EFFECT OF INITIAL ANTIRETROVIRAL REGIME ON VIROLOGICAL SUPPRESSION IN CHILDREN IN A SOUTHERN AFRICAN URBAN POPULATION: A RETROSPECTIVE RECORD REVIEW

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Declaration

I, Dr Zeenat Gaibee, declare that the work on this study is originally my work except where acknowledgements are indicated. This is an unsponsored study and was carried out for educational purposes only as a MMED for a postgraduate degree. I therefore declare no conflict of interest whatsoever.
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Abstract

EFFECT OF INITIAL ANTIRETROVIRAL REGIME ON VIROLOGICAL SUPPRESSION IN CHILDREN IN A SOUTHERN AFRICAN URBAN POPULATION: A RETROSPECTIVE RECORD REVIEW

Background

Since 2010, adult studies and clinical concerns about stavudine (d4T) toxicity had led to the phasing out of d4T from many antiretroviral treatment (ART) guidelines globally with substitution by abacavir. Recent studies, within Southern Africa, however have shown poorer virological suppression with abacavir (ABC) compared to d4T at their respective centres.

Methods

A retrospective study of HIV-positive children, who had been initiated on ART from 2005 to 2017, was conducted at an ART unit at New Somerset hospital, Western Cape, South Africa. Data was extracted from clinical notes and electronic medical records and virological suppression reviewed in those started on ABC and d4T based regimes.

Results

A total of 672 children were included in the study with a median age of 8.9 months (interquartile range (IQR) 4.1- 24.1 months) in the d4T based group and 11 months (IQR 3.5 - 29.9 months) in the ABC group. 64 of the 437 patients in the d4T containing group were transferred out, 15 reported to have died, and 49 were lost to follow up within the first 6months on treatment. Of the 181 ABC containing regimen group, 1 was transferred out to another care facility, 1 reported death within 6months of treatment and 2 children were lost to follow up. There was a noted increased risk of being virologically unsuppressed at 6months while taking ABC containing regimen compared to a d4T containing regimen. . The relative risk of being virologically unsuppressed at 6 months while taking abacavir/lopinavir (LPV/r) was 1.39 (95% confidence interval 1.03 to 1.88, p=0.04) compared to stavudine/LPV/r. The relative risk of being virologically unsuppressed at 6 months while taking abacavir/efavirenz (EFV) was 1.82 (95% confidence interval 0.98 to 3.37, p=0.054) compared to stavudine/EFV.

Conclusion

Our analysis again raises concerns about virological suppression in the abacavir era of paediatric ART, compared to the previous stavudine era, particularly in combination with LPV/r in the younger, more vulnerable children. Whether this is because of intrinsic properties of the different medications or is a marker of the evolving complexity of the South African ART rollout, may never be resolved. However, this is of concern as abacavir and LPV/r appear to be entrenched as first-line paediatric ART in a setting where attrition is high, many children are lost to follow up and virologic surveillance is not always optimal. Clinicians need to optimize retention strategies, especially of young infants, to ensure that children are retained in care, have viral load testing timeously, so that those virologically unsuppressed can be detected and treated early and appropriately.

Study Protocol

Effect of initial antiretroviral regime on virological suppression in children in a Southern African urban population: A retrospective record review
Study Investigators

Principal Investigator: Dr Dave le Roux
Co-Investigator: Dr Zeenat Gaibee
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Introduction
Paediatric access to antiretroviral treatment (ART) in Sub-Saharan Africa and other low-resource settings have demonstrated good early outcomes and studies in high-income countries have demonstrated that ART use among children effectively reduces morbidity, hospital admissions and increases long-term survival.(1) Lack of affordable and appropriate paediatric formulations have limited ART options in South Africa.(2) This study aims to compare virological suppression with abacavir to stavudine as well as the effect of concurrent diagnosis with tuberculosis (TB) virological suppression, and the medium-term effect on malnutrition.

