Treatment outcomes in perinatally-infected HIV positive adolescents and young adults after 10+ years on antiretroviral therapy

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DECLARATION

I, Kim Anderson, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part thereof has been, is currently being, or is to be submitted for another degree at this or any other university. I further declare that this work was not published prior to my registration for the degree of Master of Public Health.

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DISSERTATION ABSTRACT

There are currently more than 300 000 children under the age of 15 living with HIV in South Africa (SA). Due to a combination of recent success in preventing new vertical infections and success of paediatric antiretroviral treatment (ART) programmes in improving life-expectancy in perinatally HIV-infected (PHIV) children, the burden of paediatric HIV in SA has changed to older children. An increasing population of PHIV children on ART is reaching adolescence, yet information on long-term treatment outcomes in this group is lacking. There is very limited published data on treatment outcomes in PHIV children after ≥10 years on ART in high income countries (HIC), and none in low and middle income countries (LMIC).

We conducted a retrospective cohort study of PHIV adolescents on ART for ≥10 years at a single ART facility. The main objective of the study was to describe long-term clinical, growth, immunologic and virologic outcomes in the cohort.

Part A, the protocol, as submitted for departmental and ethical approval, details the purpose and methodology of the study.

Part B, the literature review, discusses what is known about long-term treatment outcomes in PHIV children on ART to date. It compares findings between HIC and LMIC. Long-term growth, immunologic and virologic outcomes, as well as factors associated with viral failure are described. The paucity of long-term data is demonstrated, indicating the need for further research on the topic.

Part C, the journal-ready manuscript, details the methodology, results and interpretation of the longitudinal analysis of long-term treatment outcomes among 127 PHIV-infected adolescents and young adults on ART for ≥10 years. After median follow-up of 12 years since ART initiation, 80% of the cohort were virally suppressed and 79% had optimal immunologic status (CD4 >500 cells/μl). These results are favourable overall, but >40% of adolescents were on 2nd-line ART with poorer immunologic outcomes than those on 1st-line ART, and approximately one in three children experienced viral failure during adolescence. This highlights the vulnerability of this group, which requires careful further management.

Appendices include all supporting documentation necessary for the above parts of the mini-dissertation.

References in Part A are in Harvard UCT style, as per the original protocol. The Vancouver referencing style has been used for Part B and C, in keeping with the instructions for authors as stipulated by the South African Medical Journal (appendix 5).

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I especially wish to credit Dr Paul Roux, Kidzpositive and One to One Children's Fund for initiating ART provision at Groote Schuur Hospital, thereby saving many children's lives.

The children, adolescents and caregivers attending the clinic, as well as the dedication of the clinic staff are acknowledged.

Thank you to my husband, children and mother for supporting me throughout my studies.

HISTORY OF DISSERTATION AND ROLE OF CANDIDATE

When the incidence of paediatric HIV was at its peak in South Africa in the early 2000s, I worked as a medical officer for a non-governmental organisation (NGO) called Kidzpositive (from 2002 – 2004). We provided ART to several hundred children at the Groote Schuur Hospital paediatric HIV clinic before government roll-out of ART. Only a handful of sites, funded by NGOs, provided access to ART at that time. After working at this clinic for several years, I left to raise a family. In the years that followed, ART became increasingly available in the public sector, and South Africa's ART programme has since become the largest in the world. In 2015, after a 10 year absence, I returned to work (as a clinician) at the same clinic, and noticed my handwriting, dating back as far as 2002, in many of the patients' folders attending the adolescent HIV clinic. This led to my personal interest in researching the treatment outcomes in these surviving adolescents. I designed the research protocol, which I submitted for approval in December 2015, and began the process of reviewing patients' medical records for the collection of study data in 2016. At the same time, I registered for the degree of Master of Public Health in 2016, which has enabled me to acquire the additional research skills needed to complete the analysis.

LIST OF ABBREVIATIONS

ART - antiretroviral therapy/treatment

ATAZ - atazanavir

BAZ – body mass index for age Z-score

EFV - efavirenz

GSH – Groote Schuur Hospital

HAZ – height for age Z-score

HIC - high income country

HIV - human immunodeficiency virus

LMIC – low and middle income country

LPV - lopinavir

LTFU - loss to follow-up

NHLS - National Health Laboratory Service

NGO – non-governmental organisation

NNRTI - non-nucleoside reverse transcriptase inhibitor

NRTI - nucleoside reverse transcriptase inhibitor

NVP - nevirapine

PHIV – perinatally HIV infected

PI - protease inhibitor

PMTCT - prevention of mother-to-child transmission

RTV - ritonavir

SA - South Africa

UK – United Kingdom

US(A) – United States (of America)

VF - viral failure

VL - viral load

WAZ – weight for age Z-score

WHO – World Health Organization

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PART A: PROTOCOL

1. Purpose of the Study

- The goal of the study is to examine the long-term outcomes of antiretroviral therapy (ART) in perinatally Human Immunodeficiency Virus-infected (PHIV) adolescents and young adults.
- The primary objectives are to measure viral suppression (viral load/VL) and immunologic status (CD4 results) in PHIV adolescents (age 10-19) and young adults (age 15-24) in an urban setting after 10 years or longer on ART.
- The secondary objectives are to describe:
    a) ART regimens used in the cohort (names of drugs, classes of drugs and duration of regimens used)
    b) results of resistance testing if performed
    c) growth parameters (heights and weights)
    d) history of opportunistic infections and hospital admissions
- The study hypothesis, based on available literature, is that after a mean period of follow-up on ART for 10 years or longer, approximately 50% of patients will be virally suppressed and 60% will have optimal immune status (defined as CD4 count >500 cells/µl).

2. Introduction

2.1 Background

There are currently an estimated 340 000 children under the age of 15 living with HIV in South Africa (SA) (UNAIDS, 2014). Due to a combination of recent success in preventing new vertical infections and success of paediatric ART programmes in improving life-expectancy in PHIV children, the burden of paediatric HIV in SA has changed to older children and this effect is projected to increase further by 2020 (Johnson et al., 2012). There is an increasing population of PHIV children reaching adolescence in SA's health care system, yet information on long-term treatment outcomes in this unique group of highly treatment-experienced adolescents is very limited. Adolescents are at high risk of poor adherence, drug resistance and viral failure (VF). Barriers to adherence can include busy lifestyles, treatment fatigue, high pill burdens, complex twice-daily regimens, drug side-effects and disclosure issues (Fairlie, 2014). In addition, socioeconomic difficulties related to orphanhood and stigma, as well as HIV-related behavioural and neurocognitive consequences can adversely affect adolescent adherence (Sohn & Hazra, 2013).

When VF occurs, there are limited second- and third-line ART options available in SA, particularly when protease inhibitors (PIs) have been used in the first-line regimen in children. Since national roll-out of ART started in SA in 2004, PI-based first-line therapy has been recommended for all children starting treatment at <3 years of age. Further therapeutic challenges arise in children who have failed prevention of mother-to-child transmission (PMTCT) with exposure to non-nucleoside reverse transcriptase inhibitors (NNRTIs) (Frigati,

2014), as access to alternative ART options, for example integrase inhibitors and newer PIs, can be challenging in SA.

2.2 Studies of treatment outcomes in high income countries

In high income countries (HIC), the introduction of effective combined ART in 1996 has resulted in the face of HIV changing to a chronic illness. Many PHIV children have become adolescents and subsequently transitioned to adult care. While several studies have reported on virologic and immunologic outcomes in PHIV cohorts on ART (see Table 1), very few have reported outcomes after more than a decade of treatment. Dollfus et al. (2010) followed up the French Perinatal Cohort of PHIV children born between 1985 and the end of 1993. Out of 348 children, 210 (60%) remained in care after 15 years median follow-up since birth. In this cohort, viral suppression (VL <500 copies/ml) was achieved in 56% and optimal immune status in 59%. The mean number of triple ART regimens used was 2.5. The most recent regimens used included PIs (75%), NNRTIs (31%) or both PIs and NNRTIs (11%). De Mulder et al. (2012) reported on a Spanish cohort of 112 PHIV children who had 16 years median follow-up, with analysis performed at the time of transfer to adult care. VL ≤500 copies/ml were reported in 56% and optimal immune status was recorded in 55%. The mean number of ART regimens used was 5, with 48% having used at least 3 regimens and 64% having triple class experience. Resistance prevalence was high in the 58 patients who had genotype resistance testing results available. Resistance was 51% for PIs, 77% for nucleoside reverse transcriptase inhibitors (NRTIs) and 37% for NNRTIs. 17% had triple resistance mutations and 81% had resistance to at least one drug class. The results from these 2 studies, with long follow-up periods, show disappointing virologic and immunologic outcomes, although they may not be generalizable

to SA. Many children in HIC cohorts were exposed to older, less efficacious regimens in the 1990's, and may therefore be at higher risk of acquired drug resistance mutations and VF than children in SA who generally started treatment with effective combination regimens. On the other hand, children in HIC cohorts have had the benefit of access to a wider range of antiretrovirals than children in low and middle income countries (LMIC), which may improve their outcomes.

2.3 Studies in low and middle income countries other than South Africa

Two systematic reviews of paediatric ART outcomes in LMIC highlight the paucity of long-term data. Sutcliffe et al. (2008) in a review on the effectiveness of ART in children in sub-Saharan Africa, found viral suppression was achieved in 32 – 67% of children at 36 months after ART start. A second systematic review of ART outcomes in children in LMIC compared with HIC reported favourable and comparable increases in CD4% and declines in VL, although the results reported were after only 12 months (Peacock-Villada, Richardson & John-Stewart, 2011). A review exploring viral resistance in children failing first-line regimens in LMIC found resistance rates of 88% for NNRTIs, 80% for NRTIs, and 54% for PIs – similar to those in European settings (Sigaloff et al. 2011). Overall, resistance-associated mutations were found in 90% of children who had failed first-line ART, and the risk of resistance was found to increase with increased ART duration. Resistance to ART drugs is particularly concerning in LMIC where access to alternative drugs is very limited.

2.4 South African studies

The SA national ART programme commenced in 2004. Some sites delivered ART before this, funded by non-governmental organisations (NGOs). Despite the rapid scaling-up of ART programmes in SA over the last decade, there is very little information on the long-term outcomes in children on ART in SA. A few studies have reported the outcomes after 1 – 3 years (see Table 2). Davies et al. (2009) reported on a collaborative cohort at 7 sites of 6078 children who, after 3 years on ART, achieved viral suppression (VL <400 copies/ml) in 82% and a median CD4% of 30%. In 5485 children from the same sites, Davies et al. (2011) estimated a 19% probability of VF (confirmed VL >1000 copies/ml) and a 6% probability of changing to second-line ART by 3 years. Morsheimer et al. (2014) followed-up a cohort of 613 children for a median 28 months. They reported that 85% achieved viral suppression (VL <400 copies/ml), while CD4% reached a mean of 17% after 3 years.

2.5 Study rationale

Although these figures of above 80% for viral suppression in SA cohorts are encouraging, the follow-up time in these studies is limited. Longer durations on ART, in conjunction with sub-optimal adherence and accumulation of resistance mutations, may be expected to lead to declines in viral suppression. Although national paediatric ART programmes were implemented in SA over a decade ago, the long-term outcomes of PHIV children on ART have not yet been examined. Describing the ART history and outcomes in this treatment-experienced population may help clinicians to anticipate future therapeutic challenges and plan ahead. Insight into the prevalence of viral suppression, VF, viral resistance and immune reconstitution may provide important information to guide health care providers in the

management of this group, before, during and after their transition to adult care. This study aims to provide information on long-term outcomes in South Africa, which can contribute significantly to available knowledge.

3. Methodology

3.1 Study design

- The study is a descriptive, retrospective cohort study of PHIV adolescents and young adults on ART.
- The expected duration of the study will be approximately 2 years (Table 3), although since this is a retrospective study, the actual follow-up data that will be collected will be for considerably longer.
- Primary outcome variables are VL and CD4 results.
- Secondary outcome variables:
    a) ART regimen history (drug names, class, formulations, duration of regimens and reasons for drug changes)
    b) Results of resistance testing (if performed)
    c) Clinic visit dates with corresponding height and weight measurements
    d) History of opportunistic infections and hospital admissions

3.2 Study population

The study population consists of PHIV adolescents and young adults attending the Adolescent Infectious Diseases Clinic at Groote Schuur Hospital (GSH) in Cape Town. This is a tertiary-

level clinic in an urban setting. The ART programme was initially funded and implemented by a NGO (Kidzpositive) in 2002, and was taken over by the Department of Health during 2004.

