

For the low- and middle-income countries in which the majority of the world's HIV-infected adolescents live and where mortality is a major concern, enormous obstacles exist which prevent the implementation of healthcare infrastructure to address mental health. Examples of these obstacles are lack of screening and lack of evidence for which interventions to implement.³⁴

Drug related complications:

Antiretroviral drugs that were commonly used in the early ART era such as Stavudine (D4T) and Didanosine (DDI) which fall in the category of nucleoside analogues, have been associated with side effects that are related to mitochondrial toxicity whereas the newer medications like Tenofovir (TDF) and Abacavir (ABC) have fewer metabolic effects.³⁵ D4T can cause lactic acidosis which is a potentially fatal adverse effect. Another side-effect of D4T, lipodystrophy, is characterized by the loss of subcutaneous fat in the extremities, face and buttocks which can be irreversible once advanced as well as stigmatizing and associated with decreased adherence. Substituting D4T with ABC has proven to partially reverse changes in lipodystrophy.³⁵ Other side-effects of D4T are pancreatitis and distal sensory neuropathy were indications for changing therapy.

Efavirenz has been linked to neuropsychiatric effects, which include increased risk of suicidal ideation, encephalopathy, psychosis and ataxia. The risk for toxicity has been associated with the loss of function polymorphisms of cytochrome 2B6, the main metabolising enzyme for EFV. It is estimated that about 20% of sub-Saharan Africans are genetically slow metabolisers and may be at risk of EFV toxicity.³⁵

Lopinavir/ritonavir, a protease inhibitor, is associated with gastrointestinal intolerance, hyperlipidemia and elevated transaminases as well as cardiac issues like prolonged PR interval and cardiotoxicity.³⁵

Chronic inflammation:

Inflammation is being recognized as a significant consequence of HIV infection. Paediatric studies have now shown that PHIV-infected children have a high degree of inflammation related to uncontrolled HIV replication.³⁶ The consequence of this increased inflammation includes vascular abnormalities which can result in heart disease, strokes, altered glucose metabolism, malignancy and neurologic disease.³⁶ This inflammation is decreased but not stopped by ART.³⁶ Given that HIV infection is lifelong, and with ART there is increased survival of PHIV-infected adolescents, the sequelae of this unchecked inflammation, particularly in those that are non-adherent to ART, is of concern.

Psychosocial issues:

In Africa, social factors such as being orphaned, poverty and inconsistent guardianship can result in behavioural problems and psychiatric disorders. The orphan epidemic has increased alongside the HIV epidemic with almost 50% of AIDS orphans found to be adolescents.³⁷ Due to the immediate medical concerns and the social and economic burden of HIV, families give little attention to the mental health needs of adolescents.²² These factors can affect an adolescent's access to HIV care and treatment adherence.

In low income countries, PHIV youth are born into families who have experienced severe discrimination and now have to cope with the added burden of HIV-related stigma.³⁸ Poor adherence to ART leads to emergence of drug resistance and the risk of spreading drug-resistant HIV strains when adolescents become sexually active.³⁹ The transition of adolescents from pediatric to adult HIV care services might further disrupt adherence due to adolescent anxiety, fear of the unknown, health care workers that have limited time for counselling and little experience of addressing adolescent-specific concerns.⁴⁰

Delayed disclosure of HIV status to the adolescent and a resultant lack of autonomy, substantially affects adherence.⁴¹ WHO recommends that disclosure occurs before 12 years of age, but needs to be applied to each individual.⁴¹ In a collaborative study between University of Oxford and Cape Town, they found that full disclosure to adolescents at an early age was associated with higher ART adherence and that pediatric disclosure can be done successfully in a low-resource context and in a range of government health facilities.⁴²

Study justification:

1. Gaps in the literature

Compared with infants and adults there is considerably less literature documenting the burden of HIV among adolescents and the tools for addressing their holistic health needs. Most data comes from resource rich or very low income countries. Few data is available on the spectrum and epidemiology of chronic disorders and outcomes associated with HIV infection in adolescents.

2. Hypothesis:

We hypothesize that the outcome, number of complications, treatment failure and HIV drug resistance of HIV-infected adolescents treated in a paediatric infectious disease clinic in a middle income country with a high prevalence of HIV, will differ from those reported from high income countries. We hypothesize that there will be increased morbidity in these adolescents due to more limited resources and a higher burden of infections such as TB.

A second hypothesis is that there is a difference in outcome between those that started ART below the age of 10 years and those starting treatment at age older than 10 years.

Research question:

A cross sectional analysis of perinatally HIV-infected adolescents in a paediatric infectious diseases clinic in the Western Cape, South Africa.