Background
Initially the South African ART programme used stavudine (d4T) as a first-line nucleoside reverse transcriptase inhibitor (NRTI). Stavudine was palatable and stable at room temperature, had few initial complications, and was relatively inexpensive. However late complications like lipodystrophy and lactic acidosis led to its replacement by abacavir (ABC) for children and tenofovir (TDF) for adults.(3) Abacavir, although more expensive, has better short- and long-term side effect profile, and only requires monitoring soon after initiation.(3) It has been included, along with lamivudine (3TC) and either lopinavir/ritonavir (LPV/r) or efavirenz (EFV) in the first line paediatric regimen since 2010.
After the first-line NRTI backbone was changed, concerns were raised amongst clinicians about its efficacy. (3) (4) In an initial study of a single clinic in Johannesburg, rates of virological suppression at 6 and 12 months were compared among 2036 children between 2004 and 2011. Children receiving ABC/3TC had statistically significantly lower rates of suppression, and longer time to achieve virological suppression. (4) A similar analysis was performed using pooled data from the IeDEA-Southern Africa (International Epidemiologic Databases to Evaluate AIDS in Southern Africa) collaboration. 8 paediatric ART sites contributed data; 9543 children were analysed. 70% of young children on a d4T/LPV/r-containing regimen were virologically suppressed, compared to 54% of children receiving an ABC/LPV/r-containing regimen. Amongst older children receiving efavirenz, 86% were virologically suppressed at 6 months while receiving d4T, compared to 78% of those receiving ABC. ABC was also associated with slower time to suppression and faster time to rebound after suppression, even after correcting for potential confounding factors.(5) As the data was obtained from routinely collected clinic data over several years, the authors could not determine whether the differences were due to intrinsic weakness of the ABC-containing regimen, or whether they were due to evolving social conditions and other programmatic changes that occurred at the same time. They recommended close monitoring and evaluation of paediatric ART programs.

Until recently, there was very little data directly comparing d4T to ABC in paediatric populations (4). The PENTA 5 trial showed that ABC with 3TC combined with unboosted nelfinavir (NFV) performed better than zidovudine (ZDV) plus 3TC or ZDV plus ABC with upboosted NFV.(6) The CHAPAS-3 study, a parallel-group randomised controlled trial conducted in Zambia and Uganda, compared stavudine, zidovudine or abacavir in combination with lamivudine and nevirapine or efavirenz, and found no

major differences in any adverse event or toxicity endpoint during the nearly 2.5 year follow up in ART-naive and ART-experienced children. They also found children had a good clinical, immunological and virological response regardless of backbone NRTI. (7) Significantly, there was a very high retention in this intensively-monitored clinical trial: less than 5% were lost to follow up. In this context, unlike in the IDEA collaboration of routinely-collected clinic data, where adherence was not necessarily optimised, and retention was not ideal, abacavir was not inferior stavudine, suggesting that some of the effects observed in the Technau papers may have been due to patient factors, and not necessarily due to the drug itself.
WHO guidelines which are followed by many Sub-Saharan countries have changed from using d4T to ABC ;(8,9) but in view of the Technau and Mulenga studies, and the limited paediatric ART formulations available, it is imperative that virological suppression of children receiving ABC-containing regimens is monitored, as well as their adherence to medication and retention in care.

Aims of the study
This study aims to compare the percentage of children virologically suppressed at 6 months after commencing ART, comparing d4T to ABC-containing regimens. This will be stratified into under 1 year, 1-3year and > 3years of age. The effect of concomitant TB treatment, stratified according to the same age bands, will also be assessed.

Objectives
To review viral suppression in an urban based regional hospital in the Western Cape, comparing d4T and ABC based regimens and the influence of TB, a common infection in the Western Cape population, on HIV viral suppression rates.

Study design
Retrospective analysis of routinely collected data (non-trial setting) of clinical notes as documented at a dedicated ARV clinic.

Study setting and location
The New Somerset Hospital (NSH) ARV Unit is a moderately sized urban HIV treatment centre in Cape Town, South Africa with an extensive drainage area that has been providing service to adults and children since 2005. National guidelines are followed, and children are routinely followed up at the clinic.

Study Population
Inclusion Criteria
All HIV infected children < 16years old initiated on ART who were previously ART naïve (except for exposure to perinatal PMTCT prophylaxis) that were initiated on ART during study period: January 2015 – January 2017.
Exclusion Criteria
Children attending the ARV clinic with insufficient data to identify patient or HIV status.