3.3 Inclusion and exclusion criteria

Inclusion criteria for study participants:

- ART initiation at the GSH out-patient clinic
- Alternatively, ART initiation in the GSH paediatric ward as an in-patient, provided follow-up care occurred at the GSH clinic
- age <12 years at ART initiation (the maximum age at the time for referral to the paediatric services; also serves as a proxy for perinatal route of infection)
- ART initiated between 13 May 2002 (inception of the ART programme) and 31 December 2005
- Attendance at the GSH clinic for a minimum of 10 years from ART initiation date
- Previously ART-naïve, with the exception of possible nevirapine exposure as part of the PMTCT programme which was implemented from 1999 in the Western Cape (Johnson, 2009:2)
- Children who initiated care at the clinic as part of a clinical research study will be included, provided that the study was a pharmacokinetic study and not a study comparing the effectiveness of different antiretroviral treatments or other interventions

Exclusion criteria: those who were not in care at the clinic at least 10 years after ART initiation, due to death, loss to follow-up (LTFU) or transfer of care to another institution will be excluded.

3.4 Expected number of participants

Participants will be identified from the clinic's enrolment register and attendance database. A preliminary assessment shows that 354 children enrolled for ART initiation between 13 May 2002 and 31 December 2005. Of these, 29 (8%) died, 52 (15%) were LTFU and 147 (42%) were transferred to another facility. The remaining 126 (35%) remain in active care and will form the cohort for the study. These figures are estimates; the eligibility of each participant will be assessed when the medical records are reviewed. A sample size calculation is shown in Box 1.

3.5 Study procedures and data collection methods

The required clinical data will be collected retrospectively by the study researcher (Kim Anderson), from the patients' medical records stored in the clinic. Information will be captured from the time of ART initiation up until and including 31 December 2015. The following information will be extracted from the records:

- date of birth
- gender
- PMTCT antiretroviral history
- ART regimen used at initiation (drug names and formulations)
- any drug changes made thereafter, with corresponding dates and reasons for changes
- resistance test results if performed
- CD4 results at ART initiation (absolute counts and percentages), and all subsequent CD4 results
- all available VL results (absolute values and log values)

- clinic visit dates
- growth measurements: heights and weights
- history of opportunistic infections and hospital admissions

CD4 and VL tests were performed by the National Health Laboratory Service (NHLS), which is the public laboratory service provider in SA. Laboratory results will be checked on the NHLS database. The researcher will manually enter all the data directly onto prepared data sheets (appendix 2). The data sheets will not contain any patients' names, only an allocated study number. At a later stage, the data will be captured electronically and analysed. The research findings will be submitted to an appropriate journal for publication, most likely the *South African Medical Journal* or *PloS One.*

3.6 Data safety

The data sheets will not contain any patients' names, only an allocated study number. The collected data (manual and electronic) will be stored in a locked clinic office, accessible only by the researcher and 2 other clinic doctors. The list of patients' names linking them to their allocated study number will be kept in a locked cabinet in a locked office, separate from other study documentation and accessible only by the study researcher. Electronic data will be stored anonymously on the researcher's password-protected laptop computer. This will be kept on her person at all times during the day, and securely locked in her home at night. Computer data will be backed up weekly on a hard-drive which will be stored in a locked office.

3.7 Data analysis

Continuous and categorical variables will be summarised using medians and interquartile ranges and proportions respectively. The primary outcomes, VL and CD4 trajectories, and factors associated with different trajectories, will be examined using survival analysis. Cox modelling will be used to examine probability of VF and predictors of VF, with variables for inclusion in the models selected a priori. Statistical analysis will be performed using Stata 14.0.

3.8 Definitions

- Viral suppression will be regarded as VL < 400 copies/ml
- Viral failure will be defined as two sequential VL > 1000 copies/ml that were taken between 14-365 days apart and were not measured during a treatment interruption
- CD4 results will be recorded as both absolute counts and percentages. WHO (2007) age-related classification of immunosuppression will be used (see appendix 3)
- Opportunistic infections characteristic of stage 3 and 4 HIV infection will be recorded (see appendix 4)
- Changing from first- to second-line therapy will be defined as changing at least 2 ART drugs in the regimen, one of which is a class switch from NNRTI to PI or PI to NNRTI, where the reason for changing drugs is not documented to be toxicity and the child was not virally suppressed at the time of switch
- When genotypic resistance data is available, it is reported as predicting low, intermediate or high level resistance to specific ART drugs. Drug resistance will be defined as intermediate- or high-level resistance

- LTFU will be is defined as when the last visit was >6 months before database closure in a child not known to have transferred out or died

4. Strengths and limitations

- **Strengths** of the study include the long follow-up period and that it will reflect real-world examples rather than trial settings. The extended time frame will allow for some patients to be included who might have previous gaps in care and might have been considered LTFU at an earlier stage, as some patients cycle in and out of care.
- **Limitations** of the study include the small study size, the retrospective study design and that the data comes from a single study site in a tertiary institution. In addition, since the study focuses on children on ART for at least 10 years at the same site, there is a survival bias in this cohort. Nevertheless, it is precisely this surviving group of PHIV adolescents that one wants to describe in order to improve their management during adolescence and transition to adulthood. Selection bias is a factor through LTFU among participants. There may be reduced external validity due to the fact that this is a tertiary care cohort, and that within SA the model of retaining children at a separate paediatric tertiary facility is unusual. Also, the children who have accumulated 10 years of follow up are those who started earlier in the ART programme, many of whom might have been generally known to the clinic and adherent before ART became widely available, and are therefore possibly different to children who started later in the programme. Some variables that may be related to the risk of developing VF (e.g. caregiver factors, disclosure, depression, neurocognitive deficits) are not explored in this study, but could be analysed in a further study.

5. Ethics

- **Ethical review:** The study protocol, data collection tools and other requested documents will be submitted for review and approval by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC).
- **Risks:** There is minimal risk to participants due to the nature of the study. There will be no direct contact with participants during the data collection process; all data will be gathered by retrospective review of medical records. The risk of loss of confidentiality will be minimised by keeping the captured data anonymous and storing data safely as described. Personal and sensitive information may be viewed in the patients' folders during the course of data extraction, but as the researcher who will collect the data currently works as a doctor at the clinic, it would fall within the scope of her daily work to access this type of information when consulting with patients, whilst maintaining patient confidentiality. The researcher has received training on issues of confidentiality (Good Clinical Practice training course completed in SA, and the National Institutes of Health "Protecting Human Research Participants" course) and will ensure every effort is made to maintain confidentiality.
- **Benefits:** There will be no direct benefits to the participants of the study, however the knowledge gained from the study will contribute to knowledge of treatment outcomes in adolescents and young adults with PHIV. This will help to optimise the management of PHIV adolescents and may help motivate for better second- and third–line treatments to be made available. Managers of the GSH clinic and the populations served by the clinic stand to benefit from the knowledge gained, as well as other programmes managing PHIV adolescents in the region.

- **Confidentiality:** The data sheets will not contain any patients' names, only an allocated study number. Data will be stored anonymously in a locked clinic office. The list of patients' names linking them to their study number will be kept in a locked cabinet in a locked office, separate from other study documentation and accessible only by the study researcher, in order to achieve a higher level of privacy. Data will be stored for 2 years after publication, after which time: all paper documents will be shredded and all digital files permanently deleted from all locations.

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Table 1: Studies of long-term outcomes in perinatally-HIV-infected children receiving antiretroviral therapy in countries other than South Africa

Study	Origin	Number of participants	Median follow-up/ART duration (years)	Proportion with viral suppression	CD4 count >500 cells/µl or >25%	Proportion on second-line ART or beyond
Patel et al. (2008)	USA	1236	3	NR	36-59%	NR
Dow et al. (2014)	Tanzania	161	4	73%	NR	41%
Bunupuradah et al. (2015)	Thailand	840	6	68%	69%	NR
Chokephaibulkit et al. (2014)	Asia	1061	6	68%	70%	15%
Cruz et al. (2014)	Brazil	260	7	57%	NR	63%
Souza et al. (2010)	Brazil	49	9 *	53%	82%	NR
Dollfus et al. (2010)	France	210	15	56%	59%	NR
De Mulder et al. (2012)	Spain	112	16	56%	55%	64%

Abbreviations: ART=antiretroviral therapy; USA=United States of America; NR=not reported. *mean

Table 2: **Studies of outcomes in perinatally-HIV-infected children receiving antiretroviral therapy in South Africa**

Study	Number of participants	Follow-up period	Proportion with viral suppression	CD4%	Proportion on second-line ART or beyond
Porter et al. (2015)	4945	1 year (median 11 months)	56%	NR	NR
Davies et al. (2009)	6078	3 years (median 16 months)	82%	30% (median)	NR
Davies et al. (2011)	5485	3 years (median 16 months)	NR	NR	6% probability
Morsheimer et al. (2014)	613	3 years (median 28 months)	85%	17% (mean)	NR

Abbreviations: ART=antiretroviral therapy

Table 3: Gantt chart of project management

STAGE OF STUDY	2015		2016												2017							
	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG
APPLICATIONS FOR APPROVAL	X	X	X																			
MANUAL DATA COLLECTION			X	X	X	X	X	X														
ELECTRONIC DATA CAPTURING								X	X	X	X	X	X	X								
STATISTICAL ANALYSIS														X	X	X	X	X	X			
PREPARATION FOR PUBLICATION															X	X	X	X	X	X	X	
SUBMISSION FOR PUBLICATION																					X	X

Box 1: Sample size calculation

Viral suppression is the primary outcome, and the hypothesis is that viral suppression will be found in 50% of cases. There will be approximately 100 children on the study, with at least 1 viral load in the adolescent period (or after 10 years on ART). In order to detect if it is much higher than 50%, say 65%:
Stata command: sampsi 0.5 0.65, n1(100) onesample
Output: Estimated power for one-sample comparison of proportion, to hypothesized value
Test Ho: p = 0.5000, where p is the proportion in the population

Assumptions: alpha = 0.05 (two-sided)
alternative p = 0.65
sample size n = 100

Estimated power: power = 0.8622
So a sample of at least 100 children will have at least 85% power to detect if the proportion of children with viral suppression is at least 15 percentage points more than 50% with significance of 0.05.

PART B: LITERATURE REVIEW

1. Background

There are currently an estimated 320 000 children under the age of 15 living with HIV in South Africa.[1] Due to a combination of recent success in preventing new vertical infections and success of paediatric ART programmes in improving life-expectancy in PHIV children, the burden of paediatric HIV in SA has changed to older children. This effect is projected to increase further by 2020 as PHIV children age into late adolescence.[2] Information on long-term treatment outcomes (including virologic, immunologic and growth outcomes) in this unique group of highly treatment-experienced adolescents in SA is very limited. Adolescence in general is a period characterised by physical, emotional and psychological change. It is associated with developing autonomy and sexuality, questioning authority, greater peer influence, increased impulsivity and risk taking.[3] Adolescents with HIV are at high risk of poor ART adherence, drug resistance and viral failure. Barriers to adherence can include the normal psychosocial changes of adolescence, busy schedules (school and social), treatment fatigue, high pill burdens, complex twice-daily regimens, drug side-effects and disclosure issues.[3] Youths reported “forgetting, not feeling like taking medication and not wanting to be reminded of HIV infection”[4] as common barriers to ART adherence. In addition, socioeconomic difficulties related to orphanhood and stigma, as well as HIV-related behavioural and neurocognitive consequences can adversely affect adolescent adherence.[5]

Although there is an increasing population of PHIV children on ART reaching adolescence and young adulthood, healthcare systems are often lacking in preparedness to deal with their complex and evolving needs. Psychosocial support services can significantly improve outcomes in these youths,

but in Africa HIV services dedicated to young people and their needs are scarce.[6] Mark et al.[7] surveyed HIV services for adolescents in sub-Saharan African countries and found that almost two-thirds attended to adolescents together with adults and/or children, and half had no protocols for transitioning adolescents. Globally, more research is needed to investigate transition practices from childhood to adolescent care and adolescent to adult care.[8]

In addition to healthcare system limitations, there are treatment limitations. When viral failure occurs, there are restricted second- and third-line ART options available in SA, particularly when PIs have been used in the first-line regimen. Since national roll-out of ART started in SA in 2004, PI-based first-line therapy has been recommended for all children starting treatment at <3 years of age. Further therapeutic challenges arise in children who have failed PMTCT with exposure to NNRTIs.[9] Access to alternative ART options, for example integrase inhibitors and newer PIs, is limited in SA.