4. Aim of the study

The aim of this study will be to describe the demographic details, medical and psychosocial complications, drug regimens, drug resistance and virological outcome of HIV-infected adolescents treated in a pediatric IDC in the Western Cape, South Africa.

5. Primary outcomes:

- To describe the demographic data, virological outcomes, medical and psychosocial complications of PHIV adolescents in a tertiary care clinic.

6. Secondary outcomes:

- To document the antiretroviral (ART) drug regimens that adolescents were receiving in 2015
- To document ART resistance
- To document the use of 'third line' ART
- To compare adolescents diagnosed above or below 10 years of age.
- To identify possible risk factors for virological failure

Methods and Methodology:

1. Study setting:

The study was conducted at Tygerberg Hospital, a 319 pediatric bed hospital, situated in the Western Cape of South Africa. Tygerberg Hospital is a tertiary care hospital with a pediatric Infectious Diseases ward and clinic. The clinic team comprises 2 dedicated pediatric nursing staff members, 3 medical officers, 1 HIV counsellor and 1 pharmacist, all of whom have been working at the clinic for more than 10 years and have many other responsibilities. The staff is shared with the adult clinic but on specific days are allocated to the children's clinic. The team is assisted by 2 pediatric Infectious diseases specialists once a week. The clinic serves the Northern Metro sub districts, Eastern Tygerberg, Khayelitsha, West Coast, Cape Winelands and Overberg rural districts.

The population of the Western Cape is estimated to be approximately 6 million people.³⁸ The hospital's drainage area includes the Northern Metropolitan sub districts, Khayelitsha, Eastern Tygerberg, West Coast, Cape Winelands and Overberg rural districts.

The prevalence of HIV in the Western Cape is approximately 17%³⁹, a significant number to treat.

Children with HIV are seen at all the surrounding clinics and hospitals and those with complicated disease are referred to Tygerberg Hospital. The remainder of adolescents attending the clinic began treatment at young age or live nearby and have remained at the clinic. In most institutions the cut-off age for pediatric care is 13 years after which you will be transferred to adult care. At the Tygerberg IDC, patients remain in pediatric care till they are emotionally ready for transition and according to family's request/doctor's discretion.

2. Study design:

Retrospective descriptive study describing all HIV infected adolescents between the ages of 10 to 19 years attending the IDC at Tygerberg Hospital during a 12 month period.

3. Study population:

The total number of adolescents, aged between 10 years and 19 years, attending the Pediatric IDC in the year 2015.

Inclusion criteria:

- Age between 10 and 19 years
- Confirmed HIV infection
- Entered in the clinic database of the Pediatric Infectious Diseases Clinic

Exclusion criteria:

- Patients less than 10 years or older than 19 years

4. Data collection: A list of patients that met the inclusion criteria was obtained from the Pediatric IDC database. The patient's medical folders which were available from the Pediatric IDC were then reviewed. The data collected was recorded on a data collection sheet (see appendix A)

Children who were infected through different methods but who were identified at an age less than 10 years old or during follow up, were not excluded.

Viral load was lower than detectable limit (LDL) if the value was less than 40 copies/ml. CD4 counts were only available as absolute values, percentages not documented.

Social worker referral was only documented if they were referred for social issues and did not include grant applications.

5. Data Management:

The data capture sheet was completed and loaded onto an electronic database (Microsoft Excel 2013) with the above variables. The researcher extracted all details from patient files and documented it on the data capture sheet. Each adolescent was allocated a unique study number so that the data captured reflected no identifiable information. The data was then entered into MMed candidate's personal computer with no identifying information.

6. Data Analysis:

Data was captured on the MS Excel spread sheets and with the help of the department of biostatistics data was analysed using Excel. The characteristics of the patients were described using standard descriptive analysis, including measures of central tendency (mean, median, proportions) and dispersion (standard deviations, interquartile ranges and 95% confidence intervals.)

7. Statistical methods:

Stata version 14 (StataCorp, Texas) was used to analyse the data. Descriptive analysis entailed summarising numerical data using medians and interquartile ranges in the case of non-normal distributions, and means and standard deviations if the data were normally distributed. Categorical variables were summarised using frequency tables and percentages by group. Comparisons between groups were analysed using Pearson's chi square tests for categorical variables and Mann Whitney tests for continuous variables. Binary logistic regression analysis was undertaken to assess factors associated with viral suppression. Odds ratios and 95% confidence intervals were reported.