Study Outcomes
•Primary Outcomes:
VL suppression (<50 RNA copies/ml) at 6months.
Influence of TB treatment on viral load
• Secondary Outcomes:
Weight changes, as measured in weight-for-age z-score
Retention in care review
Adherence to medication

Study Procedures
All clinical record folders of children < 16yrs of age that have been entered into the ARV clinic records will be reviewed and a data capturing questionnaire will be completed for each folder. Subjects will be de-identified once this information is captured.
ART regimen, concomitant TB treatment, weight and height at initiation and follow up, as well as viral load measured at 6 months will be abstracted from the clinical notes. Adherence will be measured qualitatively, as assessed by clinician comments in the clinical notes and counselling records. Poor tolerability will be documented if specifically mentioned in the clinic notes by the attending clinician. Missed visits will be assessed by checking dates of attendance for clinic visits. Retention in care will be quantified, and percentages calculated of children remaining in active care at 6 months, discontinued ART, lost to follow up or transferred out.

Statistical Methods
Categorical variables will be described by simple percentages.
Continuous variables will be described with medians and inter-quartile ranges
Proportions of children virologically suppressed will be compared with p values and 95% confidence intervals

Ethical Considerations
The study will involve purely folder review and not physical contact with patients. The study will involve review of already collected data and there is no direct intervention or risk to patients or their families. All patient records will be kept confidential and each patient will be assigned a study number to maintain anonymity.

Study Limitations
Being a retrospective study based in a single site urban population both sample size and population bias may exist. There may be missing data, depending on the quality of the clinicians notes and the availability of the medical records. Retention of patients within the study population may be a limiting factor as well. The population, although diverse, may not be fully representative, as patients are limited to those who fell within the New Somerset Hospital drainage area and may have required hospital admission or additional expertise at some point within their disease course.

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New Somerset Hospital Paediatric ARV Clinic Study

Name : _____ Folder No. :

Date Of Birth: _____ Allocated Study No.: _____
(dd/mm/yy)

Gender: Male Female

Treatment (Rx) initiated at NSH: Yes No
(circle most applicable)

Date of diagnosis: _____

Date of Rx initiation: _____

WHO staging at initiaton: _____

Regime started	
3TC	
d4T	
ABC	
AZT	
LPV/r	
Efavirenz	
NVP	
Ritonavir	

TB Rx : Pre- ARV initiation At ARV initiation <6/12 after ARV's > 6/12 post initiation or no TB dx
(circle correct option)

Date TB Rx started: _____ Date TB Rx stopped: _____

Viral Load: At initiation: _____ At 6months: _____
(within 5-8months post initiation)

Date: Date: *

* if unavailable, why? Missed follow up No Result Test not done Other

Weight (kg): At initiation: At 6months:

Weight for age: _____ (z-score) Weight for age: _____ (z-score)

Patient Adherence: Commented to be poor Good No comment
(Clinical impression)

Medication tolerated Yes No
Missed visits noted Yes No

PMTCT exposure: Yes No

PMTCT type: Single dose NVP Daily NVP Prolonged daily NVP AZT Other
(circle applicable) *(6 weeks)* *(>6weeks while breastfeeding)* *(Specify)*

Office use only:		
Study Applicable:	Yes	No
Further review required	Yes	No
Captured:	Date:	

Literature Review

Objectives of literature review

The objective of this literature review is to provide the reader with a background of HIV, particularly its temporal history with a focus on South African Paediatric HIV and its local and global advancement, temporal changes and rationale and the various evidence that lead to programmatic and regime guideline adjustments.

Literature Search strategy

The literature search was limited to English-language articles in MEDLINE

(www.ncbi.nlm.nih.gov). Results were limited to humans. The following search string was used:

((((("Stavudine"[Mesh]) OR stavudine) OR d4t)) AND (("abacavir"[Supplementary Concept]) OR abacavir)) AND ((((((("Child"[Mesh]) OR "Child, Preschool"[Mesh]) OR "Infant"[Mesh]) OR "Adolescent"[Mesh])) OR (((((child) OR children) OR adolescents) OR pediatric) OR paediatric))

All full text articles were reviewed and manual search from references of retrieved articles were added.