To inform the proposed study of PHIV adolescents who initiated ART >10 years ago at a facility in South Africa, this literature review aims to describe what is known about long-term treatment outcomes in PHIV children on ART to date.

2. Objectives of the literature review

The main objective of the literature review is to examine articles that report on long-term growth, immunologic and virologic outcomes (including drug resistance) in PHIV children and adolescents on ART.

3. Literature search strategy

Eligibility criteria for articles were systematic reviews, observational or experimental studies published prior to 1 January 2018, that reported on treatment outcomes in cohorts that included predominantly (>50%) PHIV children, adolescents or young adults treated with three-drug ART (mostly from at least 2 classes), or that reported separate outcomes in PHIV participants as a subset of a larger cohort. Studies that reported on virologic and/or immunologic outcomes were included if the mean/median follow-up duration was a minimum of 5 years or longer. Due to the paucity of long-term studies in SA, studies were included if SA outcomes were reported for a minimum of 3 years. Similarly, due to the shortage of studies reporting growth outcomes, specifically end of study height-for-age Z-scores (HAZ), articles were included if growth was reported for a minimum of 3 years on ART. If the duration of follow-up or ART was not reported, studies were included if median age of PHIV adolescent cohorts on ART was >10 years at analysis, as a proxy for long-term care.

The literature was searched through the PubMed database using the search terms shown in Box 1. Separate searches were conducted to identify studies on (i) immunologic and virologic outcomes and (ii) growth.

Box 1: Pubmed search terms used for literature

(HIV infections[MeSH] OR HIV[MeSH] OR HIV OR HIV1 OR HIV2 OR Human immunodeficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus) AND (Perinatally OR perinatal OR prenatal OR postnatal OR antenatal OR vertically infected) AND (Adolescent[MeSH] OR Child[MeSH] OR Adolescence OR adolescent OR adolescents OR teenagers OR teen OR youths) AND (Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiretroviral OR anti-retroviral OR antiviral OR anti-HIV agents OR ART OR ARV OR HAART)

in combination with the following terms (as 2 separate searches):

(i) AND (Treatment outcome[MeSH] OR Outcome OR effectiveness OR efficacy OR prognosis OR prognostic OR Viral load[MeSH] OR CD4 Lymphocyte Count[MeSH] OR Viral load OR CD4)

(ii) AND (Human Development[MeSH] AND Body Size[MeSH] AND Growth OR development OR BMI OR body mass index OR height OR Z-scores OR weight)

4. Results of literature search

I identified 34 studies that described long-term immunologic, virologic or growth outcomes (14 studies in HIC and 20 in LMIC). Among these studies, 29 reported long-term virologic and/or immunologic outcomes: 14 in HIC with outcomes ≥5 years' follow-up duration (of which 6 had ≥10 years follow-up duration); 9 studies in LMIC other than SA with outcomes ≥5 years; and 6 studies in SA with outcomes ≥3 year (Table 1A-D). Ten studies reported growth outcomes ≥3 years' follow-up/ART duration: 1 in a HIC, 3 in SA and 6 in other LMIC (Table 2). In addition to the 34 articles that described long-term ART outcomes that were systematically reviewed, in order to better understand viral outcomes I selectively drew on articles that described resistance and factors associated with virologic outcomes in children and adolescents.

5. Long-term virologic and immunologic outcomes in high income countries

The introduction of effective combined ART from 1996 in HIC resulted in the face of HIV slowly changing to a chronic illness. Many PHIV children have aged up to adolescence and beyond, and transitioned to adult care. There were 14 studies reporting virologic and immunologic outcomes from HIC: 7 from the US,[10–16] 1 from Canada,[17] 2 from the UK and Ireland [18,19] and 4 from other European countries.[20–23] Although several studies reported viral and immunological outcomes in PHIV cohorts on ART, very few (n=6) reported outcomes after more than a decade of treatment (Table 1A).

The six studies that reported outcomes after ≥10 years, had median duration of patient follow-up of 11 – 16 years (which was not necessarily the duration since ART start). Sample size varied from 112 – 654 patients. Median age at ART start varied from 6 – 10 years in 5 studies, but was <1 year in one US study. Median age at analysis was 12 – 19 years. Median/mean CD4 at study endpoints ranged from 444 – 720 cells/µl, while percentage with optimal immune status (defined in all studies as CD4 count >500 cells/µl in those age ≥ 5 years) ranged from 42 – 59%. Viral suppression at study endpoints was fairly poor, varying from 37 – 57% in 4 studies. Viral suppression was higher in a US study (68%) which had a much younger median age at ART start (<1 year), and better results were reported in a UK cohort (78% of those on ART were virally suppressed), but only 61% of the cohort were on ART. Cohorts of PHIV patients usually include patients who are not on ART, either due to delays in starting ART or, more commonly, due to patients interrupting treatment.

Given the limited number of studies available reporting outcomes after >10 years of follow-up, these will be described in some detail. Dollfus et al.[21] followed up the French Perinatal Cohort of PHIV children born between 1985 and the end of 1993. Out of 348 children, 210 (60%) remained in care after a median 15 years of follow-up since birth. In this cohort, at the most recent evaluation, viral suppression (VL <500 copies/ml) was achieved in 56% and optimal immune status in 59%. The most recent regimens used included PIs (75%), NNRTIs (31%) or both PIs and NNRTIs (11%).

Two studies described cohorts at the time of transfer to adult care.[18,20] De Mulder et al. reported on a Spanish cohort of 112 PHIV children who were followed-up for a median 15.6 years. VL was ≤500 copies/ml in 56% and optimal immune status was recorded in 55%. The lifetime mean number of ART regimens used was 5, with 64% having triple class experience. Collins et al. reported on the outcomes of 644 adolescents (91% PHIV) in the UK and Ireland. Median duration of follow-up in paediatric care was 10.9 years and median duration since ART initiation was 7.8 years. Median CD4 was 444 cells/µl and 42% had optimal immune status. Overall, 57% of patients were virally suppressed (VL <400 copies/ml) at transfer, whereas 74% of those on ART at transfer (357/481) were virally suppressed.

In the US, Van Dyke et al.[11] reported better outcomes in 451 PHIV children and adolescents from multiple sites where median duration of ART was 11.4 years and median age at ART start was younger (< 1 year) than in the European studies. At last assessment, median CD4 count was 728 cells/µl, 78% had a CD4% ≥ 25% and viral suppression occurred in 68% of the cohort (VL ≤ 400 copies/ml). In another US study, worse outcomes were reported by Kahana et al.[10] in a cross-sectional cohort of 649 older PHIV youths (median age 18 years vs 12 in Van Dyke study) with a similar median follow-up of 11.3 years since HIV diagnosis. Mean CD4 count was 541, and 37% of patients had undetectable VL.

Among the 8 studies with <10 years or unreported follow-up duration, only 4 studies included >50 participants (Table 1B).Median/mean age at study ranged from 15 - 26 years and the proportion virally suppressed was generally low, ranging from 31 - 65%, except for one small Swedish transitional study which was higher.[22]

Among those in cohorts who had resistance test results available (34 – 52% of individual cohorts), resistance prevalence was high, ranging from 73 – 82% resistance to at least one drug class and triple class resistance in 12 – 17%.[18,20,24,25] However, a large proportion of youths in these studies (65% in one US study [24]) may have received single or dual antiretrovirals before receiving combination ART, increasing their risk of acquiring resistance mutations. Judd et al.[26] found a high risk of triple class VF in PHIV European teenagers age 10 – 14 years (nearly 30% after 5 years on ART), highlighting the vulnerability of this age group, while a UK study observed declines in CD4s prior to adult care transition, which was considered a possible reflection of growing autonomy and worse adherence during adolescence.[27]

Results describing PHIV cohorts in HIC are limited and demonstrate generally poor outcomes. However, these results may not be generalizable to LMIC, including South Africa, as many children in the HIC cohorts were on the one hand exposed to older, less efficacious regimens in the 1990s, while on the other hand they were likely to have had access to a wider range of antiretrovirals and more tailor-made regimens in the 2000s, compared to the public health approach for children in LMIC.

6. Long-term virologic and immunologic outcomes in low and middle income countries other than South Africa

There is no published data on treatment outcomes in LMIC for 10 years or longer. This may be due to delays in the roll-out of ART programmes in LMIC, with limited numbers of survivors of paediatric HIV beyond 10 years of age and limited access to laboratory testing in ART patients. A survey of HIV treatment services for adolescents in 218 facilities in 23 sub-Saharan African countries found that VL was monitored in less than half of facilities.[8] The key challenges in adolescent service provision reported by the facilities surveyed were treatment failure and non-adherence. If children and adolescents are seen together with adults in integrated clinics they may be less easy to monitor as a distinct group, while movement of patients between facilities may also hamper efforts to track long-term outcomes.

There were 9 studies reporting virologic and immunologic outcomes after ≥5 years of follow-up from LMIC other than SA (3 in South East Asia,[28–30] 3 in Brazil [31–33] and 3 in Africa [34–36]), with outcomes reported between 5 – 9 years follow-up duration (see Table 1C). Sample size varied from 49 – 1061 patients. Median age at ART start varied from 4 – 9 years, similar to most of the HIC studies, whereas median age at analysis was younger (9 – 15 years) due to shorter follow-up duration. Median/mean CD4 at study endpoints ranged from 622 – 829 cells/µl, while percentage with optimal immune status ranged from 69 – 82%. Viral suppression at study endpoints varied between 53 – 68%. These immunologic and virologic outcomes were better than those reported in HIC studies of longer duration, most likely because of shorter follow-up durations. Declining outcomes with increasing duration may be expected in these cohorts.

Systematic reviews of paediatric ART outcomes highlight the paucity of data on long term outcomes. Sutcliffe et al.[37] in a review on the effectiveness of ART in children in sub-Saharan Africa, found viral suppression was achieved in 47 – 83% of children at 3 years after ART start, and that 71 – 85% of children with resistance to at least one class of drugs failed to achieve viral suppression. A systematic review of outcomes of ART in children in LMIC compared with HIC reported favourable and comparable increases in CD4% and declines in VL, although the results reported were after only 12 months and mean baseline CD4% in LMIC vs HIC was 12% compared with 23%.[38] Starting ART with differing disease severity makes global comparisons of treatment outcomes difficult. Similarly, Davies et al.[39] in a review of published clinical studies on paediatric ART programmes in sub-Saharan Africa found that although virologic and immunologic outcomes were comparable with HIC, the duration of follow-up was mostly limited to one year.

A review exploring viral resistance in children failing first-line regimens in LMIC (mostly in sub-Saharan Africa) found resistance rates of 88% for NNRTIs, 80% for NRTIs, and 54% for PIs – similar to those reported in European settings.[40] Overall, resistance-associated mutations were found in 90% of children who had failed first-line ART. The risk of resistance was observed to increase with increased ART duration. High prevalence of multi-drug resistance has been seen in both HIC and LMICs.[41] Increased implementation of PMTCT measures may account for higher prevalence of NNRTI resistance in some studies. Jordan et al.[42] found high rates of NNRTI resistance (53%) pre-treatment in children in sub-Saharan African countries exposed to NNRTIs through PMTCT.

In a recent cohort of 125 PHIV children and adolescents failing ART in Togo, the proportion with drug resistance mutations was high (94%), largely due to resistance to both NRTIs and NNRTIs (88%).[43] Similar findings were observed in a Tanzanian study of 213 children. Among those with VF (25%),

drug resistance mutations were found in 90%, while multi-class resistance occurred in nearly 80%.[44] Such high rates of resistance are concerning, particularly in LMIC where access to alternative drugs is very limited.