8. Ethical and Legal considerations:

The following ethical principles were adhered to during the course of this study:

a) Social value:

At the time of the study, available data suggested that HIV-related deaths are increasing in adolescents whereas decreasing in all other groups. Adolescent-specific data are limited, which present a serious impediment to measuring and monitoring progress. Not enough is known in order to develop strategies to improve their treatment outcomes. By doing this study we hope to develop strategies to improve their morbidity and mortality.

b) Respect for persons:

Only retrospectively collected data was analysed in this study. There was no direct contact between the researcher and patients

c) Privacy and confidentiality:

No patient identifying data was used on the data-capture sheet, the data was collected anonymously using a unique study number.

d) Independent review:

The protocol was approved by the Health Research Ethics Committee (HREC) of the University of Stellenbosch, with ethics approval number S15/06/133.

e) Informed consent:

There was no contact between the researcher and subject as it was a retrospective folder review, there for a waiver of consent was granted by the HREC. It was a retrospective anonymous audit, only the primary investigator retained the patient's identification, logged as a separate document in a secure location. The audit contained no deviation from standard clinical practice.

Results:**Description of study population:**

Ninety-eight patients, of whom 55 (56%) were female, met the inclusion criteria. Race was not recorded. The median age of ART initiation was 7 years (IQR: 4/12 -17). The median age at first clinic visit was 4.9 (IQR: 1.5 – 9.4) years and at last clinic visit 14 (IQR: 10 – 19) years. Fifteen (18%) were older than 10 years at their first clinic visit. The majority of adolescents were WHO Stage 3 disease (53%) and Stage 4 disease (21%) at diagnosis. There was no difference between the baseline WHO stage in adolescents diagnosed and started on treatment before 10 years and after 10 years of age ($p=0.139$) (Table 1). WHO staging was not re-classified after treatment was started. The median CD4 count at first clinic visit was 513 cells/mm³ (IQR: 264-2246). Of those diagnosed at 5 years and older (80/98) and where CD4 count at diagnosis was available (38/80), 8 had severe immunodeficiency, 8 advanced, 7 mild and 15 no HIV associated immunodeficiency according to WHO immune classification.

The median CD4 count in those below 10 years of age at diagnosis was 554 cells/mm³ (IQR: 314-1006) versus 265 cells/mm³ (IQR: 133-321) in those diagnosed above 10 years of age ($p=0.0033$). (Table 5) Viral load was not documented at first clinic visit as it was not part of South African National guidelines at the time most adolescents had their first visit.

At last clinic visit the median CD4 count was 656 cells/mm³ (IQR: 476-1650). Viral load at last clinic visit was lower than detectable limit (LDL) in 81% of patients (Table 1).

The median duration of follow-up was 8 years (IQR: 4-12). The median number of clinic visits at the Tygerberg IDC was 65 (IQR: 24-100) visits per adolescent. Hospitalization episodes at Tygerberg since first clinic visit ranged from 0 to 4 episodes with a median of 3 admissions in total. In those adolescents with more than 5 years of follow-up, the mean number of hospitalizations was one event. From the 34 (35%) patients hospitalized in the last 5 years, 27 (79%) were virologically suppressed at the time. Most hospitalizations were due to chronic medical conditions (chronic lung disease, neurological complications, HIV-associated renal disease and cardiomyopathy) and drug side effects (Abacavir hypersensitivity and Efavirenz neurological side-effects).

Outcomes:

No deaths were documented during 2015.

Viral suppression: From 94 plasma HIV RNA levels available at last clinic visit, 76 (81%) adolescents were virologically suppressed. Viral genotyping was done in 7 of the 17 adolescents (41%) with viral loads above 1000 copies/ml. The most common resistance mutations are described in Table 3.

ART initiation below 10 years of age (53/63) or older than 10 years (11/14) had no effect on viral suppression. ($p=0.6$)

Adherence: This was monitored by clinic sister/nurse by means of a pill count at each visit. There was no consistent documentation of adherence by the doctor. Forty-six of the 98 (47%) had mother/father as treatment supporter, followed by family member (30/98) and foster parent (22/98). Viral suppression was not influenced by the type of treatment supporter a patient had. ($p=0.51$)

Risk factors for virological failure: We did not identify any statistically significant associations with virological failure. [School failure ($p=0.09$); recurrent hospital admissions ($p=0.15$); social issues ($p=0.16$); medical complications ($p=0.7$); foster care ($p=0.89$) and depression ($p=0.9$)]

Chronic disease related to HIV:

The main causes of chronic morbidity are summarized in Table 4. A large proportion of adolescents had PTB (59%). The majority of patients were first diagnosed with PTB and subsequently the diagnoses of HIV was made. Skin complications, pulmonary, cardiac and neurological complications were chronic diseases documented. Most patients (82%) had skin complications. Multisystem disease was common: skin and lung (23%), skin and heart (8%), skin and kidney (6%), skin and brain (49%), lung and heart (6%) while 11% had neurological as well as pulmonary complications. Six patients had 4 system involvement involving skin, lung, heart and brain complications.