Interpretation and summary of literature

HIV continues to be a global public health concern, with the largest majority of affected people living in Sub-Saharan Africa. Despite global response from government and non-governmental organizations to reduce the HIV burden, in 2016, an estimated 36.7million people were living with HIV, 1.8 million of which were children less than the age of sixteen. [(1)]

While great strides have been taken to provide improved access and availability for adults, Sub-Saharan Africa is unique in that it is occupied by 12% of the global HIV population, but disproportionally almost 90% of children younger than 15yrs. [(2).] Limited access to paediatric antiretroviral drugs and availability of drugs in an appropriate formulation, amongst other challenges, has caused management of Paediatric HIV to lag far behind adult advancement.

In May 2001, the first ARV project was started in the Khayelitsha community in Cape Town. The South African program unlike many other African countries, was primarily domestically funded and by April 2004, the national South African Antiretroviral therapy (ART) program was launched. [(3)] The expansion of the ART program also brought with it change in ART eligibility. In 2004, immunological and clinical criteria determined ART eligibility. Children with a World Health Organization (WHO) clinical classification stage 4 or CD4 percentage of < 10% were started on antiretroviral therapy. By 2010, all children under the age of one year, regardless of CD4 or clinical stage were deemed eligible. By August 2012, the National Department of Health of South Africa, considered all HIV positive children under the age of 5, eligible for ART [(4).]

The change in ART eligibility and advancement of research, also brought with it change in regime recommendations. There was agreement in management of HIV necessitating a 3 drug ART combination consisting of 2 Nucleoside Reverse Transcriptase Inhibitors (NRTI) and either a Protease Inhibitor (PI) or Non- Nucleoside Reverse Transcriptase Inhibitors (NNRTI).

In 2004, children less than three years of age were initiated on stavudine, lamivudine and lopinavir/ritonavir, and children older than three years old, on stavudine, lamivudine and efavirenz as first line treatment. [(4)] The simplicity of d4T-containing regimens and low cost led to it becoming one of the most widely used ART drugs by 2010[(5)] but by late 2003, d4T use had become associated

with metabolic toxicity and long-term complications of lipoatrophy, peripheral neuropathy and lactic acidosis, notably more pronounced in adults than in children. Initially WHO recommended that countries switch to a lower dose of d4T to minimize side effects. This did result in some improvement, but the overall frequency of side effects seemed to remain concerning from evidence in low-resource settings. South Africa, under these guidelines, in 2010, therefore recommended replacing stavudine with abacavir in all children experiencing side effects on stavudine. The recommended first line for all new patients initiating therapy also changed to either abacavir, lamivudine and lopinavir/ritonavir for children under 3yrs old and abacavir, lamivudine and efavirenz for older children. From 2013, most children, virologically suppressed, who were previously initiated in stavudine, were switched to abacavir. [4]

After the first-line NRTI backbone was changed, however, from stavudine to abacavir, concerns were raised amongst clinicians about its efficacy. [6] [7] In an initial study of a single clinic in Johannesburg, rates of virological suppression at 6 and 12 months were compared among 2036 children between 2004 and 2011. Children receiving ABC/3TC had statistically significantly lower rates of suppression, and longer time to achieve virological suppression**.** (7) Poorer virological outcomes were observed in children on abacavir-based regimes despite more favourable pre-treatment characteristics like weight for age, height for age and CD4 percentages. The improved pre-treatment characteristics were attributed to the expanding ART programme and more inclusive eligibility criteria. These virological differences were observed in both the lopinavir/ritonavir and efavirenz groups.

A similar analysis was performed using pooled data from the IeDEA-Southern Africa (International Epidemiologic Databases to Evaluate AIDS in Southern Africa) collaboration. Eight South African paediatric ART sites contributed data which included 4 Cape Town based institutes and 2 Johannesburg based sites, both within large metropolitan areas. 9543 children were included in the study and it was noted that 70% of young children on a d4T/LPV/r-containing regimen were virologically suppressed, compared to 54% of children receiving an ABC/LPV/r-containing regimen. Amongst older children receiving efavirenz. 86% were virologically suppressed at 6 months while receiving d4T, compared to 78% of those receiving ABC.

ABC was also associated with slower time to suppression and faster time to rebound after suppression, even after correcting for potential confounding factors.[8] As the data was obtained from routinely collected clinic data over several years, the authors could not determine whether the differences were due to intrinsic weakness of the ABC-containing regimen, or whether they were due to evolving social conditions and other programmatic changes that occurred at the same time. They recommended close monitoring and evaluation of paediatric ART programs. [7] .