7. Long-term virologic and immunologic outcomes in South Africa

The SA national ART programme commenced in 2004. Some sites delivered ART before this, funded by NGOs. Despite the rapid scaling-up of ART programmes in SA over the last decade, there is little local information on the long-term outcomes in PHIV children on ART. Six studies reported virologic and immunologic outcomes,[45–50] mostly at urban centres (see Table 1D). Outcomes were reported between 3 – 8 years follow-up and sample size varied from 126 – 515 children in 5 studies, while one collaborative cohort included 6078 patients. Median age at ART start ranged from 4 - 11 years, similar to other LMIC and HIC studies. Median age at analysis (12 – 17 years), as well as immunologic and virologic outcomes, were similar to studies in other LMIC. CD4 medians at study endpoints ranged from 636 – 713 cells/µl, while only one study reported a percentage with optimal immune status (64%). Viral suppression at study endpoints varied from 69% (after 6 years median follow-up) to 82% (at 3 years).

Davies et al.[50] reported on a large collaborative cohort of 7 International epidemiologic Databases to Evaluate AIDS (IeDEA) SA sites consisting of 6078 children who, after 3 years on ART, achieved viral suppression (VL <400 copies/ml) in 82% and a median CD4% of 30%. These results are satisfactory, but the follow-up duration was very limited. In 5485 children from the same sites, a 19% probability of VF (confirmed VL >1000 copies/ml) and a 6% probability of changing to second-line ART by 3 years

was found.[51] Further analysis of the large IeDEA cohort may provide future insights, but no longer-term outcomes have yet been published.

A few smaller cohorts have reported outcomes in young adolescents after 6 – 8 years on ART. A cross-sectional study of 474 PHIV young adolescents in Cape Town, median age 12 years and median duration of ART use 7.5 years, showed favourable outcomes of median CD4 count of 710 cells/µl and VL <50 copies/ml in 76%,[45] although this cohort was recruited during late childhood/early adolescence for research and is not likely to fully represent outcomes in routine care. An adherence study among 126 adolescents in Johannesburg, aged 12 – 20, reported viral suppression in 69% after 6.3 median years ART duration.[49] A lower proportion of those in older adolescent categories (62% for 15-17 years and 68% for 18-20 years) experienced viral suppression compared to those aged 12-14 years (74%), highlighting that older adolescents appear to be particularly vulnerable, although the proportion of the cohort PHIV was not recorded. A study among 241 PHIV adolescents and young adults in Durban with median ART duration of approximately 6 years had better prevalence of viral suppression in 81%.[48]

8. Factors associated with viral failure in children and adolescents

In addition to ART adherence, a variety of factors have been associated with VF or elevated VL in PHIV children and adolescents in the literature. A number of individual socio-demographic and clinical factors have been reported to be associated with poor viral outcomes. Male gender was a risk factor in several studies,[21,45,52] although one study found female gender was a significant predictor.[10] In the US and France, racial or ethnic factors predicted poor viral outcomes,[10,16,21] but this is likely very context-specific and linked to social vulnerability. Lower CD4% at ART initiation

[53], lower current CD4 count,[18,21,28] lower CDC staging [18,20,52], higher VL (>1 million copies/ml) at ART initiation [51] and wasting [54] have been shown to predict worse virologic outcomes. Having preadolescent VF was a predictor of post-suppression virologic rebound (VL >1000 copies/ml) in an Asian adolescent cohort.[54] Belonging to cohorts from earlier calendar periods,[10,53] younger age at ART initiation [29] and older current age [10,16,45,53,55] have been associated with increased risk of elevated viral load. Socioeconomic predictors include lower level of education,[55] living out of a main urban area [52] or being raised by grandparents.[54]

Treatment-related factors associated with poor viral outcomes include previous exposure to PMTCT regimens,[51] previous non combination-ART,[18,53] increased number of previous ART regimens [10] and receiving second-line regimens.[30,54] Use of nevirapine versus lopinavir with ritonavir,[56] use of nevirapine versus efavirenz [51] and use of ritonavir as a single PI [51,57,58] are all associated with worse virologic outcomes. Both nevirapine and ritonavir (as a single PI) were commonly used as the "third drug" part of first-line paediatric regimen options in early treatment guidelines. Factors related to healthcare settings associated with elevated VL include down-referral after ART initiation in hospital versus starting ART in the primary healthcare system,[59] attending a standard paediatric clinic versus an adolescent clinic [48] and transitioning to adult care.[55]

9. Growth outcomes

Growth deficits are common in PHIV children and adolescents, and are associated with a variety of factors including malabsorption, micronutrient deficiency, impaired growth hormone production, symptomatic HIV infection, inflammation and viraemia.[60] Slow weight gain and height deficits occur frequently in PHIV children and may result in stunting and reduced final height.[61] This effect

has been seen more profoundly among African children compared with those in HIC,[62] and, once stunted, sufficient catch-up growth may not occur in order to reach normal height. In addition, long-term ART use of particular ART drugs can lead to changes in body composition, with 30 – 70% of children on ART experiencing fat redistribution,[60] which may be disfiguring and stigmatising.

Pubertal delay is characteristic of PHIV. Szubert et al.[63] measured height growth and Tanner staging in 620 adolescents in Uganda and Zimbabwe, and found a considerable delay in pubertal stages, associated with initiating ART at older ages. In addition, growth was observed to continue until later in adolescence, which may be a possible benefit to delayed puberty, as there is potential for further catch-up linear growth. A systematic review of growth reconstitution following ART in HIC versus LMIC by McGrath et al.[64] found that LMIC children were substantially shorter at ART initiation (HAZ −2.2 vs. −0.9), despite comparable age. Children in LMIC maintained worse height outcomes at 2 years, despite marked improvements following ART initiation, attributed to baseline differences that did not recover. However, the duration of studies compared in the review were short overall.

Ten studies were identified that described growth (HAZ) outcomes ≥ 3 years follow-up/ART duration (1 in a HIC [21]; 6 in LMIC other than SA [29,30,65–68]; and 3 in SA [47,50,69]) (see Table 2). The only study that reported growth outcomes after more than a decade of follow-up was a French study in which HAZ was normal (median -0.02) at median age of 15 years.[21] The remaining 9 studies from LMIC (including SA) had follow-up duration ranging from 3 – 8 years, while age at analysis varied from 12 – 18 years (but was not reported in 6 of the studies). Median/mean HAZ at ART initiation varied from -3.12 to -2.2, and at study completion varied from -2.33 after 3 years on ART to -1.04 after 6 years on ART. Despite HAZ improvements over time, in all the studies in LMIC, PHIV adolescents continued to be at least one standard deviation below normal height. The few studies that reported

on BAZ showed mean values within normal ranges, demonstrating that although stunting is common in PHIV children, body mass index is less severely affected.

Gsponer et al.[68] examined growth response up to 3 years after starting ART in 17 990 children in 5 Southern African countries, including SA. At ART initiation, a large proportion were underweight (50%) and stunted (66%). Baseline Z-scores were found to be the most important predictors of growth response. Bunupuradah et al.[67] analysed final heights reached in 273 PHIV Asian adolescents at age 18. Median HAZ at ART initiation was -2.22, which improved to -1.51 at age 18. By World Health Organization standards, 19% were stunted at age 18. Half of the children who were stunted at ART initiation remained stunted. However, most started ART late with median age at ART initiation of 11.4 years. Among the largest cohort reported in SA (6078 children from different sites), median age at ART initiation was 3.6 years and median HAZ was -2.34.[50] Median HAZ of -1.32 was reported at 3 years since ART initiation but longer-term outcomes including final height have not yet been published for this SA cohort.

10. Study rationale

There is very limited information on long-term outcomes in PHIV adolescents on ART. Although some of the figures reported for viral suppression in PHIV cohorts in South Africa are encouraging, the follow-up time in these studies is limited. Longer durations on ART, in conjunction with sub-optimal adherence and accumulation of resistance mutations, may lead to a decline in viral suppression. Although national paediatric ART programmes were implemented in SA over a decade ago, the long-term outcomes of PHIV children after ≥ 10 years on ART have not yet been reported. Describing the ART history and outcomes in treatment-experienced adolescents and young adults can help clinicians

to anticipate future therapeutic challenges and plan ahead. Insight into the prevalence of viral suppression, VF, viral resistance, immune reconstitution and factors associated with VF can provide important information to guide health care providers in the management of this group, before, during and after their transition to adult care. This study aims to provide information on long-term treatment outcomes in a cohort of PHIV adolescents on ART for ≥10 years, which can contribute significantly to available knowledge, and may help to optimise the future management of this group.

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Table 1: Characteristics of studies reporting long-term virologic and immunologic outcomes in perinatally-HIV-infected adolescents

TABLE 1A: STUDIES FROM HIGH INCOME COUNTRIES WITH >10 YEARS FOLLOW-UP

Reference	Year of public-ation	Location and time of study	Design	Sam-ple size	Median follow-up/ART (years)	Median age at ART start (years)	Median age at analysis (years)	Median CD4% at ART start	Median CD4 (cells/µl) at end of study (IQR)	% with CD4 ≥500 cells/µl	% with viral suppression at end of study	VL threshold for suppression (copies/ml)
Collins [18]	2017	UK and Ireland 2000 - 2014	PC	644	10.9	9.6	17.4	NR	444 (280 - 643)	42%	57%	<400
Kahana [10]	2015	USA 2009 - 2012	CS	649	11.3 (since HIV diagnosis)	NR	17.9	NR	541 (mean)	NR	37%	various
De Mulder [20]	2012	Spain 1997 - 2011	RC	112	15.6	5.6	18.9	NR	627 (mean)	55%	56%	≤500
Van Dyke [11]	2011	USA 2007 - 2009	RC	451	11.4	0.8	12.2	NR	728 (530 - 966)	NR	68%	≤400
Dollfus [21]	2010	France 1985 - NR	PC	210	15 (follow-up; since birth)	7.5	15	NR	557 (382 - 861)	59%	56%	<500
Foster [19] (same cohort as Collins [18])	2009	UK and Ireland 1996 - 2007		654	2 groups (11.4 and 5.1)	9	NR	13%	555 (324 - 802)	NR	Among the 61% of cohort on ART, 78% were suppressed	≤400

ART:antiretroviral therapy, IQR:interquartile range, VL:viral load, UK:United Kingdom, USA:United States of America, NR:not recorded, PC:prospective cohort, CS:cross-sectional, RC:retrospective cohort

Note: overall cohort statistics provided where available; years reported to one decimal place unless reported without a decimal in the articles

TABLE 1B: STUDIES FROM HIGH INCOME COUNTRIES WITH <10 YEARS FOLLOW-UP OR UNREPORTED DURATION												
Reference	**Year of public-ation**	**Location and time of study**	**Des-ign**	**Sample size**	**Median follow-up/ART (years)**	**Median age at ART start (years)**	**Median age at analysis (years)**	**Median CD4% at ART start**	**Median CD4 (cells/µl) at end of study (IQR)**	**% of cohort with CD4 ≥500 cells/µl**	**% of cohort with viral suppression at end of study**	**VL threshold for suppression (copies/ml)**
Neilan [12]	2017	USA 2015 - 2017	PC	1446	4.9 (mean follow-up; on ART prior to study)	NR	14.6 (mean)	NR	712 (mean)	NR	65%	<400
Ryscavage [13]	2016	USA 2004 - 2012	RC	19	NR	NR	26.3	NR	432	NR	31%	<400
Westling [22] (91% PHIV)	2016	Sweden 2013-2015	CS	34	9	NR	19	NR	NR	NR	Among the 88% of cohort on ART, 100% were suppressed	<400
Berry [14]	2015	USA 2010	CS	141	7	NR	20	NR	560 (320 - 909)	NR	61%	<400
Mirani [15] (87% PHIV)	2015	USA 2000 - 2014	PC	1201	3.7 (follow-up; ART duration not reported)	NR	20.9	NR	580 (325 - 822)	NR	NR (33% had VL>1000 during follow-up)	NR
Agwu [16]	2013	USA 2002 - 2010	RC	521	NR	NR	18.0	NR	NR	58%	63%	<398
Van Der Linden [17]) (71% PHIV)	2012	Canada 1999 - 2011	RC	45	NR	NR	18.1	NR	NR	NR	42%	<50 or <500 (various)
Bracher [23]	2007	Denmark 1996 - 2005	RC	49	5.0 (mean)	6.7	NR	14%	NR	NR	55% at 7 years	<500