Depression was documented in five patients (5%) and they were initiated on antidepressants.

There was no difference in the number of lung ($p=0.13$), cardiac ($p=0.51$), CNS ($p=0.5$), skin ($p=0.55$) complications in those starting ARV's older than 10 years and younger than 10 years. (Table5)

There was no difference in chronic diseases related to HIV between the virologically suppressed and non-suppressed patients. [CLD: ($p=0.8$); cardiomyopathy: ($p=0.24$); cor pulmonale: ($p=0.5$); HIVAN: ($p=0.18$); skin: ($p=0.14$); HIV encephalopathy: ($p=0.6$)].

Anthropometry

At first clinic visit 42% of patients were stunted (28% stunted and 14% severely stunted) and at last clinic visit 27% were stunted (15.6% stunted and 11.5% severely stunted) $p=0.02$. There was a trend to more stunting in those with later (after 10 years of age) than earlier HIV diagnosis, 7/15 (46%) versus 23/62 (37%) ($p=0.19$). At last clinic visit, 6 of 15 stunted patients (40%) were virologically suppressed, 2 were not suppressed and 6 viral loads were unknown. Of the 11 with severe stunting at last clinic visit, 8 (73%) were virologically suppressed. None of these had HIV associated chronic complications documented like CLD or renal failure. Tanner staging was not routinely documented. BMI improved with ART treatment.

Psychosocial issues:

Sixty-seven (68%) of patients were disclosed to and 20% (20/98) not known/documented. Disclosure was done by parents (42%), family members (31%) and foster parents (27%). Of the 11 patients that were not disclosed to, 7 had significant neurological disease.

More than half (55%) of the adolescents were attending a mainstream school while a third (34%) attended a special school or care centre. Forty-six (47%) of patients failed a grade and nearly 33% failed more than one grade. There was no difference in type of school attendance ($p=0.87$) or number of failed grades ($p=0.52$) between patients diagnosed less than 10 years and those diagnosed older than 10 years.

Five percent of patients were receiving family planning with 83% not documented/known. Two adolescents were currently pregnant.

Referral to a social worker was documented if the patients had complex social issues that needed to be addressed. This did not include ordinary referrals for financial assistance. More than half (57%) of the adolescents were referred to social services for issues related to abuse (verbal/physical/sexual), neglect, care giver/family issues, depression and suicidal thoughts.

Drugs:

Looking at the number of compounds patients were exposed to, the majority 47% (46/98) were on 3 different NRTI drugs, 2 patients were exposed to 5 different NRTI drugs, 21 to 4 different drugs and 29 to 2 NRTI's. The most commonly used NRTI drugs were Stavudine, Lamivudine and Abacavir. Most patients were only on 1 NNRTI drug which was Efavirenz and of the Protease inhibitors most were only on Kaletra/Aluvia.

Twenty seven (28%) were only ever on one regimen. These 27 adolescents never switched medication for drug side effects or because newer drugs became available (for example Abacavir replacing Stavudine) or because of failure. Sixty-seven (68%) remained on their first regime with single drug switches for side-effects. At last clinic visit, 61 (62%) were on a regimen containing Efavirenz and 29 (30%) on an Aluvia based regimen. Three adolescents (3%) were on 'third line drug regimens' containing Darunavir and Raltegravir. All three these patients had resistance testing. Only 1 (1%) adolescent was on Lamivudine (3TC) monotherapy at last clinic visit (Table 2). Fifty of the 61 (82%) adolescents ever started on Efavirenz never discontinued the drug and were suppressed at last visit with an average duration of 6.5 years on the drug. Eighteen of the 29 (62%) adolescents that started on Lopinavir/Ritonavir and never switched to an alternative drug, were suppressed at last visit with average duration of 3.8 years on the drug.

Drug side-effects: The most common drug side-effect was lipoatrophy due to Stavudine (D4T) in 40/56 (71%) of patients. D4T is no longer used in current regimens. Four of the 83 (5%) adolescents ever exposed to EFV, developed gynecomastia and 4/83 (5%) developed CNS complications like dizziness, drowsiness or nightmares. Abacavir hypersensitivity was reported in 4/64 (6%) patients. Hypercholesterolemia was reported in 2/46 (4%) of patients on Lopinavir/Ritonavir based regimen. One patient stopped Tenofovir (TDF) due to decreased bone mineral density. (Table 3)

Discussion:

The main finding was that, in 2015 viral suppression was achieved in 81% of the adolescents at Tygerberg IDC with only 3% requiring third line ART. Furthermore, few adolescents had chronic medical complications and there were no documented deaths that year. Another important finding was that 57% of the adolescents had psychosocial issues requiring intervention. These findings are reassuring considering that adolescents attended a clinic with minimal extra resources, in a tertiary hospital in Western Cape.