Stavudine (d4T) was and is still thought to be a highly efficacious drug and has been shown to be less likely to develop drug related mutations when compared to zidovudine (AZT) containing regimes even in absence of strict virological monitoring. [9], It is also available in triple and dual combination scored dissolvable fixed dose combination (FDC) tablets, making paediatric dosing and possibly even adherence more achievable. [10]. Stavudine containing regimens in 2011, were noted to be the least costly when compared to AZT-based and particularly ABC-based regimes. [11]. Stavudine was also noted to be safer with regard to haematological disorders than AZT, which is of particular relevance in the Sub-Saharan African context with its high prevalence of malaria, sepsis and malnutrition. [12-13].

The d4T FDC was amongst the first to be developed for children and was thus quite widely rolled out in Africa in large numbers. However, despite lipodystrophy being described in adults, it appears to be quite rare and poorly described in children, particularly those younger than 5years. Recent studies in children have also reported reversal of features of lipodystrophy on stopping d4T containing regimens in those that did develop lipodystrophy. [14-15] and understanding as to when to substitute children on d4T remains unclear, particularly in Africa.

Abacavir (ABC), a NRTI, was recommended by the World Health Organisation (WHO), as both a first-line and second-line ART regime agent, as well as amongst other European and American guidelines.[16-18]It is often prescribed with 3TC and the Arrow trial reported that the pharmacokinetics of ABC and 3TC were compatible with a once daily dose and showed good tolerance in those greater than 3 months.

Randomised control trial evidence to support the superiority of ABC stemmed from the Pediatric European Network for Treatment of AIDS (PENTA 5) trial published in 2007, which showed that ABC with 3TC combined with upboosted nelfinavir (NFV) performed better than zidovudine (ZDV) plus 3TC or ZDV plus ABC with upboosted NFV.[17] The study was conducted amongst 126 randomised children in a relatively high resourced setting. It consisted of mostly older children with a median age of 5.7years and much lower viral load (5.1 log10 copies/ml) and CD4 of 20% with only 11 (9%) of children having an AIDS defining illness unlike our South African cohorts [7]. Contextualising this study to the South African context is difficult as the trial included asymptomatic children on dual therapy as well as used nelfinavir instead of lopinavir/ritonavir or efavirenz. There were concerns that the recommendation was done with low certainty of evidence.

Hypersensitivity reactions associated with ABC remains a concern with children. Amongst adults a systematic review demonstrated a strong relation between the abacavir related hypersensitivity reaction and the HLA B5701 allele genotype [18] as well as increase risk of myocardial infarction. [19]

While the PENTA5 trial showed superior virological effectiveness of 3TC and ABC over AZT and 3TC or AZT and ABC, the CHAPAS 3 trial done in Africa did not demonstrate this.

The CHAPAS-3 (Children with HIV 1 in Africa, Pharmacokinetics and Adherence/Acceptability of Simple Antiretroviral Regimens) trial in 2015, was the first randomised controlled trial in African children to compare the three backbone NRTI's for antiretroviral treatment (ART) regimens [20]. It was an open-label, parallel-group randomised phase II/III trial conducted in Zambia and Uganda to evaluate new solid, dispersible scored antiretroviral fixed-dose combination and single drugs in African children. A total of 478 children (aged 1 month to 13 years) were randomised to study arms which received fixed-dose combination tablets of one of the three NRTIs (abacavir, stavudine, or zidovudine) plus lamivudine in combination with nevirapine or efavirenz. All combinations were dosed according to WHO weight bands. The trial included 365 ART-naive children and 113 virologically suppressed ART-experienced children on a stavudine-containing first-line regimen for 2 years or more. The trial compared the pharmacokinetics, toxicity, acceptability, adherence, efficacy and cost-effectiveness of these first-line antiretroviral regimens. [20]

Clinical outcomes for all three NRTIs presented low (4%) mortality, high (≥80%) viral load suppression rates in ART-naive children, high (>96%) maintenance of viral suppression at 48 weeks in ART-experienced children, and no evidence of differential CD4% recovery across randomised groups. It also found no major differences in any adverse event or toxicity endpoint during the nearly 2.5 year follow up in ART-naive and ART-experienced children. [20]

All three NRTI backbones with efavirenz or nevirapine were shown to have low toxicity and to produce high viral load suppression rates independent of the NRTI used. Abacavir has very low toxicity in African children, a superior resistance profile for second-line NRTI sequencing and is the only once-daily licensed NRTI fixed-dose combination (with lamivudine) for children, supporting its preferred use in first-line ART. [20] Significantly, there was a very high retention in this intensively-monitored clinical trial: less than 5% were lost to follow up. In this context, unlike in the IDEA collaboration [8] of routinely-collected clinic data, where adherence was not necessarily optimised, and retention was not ideal, abacavir was not inferior stavudine, suggesting that some of the effects observed in the Technau papers [7][8] may have been due to patient factors, and not necessarily due to the drug itself.