ART:antiretroviral therapy, IQR:interquartile range, VL:viral load, USA:United States of America, NR:not recorded, PC:prospective cohort, CS:cross-sectional, RC:retrospective cohort, PHIV:perinatally HIV-infected

Note: overall cohort statistics provided where available; years reported to one decimal place unless reported without a decimal in the articles

TABLE 1C: STUDIES FROM LOW AND MIDDLE INCOME COUNTRIES EXCLUDING SOUTH AFRICA												
Reference	**Year of public-ation**	**Location and time of study**	**Design**	**Sam-ple size**	**Median follow-up/ART (years)**	**Median age at ART start (years)**	**Median age at analysis (years)**	**Median CD4% at ART start**	**Median CD4 (cells/µl) at end of study (IQR)**	**% of cohort with CD4 ≥500 cells/µl**	**% of cohort with viral suppression at end of study**	**VL threshold for suppression (copies/ml)**
Fokam [34]	2017	Cameroon 2016	CS	145	7	NR	13	NR	NR	79%	71%	<50
Lorenzo [31]	2017	Brazil 2002 - 2013	RC	245	6.8	4.3	10.7	NR	NR	NR	60% of those on ART	≤400
Xu [28]	2017	Thailand 2010 - 2012	CS	568	5.9	9.0	14.4	NR	635 (441 - 859)	NR	82%	<1000
Cyamatare Rwabukwisi [35]	2016	Rwanda 2005 - 2008	RC	277	NR (5 year outcomes reported)	5.8	10.5	NR	NR	NR	86%	<1000
Bunupur-adah [29]	2015	Thailand 2008 - 2013	RC	840	5.6	NR	NR	NR	622 (411 - 838)	69%	68%	<50
Chokephai-bulkit [30]	2014	Asia: Thailand, Cambodia, Vietnam, Malaysia, Indonesia, India 1991 - 2011	RC	1061	6.0	8.8	14.7	7	657 (470 - 862)	70%	68%	<400
Cruz [32]	2014	Brazil 2009 - 2011	CS	260	7	NR	9.2	NR	NR	NR	57%	<50
Dow [36]	2014	Tanzania 2008 - 2013	CS and PC	161	6.4 (at first analysis)	NR	12.2	NR	829 (mean)	70%	66% at first analysis; 73% at 4 year follow-up	≤400
Souza [33]	2010	Brazil 2006 - 2007	CS	49	9.0 (mean)	4.9 (mean)	12.5 (mean)	NR	766 (mean)	82%	53%	<400

ART:antiretroviral therapy, IQR:interquartile range, VL:viral load, NR:not recorded, PC:prospective cohort, CS:cross-sectional, RC:retrospective cohort
Note: overall cohort statistics provided where available; years reported to one decimal place unless reported without a decimal in the articles

TABLE 1D: STUDIES FROM SOUTH AFRICA

Reference	Year of public-cation	Time of study	Design	Sample size	Median follow-up/ART (years)	Median age at ART start (years)	Median age at analysis (years)	Median CD4% at ART start	Median CD4 (cells/µl) at end of study (IQR)	% of cohort with CD4 ≥500 cells/µl	% of cohort with viral suppression at end of study	VL threshold for suppression (copies/ml)
Brittain [45]	2017	NR	CS	474	7.5	4.5	12.0	NR	710 (564 - 949)	NR	76%	<50
Davies [46] (69% considered PHIV)	2017	2004 - 2014	RC	460	5.5	8.4	12.8	12.8	636 (387 - 876)	64%	78%	<400
Githinji [47] (same cohort as Brittain[45])	2017	2013 - 2015	PC	515	7.6	5.0	12.0	NR	713 (561 - 958)	NR	NR	NR
Zanoni [48]	2017	2007 - 2015	RC	241	5.6	2 groups (11.2 and 9.4)	2 groups (17.3 and 16.0)	NR	NR	NR	81%	<400
Maskew [49] (proportion PHIV not reported)	2016	2013 - 2015	PC	126	6.3	NR	15	NR	NR	NR	69%	<400
Davies [50]	2009	1999 - 2008	PC	6078	1.3 (3 year outcomes reported)	3.6	NR	NR	NR	NR	82% at 3 years	<400

ART:antiretroviral therapy, IQR:interquartile range, VL:viral load, NR:not recorded, PC:prospective cohort, CS:cross-sectional, RC:retrospective cohort, PHIV:perinatally HIV-infected

Note: overall cohort statistics provided where available; years reported to one decimal place unless reported without a decimal in the articles

Table 2: Studies reporting long-term growth in perinatally-HIV-infected adolescents

Reference	Year of public-ation	Location and time	HIC/ LMIC	Design	Sample size	Median follow-up (years)	Median age at ART start (years)	Median age at analysis	Mean BAZ at ART start (SD)	Mean BAZ at study end (SD)	Median HAZ at ART start (IQR)	Median HAZ at study end (IQR)
Githinji [47]	2017	South Africa 2013 - 2015	LMIC	PC	515	7.6	5.0	12.0	NR	NR	NR	-1.3† (1.0)
Seth [65]	2017	India 2008 - 2014	LMIC	RC	103	NR (3 year outcomes reported)	6.8	NR	-1.18 (1.61)	-1.00 (1.11) at 3 years	-3.12† (1.36)	-2.33† (1.55) at 3 years
Boettiger [66]	2016	Asia* 2008 - 2014	LMIC	RC	534	3.6	11.8	NR	NR	NR	-2.3 (-3.6 to -1.4)	-1.6 after 5 years ART
Bunupura-dah [67]	2016	Asia* 2003 - 2013	LMIC	RC	273	7.3	11.4	18.0	NR	NR	-2.2 (-3.2 to -1.4)	-1.5 (-2.2 to -0.9)
Bunupura-dah [29]	2015	Thailand 2008 - 2013	LMIC	RC	840	5.6	NR	NR	NR	NR	NR	-1.04 (-1.96 to -0.18)
Chokephai-bulkit [30]	2014	Asia* 1991 - 2011	LMIC	RC	1061	6.0	8.8	14.7	NR	NR	NR	-1.71 (-2.5 to -1.0)
Shiau [69]	2013	South Africa 2005 - 2007	LMIC	RCT	195	NR (4 year outcomes reported)	0.9†	NR	-0.43 (2.11)	0.41 at 4 years	-3.12† (1.68)	-1.21† at 4 years
Gsponer [68]	2012	South Africa, Malawi, Zambia, Zimbabwe, Mozambique NR	LMIC	PC	17990	2† (3 year outcomes reported)	1.3 – 6.4 (range; reported by site;12 sites)	NR	NR	NR	-2.84 to -1.75 (range; reported by site)	NR
Dollfus [21]	2010	France 1985 - NR	HIC	PC	210	15	7.5	15	NR	0.02 (-1.02 to 1.26) median	NR	-0.02 (-0.85 to 0.86)
Davies [50]	2009	South Africa 1999 - 2008	LMIC	PC	6078	1.3 (3 year outcomes reported)	3.6	NR	NR	NR	-2.34 (-3.28 to -1.43)	-1.32 (-2.02 -to -0.6) at 3 years

HIC:high income country, LMIC:low/middle income country, SD:standard deviation, IQR:interquartile range, NR:not recorded, PC:prospective cohort, RC:retrospective cohort, RCT:randomised controlled trial, BAZ: body mass index for age Z-score, HAZ:height for age Z-score

Note: years reported to one decimal place unless reported without a decimal in the articles; WHO growth standards used for BAZ and HAZ; HAZ reported to two decimal places unless reported to one in the articles

*all 3 Asian studies were on the same collaborative cohort that included Cambodia, India, Indonesia, Malaysia, Thailand and Vietnam †mean (SD)

PART C: JOURNAL MANUSCRIPT

Treatment outcomes in perinatally-infected HIV positive adolescents and young adults after 10+ years on antiretroviral therapy

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Note: The journal manuscript is in keeping with requirements set out in the instructions for authors of South African Medical Journal (appendix 5).

A deviation, in keeping with instructions for the mini-dissertation, is that co-authors have not been listed. Their contributions, have been noted in the acknowledgements section of the mini-dissertation.

Conflicts of interest: None

1. Abstract

Background: The burden of paediatric HIV in South Africa has shifted to older children and adolescents. Nevertheless, information on long-term treatment outcomes of perinatally-HIV-infected (PHIV) children is limited.

Objectives: We examined long-term immunologic and virologic outcomes of children who were in care at least 10 years after starting antiretroviral therapy (ART).

Methods: We performed a retrospective cohort study of 127 PHIV children who initiated ART at a Cape Town clinic between 2002 and 2005, and had follow-up for ≥ 10 years from ART initiation date. CD4 counts and viral loads (VL) were analysed for each successive year on ART. Treatment history, resistance test results, growth data, hospital admissions and opportunistic infection history were described.

Results: At ART initiation, median age was 2.6 years (IQR 1.3 – 4.9) and mean CD4 percentage was 13.7% (95% Confidence Interval [CI] 13.6 – 13.9). The first ART regimen was non-nucleoside reverse transcriptase inhibitor-based (64%) or protease inhibitor-based (36%). Median follow-up was 12.2 years (interquartile range [IQR] 11.1 – 13.0). At the last assessment, 50% of patients were on 1st-line and 43% on 2nd-line ART. At the last assessment, median CD4 count was 686 cells/µl (IQR 545 – 859) and 79% had CD4 >500 cells/µl (92% of those on 1st-line vs 71% of those on 2nd-line ART; p=0.003). At the last assessment, 80% of patients were virally suppressed (VL <400 copies/ml) (86% of those on 1st-line vs 71% on 2nd-line ART; p=0.183).The 10-year probability of experiencing viral failure was 56.7% (95% CI 48.3 – 65.5%) and the 10 year probability of switching to 2nd-line ART was 45.7% (95% CI 37.5 - 54.8%). The probability of experiencing viral failure between the age of 10 and 18 was 37.4% (95% CI 25.4 – 52.8%).

Conclusions: Virologic and immunologic outcomes were good overall in PHIV children who remained in care for ≥10 years, but >40% of children were on 2nd-line ART with poorer immunologic outcomes. Maintaining virologic and immunologic control in adolescence presents a challenge.

2. Introduction

There are currently an estimated 320 000 children under the age of 15 years living with Human Immunodeficiency Virus (HIV) in South Africa (SA).[1] Due to a combination of recent success in preventing new vertical infections and success of paediatric antiretroviral therapy (ART) programmes in improving life-expectancy in perinatally-HIV-infected (PHIV) children, the burden of paediatric HIV in SA has changed to older children, and this effect is projected to increase further by 2020.[2] There is an increasing population of PHIV children on ART reaching adolescence in SA's health care system, yet information on long-term treatment outcomes in this unique group of highly treatment-experienced adolescents is very limited. Adolescence in general is a period characterised by physical, emotional and psychological change. It is associated with developing autonomy and sexuality, questioning authority, greater peer influence, increased impulsivity and risk taking.[3] Adolescents with HIV are at high risk of poor ART adherence, drug resistance and viral failure (VF). Barriers to adherence can include busy schedules (school and social), treatment fatigue, high pill burdens, complex twice-daily regimens, drug side-effects and disclosure issues.[3] In addition, socioeconomic difficulties related to orphanhood and stigma, as well as HIV-related behavioural and neurocognitive consequences can adversely affect adolescent adherence.[4]

Many PHIV children are reaching adolescence and beyond, transitioning to adult care, yet healthcare systems are often lacking in preparedness to deal with the complex and evolving needs of PHIV children as they age into adolescence and young adulthood. In Africa, HIV services dedicated to young people and their needs are scarce[5] and when viral failure occurs, there are limited second- and third-line ART options available, particularly when protease inhibitors (PIs) have been used in the 1st-line regimen in children. While several studies have reported on viral and immunological outcomes in PHIV cohorts on ART, few have reported the outcomes after more than a decade of treatment.[6-11] Viral suppression ranged from 37 – 68% and optimal immune status (CD4 count >500 cells/µl) ranged from 42 – 59% in these studies, which were all from high income countries. These studies may not be generalizable to low and middle income countries (LMIC), including SA, as many children in these cohorts were on the one hand exposed to older, less efficacious regimens in the 1990s, while on the other hand they were likely to have had access to a wider range of antiretrovirals and more tailor-made regimens than children in LMIC in the 2000s.