The majority (75%) of the cohort of PHIVA that are described started attending the IDC at a median age of 4.9 (1.5-9.4) years and remained in the clinic for 8 (IQR: 4-12) years. Only 18% of the adolescents started ART after the age of 10 years. This older group of patients are similar to those reported from Zimbabwe whose average age was eleven years.⁴³ This is not similar to studies reported from high developed countries where 62% of adolescent patients attending HIV-clinics were diagnosed and commenced on treatment prior to their first year of life.^{44, 45} Based on these factors, one would expect the outcome, medical complications and treatment success to differ in well-resourced countries compared to low income countries. This study however indicates that good outcomes and few medical complication can be achieved in a middle income country where adolescents are treated in government clinics with minimal extra resources. It is highly likely that the outcomes will improve even further, in low and middle income countries as a greater proportion of HIV-infected children are diagnosed and started on treatment within the first few months of life.

In a study from Zimbabwe the majority of adolescents were diagnosed with WHO HIV stage 3 or stage 4 disease,⁴³ similar to this study where those diagnosed older than 10 years, 53% had stage 3 and 21% stage 4 disease. In resource limited settings up to 75% of PHIV infected youth have CD4 counts below 200 cells/mm³ at the time of diagnosis.⁴³ This is illustrated by a study in Zimbabwe where adolescents had median CD4 count of 101 cells/mm³ (IQR: 35-197).⁴³ In contrast, at Tygerberg IDC the median CD4-T cell count at diagnosis was 513 cells/mm³ (IQR: 264-2246). This higher CD4 count is misleading because the majority of children were diagnosed not in the adolescent period but as children (where CD4 percentage is the preferred measure). In our cohort those diagnosed in the adolescent period had a median CD4 count of 265 which is similar to the Zimbabwean cohort.

The encouraging viral suppression outcome (81% LDL at last clinic visit) may be due to the fact that most patients have been followed up over a prolonged period at the same clinic by the same dedicated pediatric team. Adherence and drug side-effects are screened for on a regular basis and patients psychosocial needs are addressed as far as possible. In many resource-rich as well as low income countries, adolescents are sometimes transferred to adult care services at a predefined cut off age when they are emotionally not ready which further disrupts adherence.⁴⁶

Many of the adolescents at the IDC (67%) are still on their first regimen, unchanged in 27 (28%), with few single drug switches made due to side-effects in the majority. Stavudine was replaced by Abacavir in the National guidelines in 2010 due to the side effect of lipoatrophy and children were systematically switched to Abacavir provided they were suppressed. In this cohort of adolescents 71% were documented to have lipoatrophy or lipodystrophy as a result of using Stavudine (Table 2). Only 3% were on third line drugs and one patient was on 3TC monotherapy at last visit. This finding is promising when comparing the results with an urban cohort of PHIVA in the United States where the adolescents had been exposed to a median of eight different ARVs across three classes due to resistance and toxicity.⁴⁷

From the 17 patients not virologically suppressed, only 7 (41%) had resistance testing. The remainder were thought to be non-adherent and did not qualify for resistance testing. The most common mutations are summarized in Table 3. Low numbers of adolescents on '3rd line therapy' is reassuring when

compared to well-resourced settings where they face challenges regarding extensive resistance.^{48,49} This however, still indicates that non-adherence is a problem in those that are failing ART.

The majority of PHIV-infected youth in Sub-Sahara Africa have severe immunosuppression and a heavy burden of chronic complications, mainly growth failure, lung and cardiac disease.⁴³ By contrast, approximately 80% of the PHIV infected adolescents in resource-rich countries have been on longstanding combination ART, many having initiated therapy when they were under two years old and therefore with fewer chronic complications.⁵⁰ In this study 42% of patients were stunted at first presentation with some catch up growth after initiation of ART; with 27% stunted at last visit ($p=0.02$). In resource limited settings the incidence of stunting can be up to 60% at diagnosis.⁴³ When the height for age in those diagnosed less than 10 years were compared to those older than 10 years it was found that there was no difference ($p=0.19$). Although catch-up growth can be achieved after initiation of antiretroviral treatment, children who begin treatment in later childhood are typically unable to regain their height potential therefore the best outcomes are in those children started on ARV's in first years of life.⁵¹

The prevalence of prior TB in this population was very high. Most patients were first diagnosed with TB (53%) and subsequently the diagnosis of HIV was made. Fifty-nine (59%) patients were diagnosed with PTB and 17% with extra-pulmonary TB during the course of their disease. This is similar to the 70% of patients diagnosed with TB in low income countries.⁴³ Two patients (2%) had multidrug-resistant TB and 1 patient (1%) had extensively drug resistant TB. All patients were successfully treated for TB including the XDR-patient.