Recently, the Cassim study [21], looked at the efficacy of abacavir versus stavudine in South African children and was based at the Paediatric Wellness Programme (PWP) at the Perinatal HIV Research Unit in Soweto, a prospective cohort of HIV1 infected children, the majority of whom are perinatally infected. The retrospective cohort study identified 57 eligible ABC cases and 114 matched d4T cases. Only children who were ART naïve at time of enrolment and who had initiated ART < 3years age were included. The groups shared similar temporal distribution to other South African cohorts with most d4T participants visits ranged from 2005 – 2011 and ABC between 2010 – 2013 with a median age of 3.11 (IQR: 1.98 – 6.05) months. Pre-ART, it was noted more children in the ABC group had a viral load < 100000 copies/ml (17.8% vs 2.8%) however no difference in virological, immunological and clinical outcomes were noted between children receiving ABC or d4T based antiretroviral therapy in Soweto. No difference in anthropomorphic measures of HAZ, WAZ and WLZ at 6months and 12months and no difference in the proportion of children with adherence levels > 90% for ABC and d4T based groups were appreciated either. [21] Whilst PWP is a programmatic cohort, it is run from within a well-established research unit by healthcare workers trained in the implementation of clinical trials and the stringent management implemented here, and this may not be as well appreciated in resource-low settings.

Concerns are also raised on reviewing recent data on rapid clearance of ABC and whether current dosing recommendations , particularly in children and adolescents are high enough to avoid subtherapeutic levels. [22] Studies have inferred that the combination of inadequate dose changes during growth and development, incomplete viral suppression, adherence issues and lack of access to adequate paediatric ART formulations may all contribute to treatment failure and ART resistance. Sequencing of ART regimens after first line regimen failure becomes difficult in low- or middle-income countries (LMIC) with limited ART available options, which often rely on WHO recommendations and cost considerations. WHO recommendations suggest that 3TC in combination with either AZT or d4T, be replaced by ABC and didanosine (ddI), however to note that very little data from LMIC was available at the time the guidelines were published to validate the recommendations.[23]. A study in Kampala, of children failing NRTI-NNRTI regimes showed that only 2 of 19 children would have been fully susceptible to ABC, ddI, and ritonavir-boosted lopinavir as a suggested WHO empiric second-line treatment [24]. With very little access to resistance testing in many LMIC, this becomes problematic. Failure after using ABC may result in the acquisition of K65R

mutation with possibly prevents subsequent use of tenofovir later, making long term management more difficult.

Conclusion

Up until very recently, very little good evidence was available with regard to optimising paediatric HIV care. Guidelines still rely heavily on adult studies which is not always be related to paediatric needs or physiology. Limited paediatric drug availability and appropriate formulations make management and interpretation of programs difficult. The New Somerset Hospital ARV unit, a unique multicultural urban unit have been following WHO and South African National Health guidelines since its inception but very little is known about its efficacy as a unit or if the findings of this unit mirror the concerns of the Technau studies with similar challenges or the more research-like units noted no particular differences in regimes. This study aims to explore the New Somerset Unit Paediatric unit to best optimise care for its patients. This study aims to compare the percentage of children virologically suppressed at 6 months after commencing ART, comparing d4T to ABC-containing regimens.