There are no published data on outcomes in PHIV children in LMIC on ART for 10 years or longer. Although national paediatric ART programmes were implemented in South Africa over a decade ago, the long-term outcomes of PHIV children on ART have not yet been described. This study aimed to contribute to available knowledge by describing local outcomes, which can aid in anticipating future challenges and planning further management in treatment-experienced adolescents and young adults. The main objective of the study was to describe long-term clinical, growth, immunologic and virologic outcomes in PHIV children on ART.

3. Methods

We conducted a retrospective cohort study of PHIV adolescents on ART. Primary outcomes were annual viral load (VL) and CD4 results. Secondary outcomes were ART regimen history, resistance test results, height and weight measurements, history of opportunistic infections and hospital admissions. The study population consisted of PHIV adolescents and young adults attending the Adolescent Infectious Diseases Clinic at Groote Schuur Hospital (GSH) in Cape Town. This is a tertiary-level clinic in an urban setting. The paediatric ART programme was initially implemented in 2002 by a non-governmental organisation (Kidzpositive), and was taken over by the Department of Health during 2004. Approval for the research was obtained from the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC Ref: 891/2015).

Participants were identified from the clinic's enrolment register and attendance database. Inclusion criteria were: (1) ART initiation at the GSH paediatric clinic or in the GSH paediatric ward (with follow-up at the clinic), (2) age <12 years at initiation (maximum age for referral to paediatric services; also serves as a proxy for perinatal route of infection), (3) ART initiation between 13 May 2002 (inception of the ART programme) and 31 December 2005, (4) attendance at the clinic for a minimum of 10 years since ART initiation date, including those who had previous gaps in care or had been transferred out but returned and were in care ≥10 years after ART start, (5) previously ART-naïve, with the exception of possible nevirapine exposure as part of the prevention of mother-to-child transmission programme implemented in the Western Cape from 1999 and (6) children who initiated care at the clinic as part of a clinical research study were included, provided that the study was a pharmacokinetic study

and not a study comparing the effectiveness of different antiretroviral treatments or other interventions. We excluded those who were not in care at the clinic at least 10 years after ART initiation, due to death, loss to follow-up (LTFU) or transfer of care to another institution.

Clinical data was collected from the patients' clinical records and laboratory results were obtained from the National Health Laboratory Service. Information was captured from the time of ART initiation until the censoring date when LTFU, death or transfer occurred or until the study ended on 31 December 2015 if still in active care. Data were compiled into Excel spreadsheets and uploaded to Stata version 14 for analysis. Kaplan-Meier survival analysis and Cox proportional hazard methods of analysis were applied to identify time to VF and factors associated with VF. Independent variables for inclusion in multivariable models were selected a priori.

Viral suppression was regarded as VL <400 copies/ml. Viral failure was regarded as two sequential VL >1000 copies/ml that were >24 weeks since ART initiation, taken between 14-365 days apart and not measured during a treatment interruption. Annual CD4 and VL was defined as the measure taken nearest to but within ± 6 months of the respective annual time points. World Health Organization (WHO) age-related classification of immunosuppression was used.[12] Optimal immune status was defined as CD4 >500 cells/µl in those >5 years old. Changing from 1st- to 2nd-line therapy was defined as changing at least 2 ART drugs in the regimen, one of which was a class switch from non-nucleoside reverse transcriptase inhibitor (NNRTI) to PI, or PI to NNRTI, where the reason for changing drugs was due to VF, was not due to toxicity and the child was not virally suppressed at the time of switch. Genotypic drug resistance was defined as intermediate- or high-level resistance. LTFU was defined as no visit

for >6 months before database closure in a child not known to have transferred out or died. WHO child growth standards were used to calculate Z-scores.[13]

4. Results

4.1 Cohort characteristics

Between May 2002 and December 2005, 349 children enrolled for ART initiation. Prior to reaching 10 years of follow-up, 29 (8%) died, 33 (9%) were LTFU, 150 (43%) were transferred to other facilities (with no transfer back to GSH) and 10 (3%) had missing records. The remaining 127 (36%) remained in care for ≥10 years and formed the study cohort. At ART initiation, the median age of the 127 children included in the study was 31 (interquartile range (IQR) 16 – 58) months and median CD4% was 13% (IQR 9 - 18), with 63% of the children classified as severely immune suppressed. ART was started as in-patients in 12 (9%) of the children. Children were followed up for a median of 12. 2 (IQR 11.1 – 12.9) years, with a mean number of 6 clinic visits per year. Among the cohort, 26 (20%) had transferred care to other facilities and subsequently transferred back again, predominantly for adolescent support. In the study period following 10 years since ART initiation, 1 patient died, 2 were LTFU and 19 (15%) transferred to other clinics. Participants' ages ranged from 10 – 22 years at study close. Characteristics of the children at ART initiation and at the last assessment are shown in Table 1.

Table 1: Characteristics of 127 children at antiretroviral therapy start and at last assessment

Characteristic		At ART start	At last assessment
Sex (n; %)	Male	62 (48.8)	
	Female	65 (51.2)	
Age (median; IQR)	Years	2.6 (1.3 - 4.9)	15.1 (13 - 17.7)
Age category (n; %)	<1 year	23 (18)	
	1 - 4 years	73 (58)	
	5 - 9 years	26 (20)	
	10 - 14 years	5 (4)	60 (47.2)
	≥15 years		67 (52.8)
Year of ART start (n; %)	2002	33 (26)	
	2003	52 (41)	
	2004	23 (18)	
	2005	19 (15)	
Previous exposure to PMTCT	Known exposed	9 (7.1)	
(n; %)	Known unexposed	32 (25.2)	
	Unknown	86 (67.7)	
CD4 % by age category (median; IQR)	<1 year	9.7 (6.9 - 17.0)	
(n=121 at ART start)	1 - 9 years	14.0 (10.0 – 18.0)	
	10 - 14 years	9.0 (7.0-22.7)	30.5 (27.0 - 36.9)
	≥15 years		27.9 (21.2 - 33.5)
CD4 absolute count (median; IQR) (n=122 at ART start)		502 (275-813)	686 (545 - 859)
Immune suppression category* (n; %)	None	13 (10.7)	100 (78.7)
(n=121 at ART start)	Mild	8 (6.6)	12 (9.4)
	Advanced	24 (19.8)	10 (7.9)
	Severe	76 (62.8)	5 (4)
VL >1 million copies/ml (n; %) (n=80)		14 (17.5)	0
VL <400 copies/ml (n; %)		n/a	101 (79.5)
WAZ (median; IQR) (n=115)	Overall	-1.97 (-3.23 to -0.66)	
WAZ category (n; %)	≥-2	58 (50.4)	
	<-2	57 (49.6)	
HAZ (median; IQR) (n=113)	Overall	-2.92 (-4.09 to -1.95)	-1.52 (-2.22 to -0.79)
HAZ category (n; %)	≥-2	31 (27.4)	87 (68.5)
	<-2	82 (72.6)	40 (31.5)
BAZ (median; IQR) (n=113 at ART start)	Overall	0.2 (-0.78 - 1.25)	-0.16 (-1.04 - 0.56)
BAZ category (n; %)	≥-2	98 (86.7)	120 (94.5)
	<-2	15 (13.3)	7 (5.5)
c-ART regimen (n; %)	NVP + 2 NRTIs	78 (61.4)	12 (10)
(n=120 at last assessment)	LPV/rtv + 2 NRTIs	34 (26.8)	63 (52.5)
	rtv + 2 NRTIs	12 (9.5)	-
	EFV + 2 NRTIs	3 (2.4)	21 (17.5)
	ATAZ/rtv + 2 NRTIs	0	17 (14.2)
	Other	0	7 (5.8)

All children were included unless n is specified. ART:antiretroviral therapy, IQR:interquartile range, PMTCT:prevention of mother-to-child transmission, VL:viral load, WAZ:weight for age Z-score, HAZ:height for age Z-score, BAZ:body mass index for age Z-score, c-ART:combination ART, NVP:nevirapine, NRTI: nucleoside reverse transcriptase inhibitor, EFV:efavirenz, LPV:lopinavir, rtv:ritonavir, ATAZ:atazanavir
*Immunodeficiency categories: None if <11 months and CD4>35%, 12-35 months and >30%, 36-59 months and >25%, >5 years and >500 cells/µl; Mild if <11 months and 30-35%, 12-35 months and 25-30%, 36-59 months and 20-25%, >5 years and 350-499 cells/µl; Advanced if <11 months and 25-29%, 12-35 months and 20-24%, 36-59 months and 15-19%, >5 years and 200-349 cells/µl; Severe if <11 months and <25%, 12-35 months and<20%, 36-59 months and <15%, >5 years and <15% or <200 cells/µl

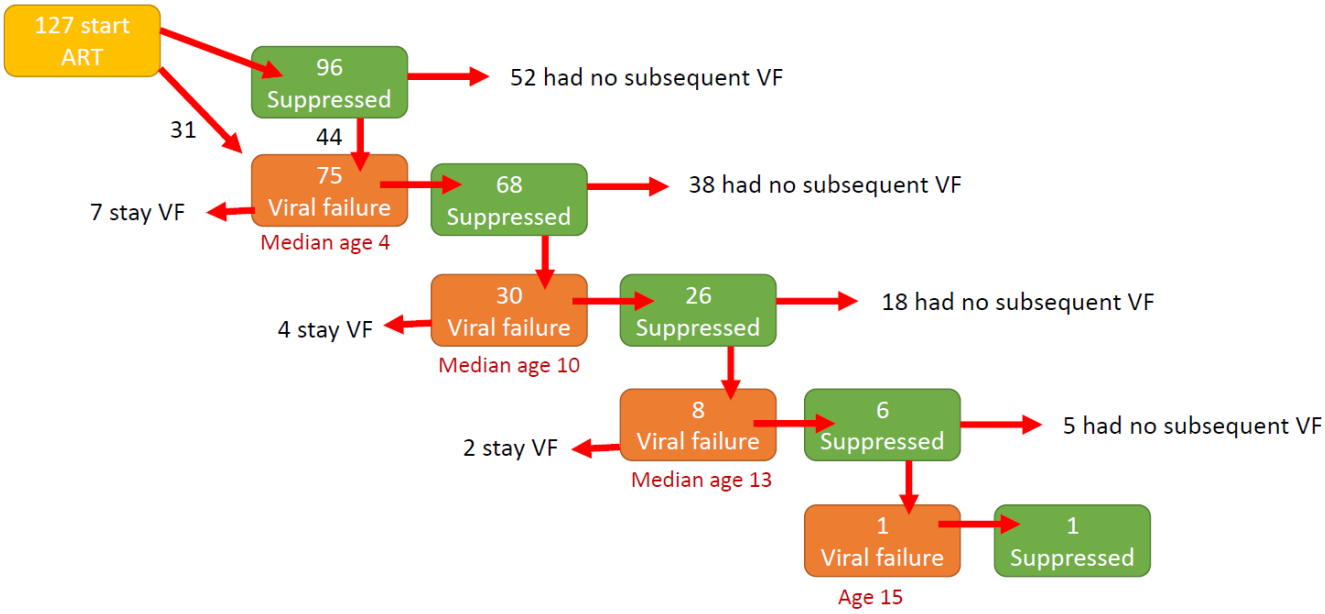

Figure 1: Flow diagram of cohort progression to viral suppression and viral failure (VF) since antiretroviral therapy (ART) initiation

4.2 Treatment history

At ART initiation 64% of children were on NNRTI-based and 36% on PI-based regimens. Over time, there were 91 instances of documented patient- or caregiver-initiated treatment interruptions, which occurred in 40 (31%) patients. Drug switches due to lipodystrophy were made in the regimens of 64 (50%) patients at a median age of 11 years, mostly attributable

to stavudine but also zidovudine and didanosine. At the last assessment, 50% of patients were on 1st-line ART, 43% were on 2nd-line ART, 3% on salvage- or mono-therapy and 4% on no ART. Among those on combination-ART, 28% were on NNRTI-based and 72% on PI-based regimens. One patient was using an integrase inhibitor.