Compared to LMIC where CLD has been documented in up to 86% of patients⁵⁰, only 23% patients were labelled as having CLD with 10% diagnosed with bronchiectasis and 13% with LIP. PTB had a strong association with both bronchiectasis (90%) and LIP (62%) ($p=0.12$). Accurately diagnosing CLD, in those adolescents who have it may prevent them from receiving multiple presumptive TB treatment courses.⁵²

Cardiac disease was only documented in a few patients, limited to cardiomyopathy (2%) and cor pulmonale (2%). In a study in Harare, 67% of PHIVA had left ventricular hypertrophy, 31% right ventricular dilatation and 4% pulmonary hypertension. Of note more than half of these patients were asymptomatic despite high frequency of echo abnormalities.⁵³ It could be speculated that this could be the reason for the low incidence of cardiac disease as patients are not routinely screened for cardiac abnormalities.

Skin complications were the most frequently documented complication with 82% of patients having had 2 or more skin complications of which papular pruritic eruption (50%) and dermatitis (43%) were the most common. This correlates with patients in Zimbabwe where skin complications are common in 70%.⁵⁴

The median hospital admissions since diagnosis were 3 (IQR: 0-4). In the last 5 years, most hospitalized patients (79%) were virologically suppressed. Common reasons for admission were drug side-effects (ABC hypersensitivity and Efavirenz neurological complications) and chronic medical complications like CLD, seizures, DCMO and HIV related kidney disease.

In resource rich settings there are high rates of admission for psychiatric reasons, but in resource poor settings there is little or no evidence of the psychological impact, depressive symptoms and psychiatric admissions for HIV-infected adolescents.^{55,56} The lack of screening programmes for mental health disorders, and the minimal healthcare infrastructure to address these issues are potential obstacles.⁵⁷

Psychosocial issues were reported in 57% of adolescents. Some reasons known for referral were behavioural problems in 11% and 5% known with depression. Other psychosocial problems included referral to social services for issues with family dynamics, neglect, abuse, violence and extreme poverty.

Sexual identity issues and suicidal thoughts were reported and referred to psychologists and psychiatry. In LMIC the need for psychosocial support is evidently poorly explored. This area needs further investigation to determine the level of support needed.

A very concerning finding was the poor documentation of contraceptive use with only 5% of patients known to be on contraception. Pregnancy was documented in 2 patients. This is an issue in both resource rich and poor settings that need urgent attention.⁵⁸

Strengths and weaknesses:

This study presents limitations inherent to the retrospective method. It is also limited by the fact that it is a cross sectional analysis and data on transfer out or loss to follow up as well as morbidity and mortality prior to 2015 was not captured. Data on clinical examination and laboratory values were obtained from routine medical records and thus may not be complete. We evaluated patients seen at tertiary referral hospital and the results/data cannot be generalized to smaller hospitals and clinics in the Western Cape. Viral suppression was assessed based on viral load at last clinic visit and does not reflect the individual adolescent's prior viral loads.

A novel aspect of this study is that some patients were diagnosed at younger ages. This may have resulted in fewer chronic medical complications. These findings indicate that a good outcome can be achieved in a setting with limited resources, where patients are managed in a holistic fashion and managed by the same dedicated clinicians until emotionally ready to transition to adult care. The virological outcome findings compare to those in high income countries. This study also revealed that psychosocial complications are a major issue and that there is a big need to address these issues in order to improve the outcome in this population group.

Conclusions and Recommendations:

Although there are fewer chronic medical complications than noted in other African cohorts, there are significant psychosocial and educational issues and more focused interventions are needed to address these.

Virological outcomes in this cohort are relatively good and compare favourably to international cohorts although this is only a reflection of those PHIVA currently in care at the clinic.

Better documentation of adherence, contraception, transition plans are needed.