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EFFECT OF INITIAL ANTIRETROVIRAL REGIME ON VIROLOGICAL SUPPRESSION IN CHILDREN IN A SOUTHERN AFRICAN URBAN POPULATION: A RETROSPECTIVE RECORD REVIEW

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Introduction

Paediatric antiretroviral therapy (ART) in Sub-Saharan Africa and other low-resource settings has demonstrated good early outcomes and studies in high-income countries have demonstrated that ART use among children effectively reduces morbidity, hospital admissions and increases long-term survival. [(1)] Lack of affordable and appropriate paediatric formulations have limited ART options in South Africa. [(2)]

Initially, the South African ART programme used stavudine (d4T) as a first-line nucleoside reverse transcriptase inhibitor (NRTI). Stavudine was palatable and stable at room temperature, had few initial complications, and was relatively inexpensive. However late complications like lipodystrophy and lactic acidosis, more pronounced in adults than children, led to its replacement by abacavir (ABC) for children and tenofovir (TDF) for adults.[(3)] Abacavir, although more expensive, is thought to have a better short- and long-term side effect profile, and only requires monitoring soon after initiation.[(3)] It has been included, along with lamivudine (3TC) and either lopinavir/ritonavir (LPV/r) or efavirenz (EFV) in the first line paediatric regimen since 2010.

After the first-line NRTI backbone was changed, concerns were raised amongst clinicians about its efficacy. [(4,5)] In an initial study of a single clinic in Johannesburg, rates of virological suppression at 6 and 12 months were compared among 2036 children between 2004 and 2011. Children receiving abacavir/3TC had statistically significantly lower rates of suppression, and longer time to achieve virological suppression. [(4)] A similar analysis was performed using pooled data from the IeDEA-Southern Africa (International Epidemiologic Databases to Evaluate AIDS in Southern Africa) collaboration [(6)]. Eight paediatric ART sites contributed data; 9543 children were analysed. 70% of young children receiving stavudine/LPV/r-containing regimen were virologically suppressed, compared to 54% of children receiving an abacavir/LPV/r-containing regimen. Amongst older children receiving efavirenz, 86% were virologically suppressed at 6 months while receiving stavudine, compared to 78% of those receiving abacavir. Abacavir was also associated with slower time to suppression and faster time to rebound after suppression, even after correcting for potential confounding factors.[(6)] As the data was obtained from routinely collected clinic data over several years, the authors could not determine whether the differences were due to the intrinsic weakness of the abacavir-containing regimen, or whether they were due to evolving social conditions and

other programmatic changes that occurred at the same time. They recommended close monitoring and evaluation of paediatric ART programs.

WHO guidelines which are followed by many Sub-Saharan countries have changed from using stavudine to abacavir;[7,8] but in view of the concerns of virological suppression using abacavir, ongoing surveillance of abacavir efficacy is needed. This study aims to compare the percentage of children virologically suppressed at 6 months after commencing ART, comparing d4T to ABC-containing regimens.

Methods

The study was a retrospective patient record review conducted at New Somerset Hospital, an urban secondary level government hospital within the Cape Town central business district, providing care to large mixed population drainage area. The antiretroviral (ARV) Referral Unit was initiated in 2005 and serves both adults and children.

Patient records of all HIV infected children less than 16 years of age at the time of initiation of treatment, who were initiated on treatment from January 2005 to January 2017, were identified. Patients with inconclusive HIV status or ART regime were excluded. HIV status of all patients was confirmed using HIV polymerase chain reaction (PCR) in those less than 18 months and 2 separate enzyme-linked immunosorbent assay (ELISA) tests on those older than 18 months prior to entering the clinic database. Patients records were reviewed from the time they were initiated onto treatment up until the end of study date, or until they either died, were transferred out for care at another facility or were deemed lost to follow up.

Demographic and clinical details, including laboratory results and ART initiation data, were routinely recorded by clinicians in paper records held in the ARV Referral Unit from 2005 to 2010; after 2010, data was also electronically captured to Tier.Net database. The paper-based summary folders in the ARV Referral Unit were reviewed; this was supplemented by comparison with the Tier.net database. All viral loads were processed in the same laboratory, the National Health Laboratory Service Virology laboratory at Groote Schuur Hospital, using NucliSens EasyQ HIV-1, (2008 - Sept 2010), Abbott M2000 Realtime, (Sept 2010 - June 2015) and Roche COBAS Ampliprep/COBAS Taqman (June 2015- present). Children were considered virologically suppressed if the viral load was undetectable, i.e. below the limit of detection of the assay that was being used at that time.