4.3 Virologic outcomes

After ART initiation, 76% of children initially had viral suppression and 41% maintained good virologic control, never experiencing VF throughout follow-up (Figure 1). Two children never experienced viral suppression throughout follow-up.

The Kaplan-Meier 10 year probability of experiencing VF was 56.7% (95% CI 48.3 – 65.5). Among those that experienced VF (75/127; 59%), VF occurred at a median age of 4 years (IQR 2.9 – 8.5) and median duration on ART of 1.5 years (IQR 1.1 – 2.7). The 10 year probability of switching to 2nd-line ART was 45.7% (95% CI 37.5 -54.8). Factors associated with first episode of VF were analysed by Cox proportional hazards modelling (Table 2A). Female sex was independently associated with a 0.44 times lower hazard of developing VF (95% CI: 0.23 – 0.85). Use of suspensions in the ART regimen, compared with use of tablets only, was associated with a 3.48 times increased hazard of VF (95% CI: 1.13 – 10.75).

At the last assessment, 80% of the cohort were virally suppressed (86% on 1st-line vs 77% on 2nd-line; p=0.183). There was no significant difference in the proportion virally suppressed on NNRTI- vs PI-based regimens (89% vs 78%; p=0.169), by age 10 – 14 vs ≥ 15 years at last assessment (83% vs 75%; p=0.224) or by history of previous exposure to single-PI ritonavir vs

not (72% vs 81%; p=0.41). The Kaplan-Meier probability of experiencing VF between the age of 10 and 18 was 37.4% (95% CI 25.4 – 52.8%). VF occurred at a constant rate throughout adolescence (Figure 2A). Advanced immunodeficiency (CD4 <350 cells/µl) at age 10 was independently associated with a 4.05 times increased hazard of developing VF during adolescence (95% CI: 1.04 – 15.82). In addition, having a history of previous VF before the age of 10 was independently associated with a 3.20 times increased hazard of developing VF after the age of 10 (95% CI 1.05 – 9.74). The proportion of patients virally suppressed at each year since ART initiation increased gradually until 8 years since ART initiation and thereafter decreased (Figure 2B).

Ten percent of the cohort had drug resistance documented, which was found in 13 out of the 16 children tested. Of these, 2 had nucleoside reverse transcriptase inhibitor (NRTI) resistance, 2 had NNRTI resistance, 7 had both NNRTI and NRTI resistance and 2 had both PI and NRTI resistance.

4.4 Immunologic outcomes

At the last assessment, 4% of the cohort had CD4 <200 cells/µl and 79% had CD4 >500 cells/µl. Patients on 1st-line ART at last assessment were more likely to have CD4 >500 cells/ µl vs those on 2nd-line, (92% vs 71%; p=0.003). Similarly, those on NNRTI-based regimens were more likely to have CD4 >500 cells/µl vs those on PI-based regimens (94% vs 77%; p=0.003). Stratified by age 10 – 14 vs ≥ 15 years at last assessment, 92% vs 62% (p<0.001) had CD4 >500 cells/µl. The percentage of patients with optimal immunologic status at each year since ART initiation showed increases until 7 years and thereafter decreased (Figure 2C).

4.5 Growth

At ART initiation, median height-for-age Z-score (HAZ) was -2.92 (IQR -4.09 to -1.95) and 73% of the children were growth stunted (HAZ <-2). At the last assessment, median HAZ was -1.52 (IQR -2.22 to -0.79) and 32% were growth stunted. Although HAZ improved over time, it remained below WHO standards (Figure 2D and 2E).

4.6 Clinical outcomes

The number of hospital admissions was highest in the first year after ART initiation, and decreased thereafter (Table 3A). The most common reasons for admissions were lower respiratory tract infections (46%) and pulmonary tuberculosis (TB) (10%). The incidence of TB was high: 53 episodes of TB were diagnosed in 51 patients (40% of the cohort) after >4 weeks since ART initiation (Table 3B). Among those who developed TB >24 weeks since ART initiation, 56% were not virally suppressed at the most recent assessment. Chronic lung disease was documented in 33 (26%) of the cohort.

Table 2: Factors associated with (A) first episode of viral failure and (B) viral failure after the age of 10, from multivariate Cox modelling

(A)	Factor associated with first VF		Adjusted HR	95% CI	p-value
	Sex	male	1		
		female	0.44	0.23 - 0.85	0.014
	Type of regimen	NNRTI-based	1		
		PI-based	0.62	0.20 - 1.98	0.423
	Current age	(years)	1.05	0.89 - 1.24	0.568
	Programme year	2002	1		
		2003	0.87	0.41 - 1.84	0.709
		2004	0.94	0.19 - 4.79	0.943
		2005	0.24	0.05 - 1.18	0.079
	Severe immune suppression at ART start		1.42	0.63 - 3.23	0.400
	VL > 1 million at ART start		1.45	0.62 - 3.37	0.391
	Drug formulations	tablets only	1		
		use of suspensions	3.48	1.13 - 10.75	0.030

(B)	Factor associated with VF after age 10*		Adjusted HR	95% CI	p-value
	Sex	male	1		
		female	1.44	0.64 - 3.24	0.378
	Type of regimen	NNRTI-based	1		
		PI-based	0.75	0.25 - 2.27	0.612
	Age at ART start	(years)	1.11	0.93 - 1.32	0.232
	Programme year	2002	1		
		2003	1.52	0.54 - 4.25	0.428
		2004	1.51	0.37 - 6.07	0.563
		2005	2.2	0.41 - 11.98	0.360
	Previous VF <10 years old		3.2	1.05 - 9.75	0.040
	CD4 <350 at age 10		4.05	1.04 - 15.82	0.044

*10 children with VF at age 10 were excluded from analysis
VF:viral failure, HR:hazard ratio, NNRTI:non-nucleoside reverse-transcriptase inhibitor, PI:protease inhibitor, ART:antiretroviral therapy, VL:viral load

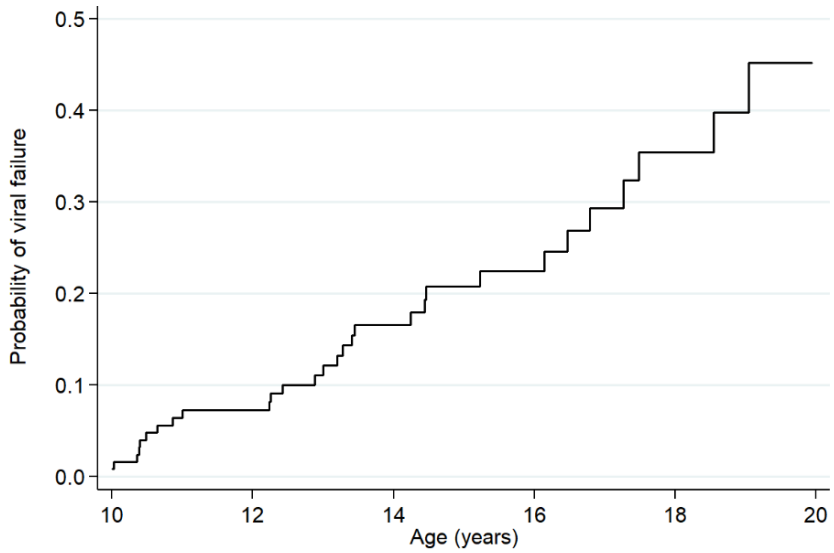

Figure 2A: Kaplan Meier probability of viral failure after age 10 years

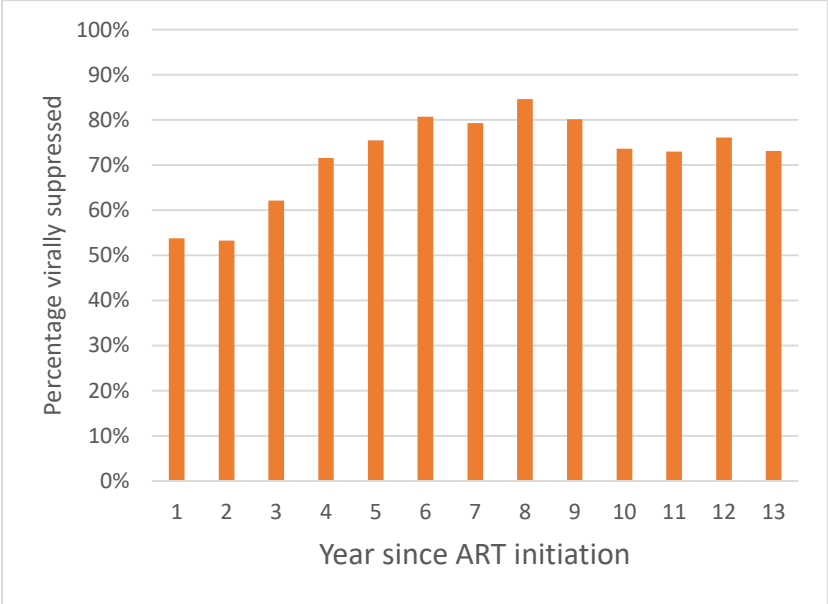

Figure 2B: Percentage of patients virally suppressed at each year since antiretroviral therapy initiation

Figure 2 (A – E): Virologic, immunologic and growth outcomes

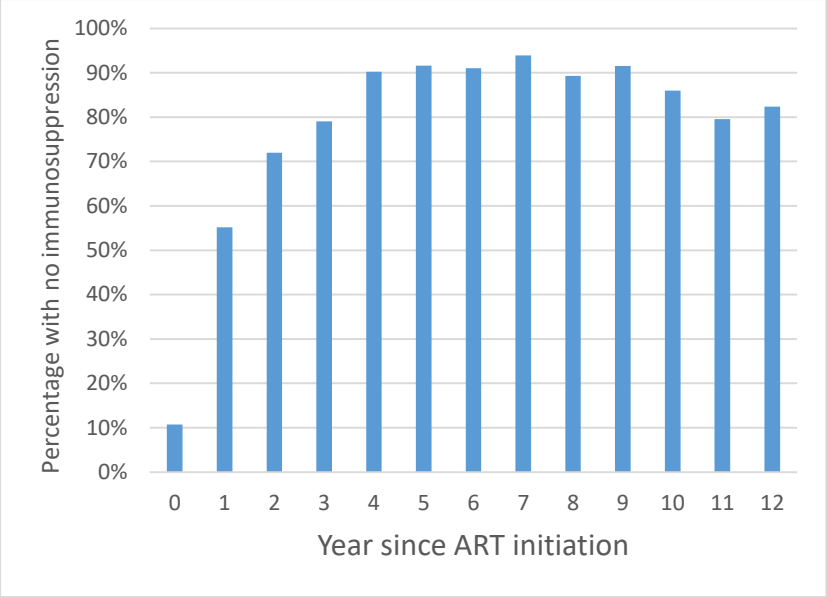

Figure 2C: Percentage of patients with optimal immunologic status* at each year since antiretroviral therapy (*classified as age <11 months and CD4>35%, age 12-35 months and >30%, age 36-59 months and >25%, age >5 years and >500 cells/µl)