Appendix AData Capture Sheet:**Patient ID number:****Patient Folder number:****Questions:**

1. Date of Birth:
2. Date of Diagnosis:
3. Male or female:

Male:	Female:

4. WHO stage at diagnosis:

Stage 1	Stage 2	Stage 3	Stage 4

5. Date of initial Weight measurement:
Initial weight:
6. Date of most recent weight measurement:
Most recent weight:
7. Date of initial height measurement:
Initial height:
8. Date of most recent weight measurement:
Most recent height:
9. Initial BMI:
10. Current BMI:
11. HIV drugs:

Drug Name:	Yes/No	Date started:	Date stopped:	Reason for stopping:
Abacavir/ABC:				
Lamivudine/3TC:				

Efavirenz/EFV:				
Kaletra:				
Stavudine/D4T				
Zidovudine/AZT				
Didanosine/DDi				
Nevirapine:				
Aluvia				
Combivir				
Tenofovir/TDF				

a) Start Regimen:

b) Current Regimen:

- A) Inappropriate Historical Regimen 1: D4T, 3TC, Ritonavir
- B) Appropriate Historical Regimen 1: D4T, 3TC, Kaletra
- C) Current Regimen 1 -- < 3 years old: ABC, 3TC, Kaletra
- D) Current Regimen 1 -- > 3 years old: ABC, 3TC, Efavirenz
- E) 2nd Line: AZT, 3TC, Kaletra
- F) 3rd Line: Darunavir, Raltegravir, AZT, TDF, 3TC, Etravirine
- G) Other:

12. Date of initial CD4 count:

Initial CD4 count:

11. Date of most recent CD4 count:

Most recent CD4 count:

12. Date of initial HIV viral load:

Initial HIV viral load:

13. Date of most recent HIV viral load

Most recent HIV viral load

14. Date of transfer out (if applicable):

15. Loss to follow up: Loss to follow up if last clinic visit more than 6 months ago

16 Resistance testing ever done?

1. Yes	2. No

17 Did doctor/parents disclose to patient:

1. Yes	2. No	3. Unknown

18 Does patient attend clinic with supporter:

1. Yes	2. No

If yes, who?

19 Type of School attendance:

1.Normal medium school	2.special school	3.care centre

20. Ever failed grade?

1. Yes	2. No	3. Not documented

21. Ever pregnant?

1.Yes	2.No

20 Contraception:

1.Yes	2.No	3.Unknown

21 Previous PTB?

1. Yes	2. No

22 Previous MDR TB?

1. Yes	2. No

23 Systemic Complications:

1. lung disease	2. Cardiac pathology	3. Renal Pathology	4. Skin disease	5. CNS Pathology	6. Depression
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Lung disease: 1-Bronchiectasis

2-LIP

3-PJP

4-other

5-nil documented

Cardiac pathology: 1- cardiomyopathy

2-pericarditis

3- Myocarditis

4- Other

5 nil documented

Renal Pathology: 1- HIVAN

2- other

3-nil documented

Skin disease: 1- dermatitis

2- tinea capitis, corporis

3- papular pruritic eruption

4- molluscum contagiosum

5- other

6 – nil documented

CNS pathology: 1- HIV encephalopathy

2- spastic diplegia

3- cerebral palsy

4- seizures

5- neurodevelopmental delay

6 – ADHD

7 – other

8 – nil documented

Depression: 1 = on antidepressants

2 = not on antidepressants

24 Total number of hospital admissions at Tygerberg Hospital:

25 Social worker Referral:

1. Yes	2. No

Appendix B

Table 1: Demographic data of the patients included in the study

Characteristic:	First clinic visit	Last clinic visit
Age	4.9 (1.5-10)	14 (10-19)
Diagnosed at < 10yrs of age	65/98 (81)	
Female	55/98 (56)	
WHO stage at dx		
Stage 1	2/98 (2)	
Stage 2	20/98 (20)	
Stage 3	52/98 (53)	
Stage 4	21/98 (21)	
Unknown	3/98 (3)	
CD4, cells/mm ³	513 (264-2246)	656 (476-1650)
Anthropometry:		
Underweight for age	15/92 (16)	19/94 (20)
Severely underweight	6/92 (7)	6/94 (6)
Normal weight	71/98 (77)	69/94 (70)
Unknown	3/98 (3)	4/98 (4)
Height, cm	109 (65-165)	151 (107-170)
Stunted	25/90 (28)	15/97 (16)
Severely Stunted	13/90 (14)	11/97 (12)
Normal height	52/98 (58)	70/97 (72)
Unknown	8/98 (8)	2/98 (2)
Wasted	4/94 (4)	5/95 (5)
Severely wasted	5/94 (5)	2/95 (2)
Overweight	4/94 (4)	4/94 (4)
BMI(mass/height ²)	16 (9-29)	19 (14-29)
Normal BMI	81/94 (86)	85/95 (89)
Unknown	4/94 (4)	4/94 (4)

All categorical variables were expressed as N (%) and all continuous as median (IQR) or mean (SD)

Stunted: Height for age below -2 Z score

Severely stunted: height for age below the -3 Z score

Wasted: weight for height below the -2 Z score

Severely wasted: weight for height below the -3 Z score

BMI: Body mass index

Table 2: Drugs used at Tygerberg Infectious diseases clinic and number of reported side-effects of each drug:

Drug name:	Ever exposed to drug N (%) N/98	Number of patients on specific drug at last clinic visit N (%)	Number of patients with drug previous side effects N (%)
D4T	56 (57)	2 (2)	40(71) Lipodystrophy/lipoatrophy
ABC	64 (65)	56 (57)	4 (6) ABC Hypersensitivity
3TC	93 (97)	87 (89)	0 (0)
EFV	83 (85)	61 (62)	4 (5) Gynaecomastia 4(5)CNS complications
AZT	34 (35)	19 (17)	8 (24) anaemia
DDI	11 (11)	0 (0)	0 (0)
ALUV/KAL	46 (47)	29 (30)	2(4.0) Hypercholesterolemia
TDF [#]	16 (16)	15 (15)	1 (6) Bone mineral density decreased
NVP	6 (6)	2 (2)	2 (33) hepatitis
DAR	3 (3)	3 (3)	0 (0)
RALTEG	2 (2)	2 (2)	0 (0)

D4T: Stavudine; ABC: Abacavir; 3TC: Lamivudine; EFV: Efavirenz; AZT: Zidovudine; DDI: Didanosine; ALUV/KAL: Aluvia/Kaletra; TDF: Tenofovir; NVP: Nevirapine; Dar: Darunavir; Raltegravir

#TDF: includes individual drug (11%) as well as TDF as part of fixed drug combination tablet (5%).

Table 3: Resistance mutations that occurred in 7 patients:

NRTI resistance mutations: N/7	NNRTI resistance mutations: N/7	PI resistance mutations: N/7
M184V (5)	G190EQ (1)	154VTAM (2)
T215YF (2)	K103NS (2)	V82ATSF (4)
M41L (2)	V106AM (2)	L76V (2)
D67N (3)		M461IL (2)
K70R (1)		

NRTI: Nucleoside reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: Protease inhibitors

Table 4: Different medical complications documented:

Medical complication:	N (%)	N=98
Prior Tuberculosis:		
Pulmonary Tuberculosis	58 (59)	
Extra pulmonary tuberculosis	17 (17)	
MDR TB	2 (2)	
XDR TB	1 (1)	
Lung complications:		
Bronchiectasis	10 (10)	
LIP	13 (13)	
PJP	1 (1)	
CLD	23 (23)	
Cardiac complications:		
Cardiomyopathy	2 (2)	
Pericarditis	0 (0)	
Myocarditis	0 (0)	
Cor Pulmonale	2 (2)	
Renal complications:		
HIV nephropathy	1 (1)	
Enuresis	6 (6)	
Skin diseases:		
Dermatitis	42 (43)	
Tinea	30 (31)	
PPE	49 (50)	
Molluscum contagiosum	6 (6)	
Impetigo	11 (11)	
Warts	4 (4)	
Herpes zoster	6 (6)	
Neurological complications:		
Encephalopathy	8 (8)	
Cerebral Palsy	3 (3)	
Seizures	9 (9)	
Neurodevelopmental delay	12 (12)	
ADHD	5 (5)	
Behavioural disorder	11 (11)	

MDR: multidrug resistant; XDR: extensively drug resistant; LIP: lymphocytic interstitial pneumonitis; PJP: pneumocystis jiroveci; CLD: chronic lung disease; PPE: papular pruritic eruption

Table 5: Comparison of those that started ART before the age of 10 years and those that started ART after the age of 10 years.

	Diagnosed < 10 years: N=64	Diagnosed > 10 years: N=15	P – value
WHO staging at dx			
Stage 1	1 (2)	1 (7)	0.139
Stage 2	11 (18)	6 (40)	
Stage 3	38 (61)	7 (47)	
Stage 4	12 (19)	1 (7)	
Anthropometry at diagnosis:			
Stunted	24 (39)	1 (7)	0,44
Severely stunted	9 (15)	4 (30)	
Normal length	42 (68)	10 (67)	
Anthropometry at last visit:			
Stunted	12 (19)	3 (20)	0.8
Severely stunted	11 (18)	4 (27)	
Normal length	59 (95)	11 (73)	
CD4count	554	265	0.003
Failed grades	32 (49)	6 (40)	0.520
Social issues	39 (60)	6 (40)	0.160
School			
Special school	15 (23)	4 (27)	0.870
Care centre	2 (3)	1 (7)	
Lung disease	19 (30)	5 (33)	0.130
Cardiac disease	2 (3)	1 (7)	0.510
Skin disease	56 (86)	12 (80)	0.550
CNS disease	23 (35)	4 (27)	0.520

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