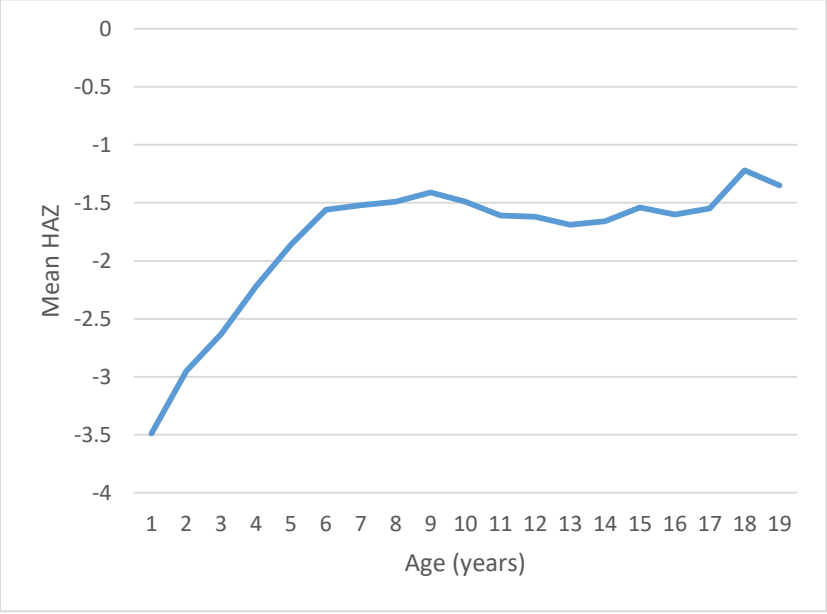

Figure 2D: Mean height-for-age Z-score (HAZ) by age

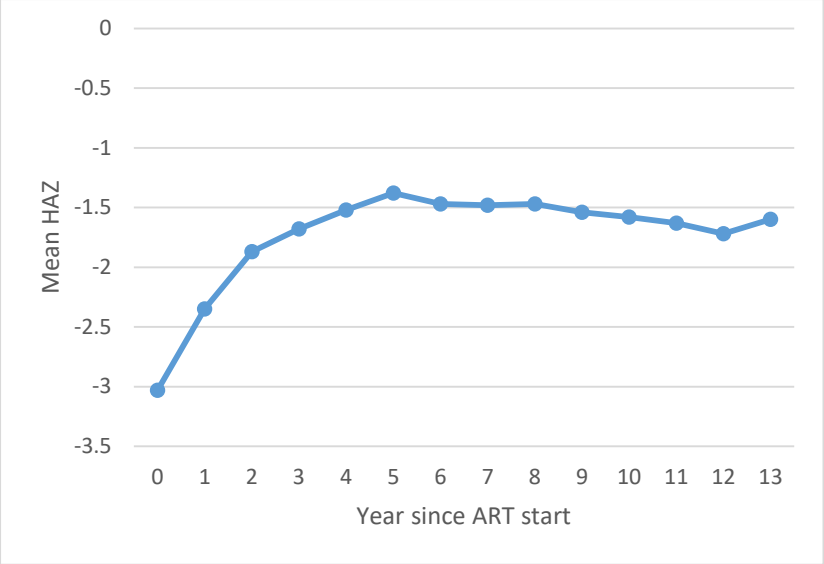

Figure 2E: Mean height-for-age Z-score (HAZ) by time since antiretroviral therapy initiation

Table 3: Clinical outcomes of 127 children on antiretroviral therapy: (A) hospital admissions and (B) tuberculosis incidence

(A)	Year since ART start	Number of hospital admissions	Children with hospital admissions (n; %)	Most common reasons for admission
	<1	92	53 (42)	LRTI (51%) GE (8%) LRTI and GE (8%) Septicaemia (8%) PTB (5%)
	≥1 and <5	67	43 (34)	LRTI (40%) PTB (16%) GE (9%) Septicaemia (6%)
	≥5 and <10	42	24 (19)	LRTI (45%) Measles (19%) GE (7%)
	≥10 and <15	20	14 (11)	LRTI (40%) PTB (20%) Appendicitis (10%) Epilepsy (10%)

(B)	Time of TB diagnosis since ART start	Patients with TB diagnosis (n, %)	% not virally suppressed at TB diagnosis	% with advanced or severe immune suppression
	On TB treatment at ART start or < 4 weeks of ART start	15 (12)	n/a	86%
	≥ 4 weeks and ≤ 24 weeks	4 (3)	n/a	100%
	> 24 weeks and ≤ 1 year	5 (4)	40%	50%
	> 1 year and ≤ 5 years	23 (18)	58%	25%
	> 5 years ≤ 10 years	12 (9)	64%	14%
	> 10 years	9 (7)	44%	44%

ART:antiretroviral therapy, LRTI:lower respiratory tract infection, GE:gastroenteritis, PTB:pulmonary tuberculosis, TB:tuberculosis (any site)

5. Discussion

To our knowledge, this is the first published study of outcomes after more than ten years in HIV care of PHIV children in South Africa. After median follow-up of 12 years on ART, 80% of this cohort were virally suppressed and 79% had optimal immune status. These results compare favourably with studies in high income countries.[6-11] However, these PHIV adolescents comprise a vulnerable group, with impaired growth outcomes and ongoing burden of clinical disease. Maintaining virologic control and optimal immune status in adolescence may be challenging. A high proportion of patients have already had at least one episode of confirmed VF before adolescence and approximately one in three children experience new confirmed VF between age 10 and 18 years.

Both immunologic and virologic outcomes initially improved substantially after ART initiation in this group, but appeared to deteriorate about 10 years after ART start. Understanding the reason for these deteriorating outcomes is crucial to developing targeted interventions to address them. In this respect, VF occurred at a constant rate after age 10 years, similar to results in Asian adolescents.[14]. Entering adolescence with CD4 <350 cells/µl or with a history of previous viral failure were predictors of experiencing new VF during adolescence. In addition, it was notable that adolescents >15 years, those on 2nd-line therapy and those on PI-based therapy were more likely to have CD4 <500 cells/µl.

Across the entire follow-up period, we found an increased hazard of VF in children using suspensions. This is not surprising as some suspensions are unpalatable, giving accurate doses is more difficult compared to tablets, especially if a child vomits or spits out the medicine, and

frequent weight-based dosage changes are needed as the child grows, with risk of errors (by clinicians or caregivers). Optimising drug formulations across the paediatric age range may reduce the risk of VF and drug resistance, facilitating better adolescent outcomes. Resistance testing is not routinely performed in SA when changing from an NNRTI-based regimen due to VF, nor is it routinely performed when VF occurs in patients on a PI-based regimen if ongoing poor adherence is observed. The true incidence of resistance is therefore likely to be higher than the 10% documented.

The high burden of stunting, hospitalisation and clinical disease, especially TB, despite several years on ART in our cohort, is notable. The majority of incident TB cases occurred in patients who were not virally suppressed. This is consistent with findings in adult studies that HIV-infected patients with high VL are at high risk of TB, irrespective of CD4 counts.[15-16] One in four children in our cohort had chronic lung disease, a well-known complication among PHIV adolescents, particularly in sub-Saharan Africa.[17-18] Despite HAZ improvements in childhood, in this study and others in LMIC,[19-20] PHIV adolescents continue to be at least one standard deviation below normal height, with potential impact on final adult height.

This is one of the first studies with >10 years of follow-up of PHIV adolescents from sub-Saharan Africa. Strengths of our study include the detailed long-term individual trajectories, including viral load and clinical outcomes, and that the study reflects the real-world rather than trial settings. The extended time frame allowed for inclusion of patients who had previous gaps in care or transfer out and who at an earlier stage would have been considered LTFU or transferred to another site. Limitations of the study include the small sample size, the retrospective study design, and that the data comes from a single study site in a tertiary care

institution. Since we focused on children on ART for at least 10 years at the same site, there is survival bias in this cohort. Nevertheless, it is precisely this surviving group of PHIV adolescents that needs to be described in order to optimize management during adolescence and transition to adulthood.

There may be reduced external validity due to this being a tertiary care cohort. Within SA and sub-Saharan Africa more broadly the model of retaining children at a separate paediatric tertiary facility is unusual. In addition, there is selection bias in the current cohort of children with ≥10 years of follow up as many were long-term survivors and regular clinic attendees during the era before ART was widely available. Subsequent cohorts of adolescents will have had the advantage of starting ART before the onset of severe disease. The children in this study benefitted from tertiary-level support available at the clinic (psychologists, social workers, counsellors and peer support groups), so results from the study may not be generalizable to children treated at primary care level where HIV services dedicated to young people and their needs are often lacking. Some variables that may be related to the risk of developing VF, for example caregiver factors, disclosure, depression and neurocognitive deficits, were not explored in this study.

6. Conclusions

The long-term virologic and immunologic outcomes were good overall in PHIV children remaining in care for ≥10 years. However, a worsening trend was observed in adolescence, which may be reflective of growing autonomy and worse adherence during adolescence. Given their long-term treatment histories including prior viral failure and ongoing clinical

disease burden, these adolescents will require careful management as they transition to adult care and beyond. There is a need for similar studies of long-term outcomes in PHIV children at other sites in South Africa, particularly in primary care settings, as well as further studies of PHIV individuals after they have transitioned to adult care.

6. References

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PART D: APPENDICES

Appendix 1: Letter of approval from UCT Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

10 December 2015

HREC REF: 891/2015

A/Prof M Davies
Public Health & Family Medicine
Falmouth Building

Dear A/Prof Davies

PROJECT TITLE: TREATMENT OUTCOMES IN PERINATALLY-INFECTED HIV POSITIVE ADOLESCENTS AND YOUNG ADULTS AFTER 10+ YEARS ON ANTIRETROVIRAL THERAPY (MPH-candidate-Dr K Anderson)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th December 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Kim Anderson will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

pp T Burgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

Appendix 2: Data collection sheets

PATIENT	(UNIQUE AND ANONYMOUS CODE TO IDENTIFY COHORT PATIENT)
DATE OF BIRTH (dd-mm-yyyy)	
MALE/FEMALE (M/F)	
PMTCT HISTORY	(DRUG NAME AND DURATION or "NONE" or LEAVE BLANK IF UNKNOWN)
RESISTANCE TESTING	(IF PERFORMED: DATE, RESULT, RECOMMENDATIONS. IF NOT: LEAVE BLANK)

PATIENT	(CODE)	-LINE
ART_ID	(ART DRUG NAME)	(1 or 2 or 3)
ART_SD (dd-mm-yyyy)	(DATE OF DRUG START)	
ART_ED (dd-mm-yyyy)	(DATE OF DRUG STOP)	
ART_RS	(REASON FOR STOPPING; LEAVE BLANK IF NOT STOPPED)	
ART_ID		
ART_SD (dd-mm-yyyy)		
ART_ED (dd-mm-yyyy)		
ART_RS		
ART_ID		
ART_SD (dd-mm-yyyy)		
ART_ED (dd-mm-yyyy)		
ART_RS		
ART_ID		
ART_SD (dd-mm-yyyy)		
ART_ED (dd-mm-yyyy)		
ART_RS		

PATIENT NUMBER:

DATE (dd-mm-yyyy)	CD4 COUNT - ABS	CD4 %

PATIENT NUMBER:

DATE (dd-mm-yyyy)	VIRAL LOAD - COUNT	LOG VALUE

PATIENT NUMBER:

CLINIC VISIT DATE (dd-mm-yyyy)	HEIGHT (cm)	WEIGHT (kg)

RECORD OF OPPORTUNISTIC INFECTIONS (OIs) - PATIENT NUMBER:

DATE (dd-mm-yyyy)	OI (DIAGNOSIS)	ADMISSION? (YES OR NO)	IF YES, DURATION (DAYS)

Appendix 3: Table of WHO immunological classification for established HIV infection

HIV-associated immunodeficiency	**Age-related CD4 values**			
	<11 months (CD4%)	12 – 35 months (CD4%)	36 – 59 months (CD4%)	>5 years (absolute count/µl or CD4%)
None or not significant	>35	>30	>25	>500
Mild	30 - 35	25 - 30	20-25	350 - 499
Advanced	25 - 29	20 - 24	15 - 19	200 - 349
Severe	<25	<20	<15	<200 or <15%

Appendix 4: Table of opportunistic infections for data capturing of clinical outcomes

Stage 3 and 4 opportunistic infections of HIV, adapted from WHO clinical staging of HIV disease in adults, adolescents and children (2013):

Unexplained persistent diarrhoea (≥14 days in children; >1 month in adults/adolescents)
Persistent oral candidiasis
Lymph node tuberculosis
Pulmonary tuberculosis
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Symptomatic lymphoid interstitial pneumonitis
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
Pneumocystis (jirovecii) pneumonia
Chronic herpes simplex infection (>1 month)
Oesophageal candidiasis
Extrapulmonary tuberculosis
Cytomegalovirus infection
Central nervous system toxoplasmosis
Extrapulmonary cryptococcosis, including meningitis
Disseminated nontuberculous mycobacterial infection
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)
Recurrent septicaemia (including nontyphoidal Salmonella)
Atypical disseminated leishmaniasis

Appendix 5: Author guidelines for the South African Medical Journal

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study. Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text. Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.

- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.

- Click Actions > Cite
- Alongside 'url =' copy the URL between { }.
- Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
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