Where enough information was available, an assessment was made of patient adherence and medication tolerability, as well as prevention of mother to child transmission (PMTCT) programme exposure and World Health Organisation (WHO) clinical staging. Tolerability was assessed by the attending clinician at the time of the patient's clinic visit. Adherence was

inferred by clinical suspicion and whether regular follow up was fulfilled as medications were only supplied with each visit. Children were considered "lost-to-follow-up" if there were no documented clinical visits within the first 6 months.

Study approval was obtained from the Western Cape Government Health Research Department (WC_2017RP43_111) and ethics approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC Ref 236/2017).

Statistical Analysis

Data was captured in Excel; analyses were performed in Stata (College Station, Texas, USA). Categorical variables were described using percentages, continuous variables using and medians and inter-quartile ranges. We compared risk of virological unsuppression at 6 months with or without tuberculosis (TB) treatment and on different ART regimens using crude and adjusted prevalence ratios from modified Poisson regression, with robust error variance estimation [(9)].

Results

From 2005 – 2017, 672 children initiated ART at New Somerset Hospital; 529 (84%) were classified as WHO stage of 3 or 4 disease severity at time of initiation of ART, 51 (7.5%) as stage 1 or 2, and 92 (13.5%) had no documented stage. More children (437, 65%), received a stavudine-containing regimen than an abacavir-containing regimen (181, 27%); the median ages were similar, table 1. More children receiving stavudine were transferred out (15% vs 0.5%), were lost to follow up (11% vs 1%) or died (3% vs 0.5%); and only 33% of children initiated on stavudine had a 6-month viral load result, compared to 50% of those initiated on abacavir. Tolerability and adherence were reported to be better with abacavir compared to stavudine, but information was frequently not available.

Regimens consisted of 2 nucleoside or nucleotide reverse transcriptase inhibitors (NRTI's): lamivudine, and one of either stavudine, abacavir or zidovudine. In addition, children received either a protease inhibitor, lopinavir/ritonavir (LPV/r) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz (EFV). Children receiving lopinavir-ritonavir were younger than those receiving efavirenz, table 2. Of the 229 children with a 6-month viral load result, more children receiving stavudine were virologically suppressed compared to abacavir: 56% for stavudine/LPV/r compared to 39% for abacavir/LPV/r, and 73% for stavudine/EFV compared to 50% for abacavir/EFV, table 2 and figure 1.

In addition, children commenced on treatment for tuberculosis (TB) at the time of ART initiation or within the first 6months after ART initiation were less likely to be virologically suppressed at 6months than children not treated for tuberculosis. Of 23 children commenced on early TB treatment, 14 (61%) were unsuppressed, compared to 95 of 213 children (45%) who did not receive TB treatment in the first 6months of ART, risk ratio 1.36 (95% CI 0.95 – 1.96, p=0.09), table 3.

There was an increased risk of being virologically unsuppressed at 6 months while using an abacavir-containing regimen compared to a stavudine-containing regimen. This was statistically significant for the children using lopinavir-ritonavir, but not for those using efavirenz. The unadjusted risk of being virologically unsuppressed at 6 months while using abacavir/LPV/r was 1.39 (95% confidence interval 1.03 to 1.88, p=0.04) compared to stavudine/LPV/r. The relative risk of virological unsuppression of

abacavir compared to stavudine was greater among children using efavirenz (1.82, 95% CI 0.98 – 3.39, p=0.06), and was unchanged by concomitant TB treatment status. These estimates however lacked precision due to limited sample size of children using efavirenz. There was a trend towards lower risk of virological unsuppression among older children, but this was not statistically significant, table 3. Other thresholds of virological suppression (<40 copies per ml, less than 100 copies per ml) showed similar inferences, but precision was limited by small sample size (data not shown). Other analysis-based multivariable comparisons were not possible due to the small sample size in the sub-groups that were analysed.

Discussion

Our study reviewed a 12 year period in an urban centre, we observed an increased risk , at 6months post ART initiation, of being virologically unsuppressed while taking abacavir compared to stavudine (unadjusted risk 1,39, 95% CI 1.03 – 1.88, p=0.03) . This was similar to the results of the multi-cohort study of the IeDA Southern Africa collaboration from June 2014, which showed 54% of children were virologically suppressed on abacavir/LPV/r, versus 70% of children who were suppressed on stavudine/ LPV/r; and 78% were suppressed on abacavir-efavirenz, versus 86% who were suppressed on stavudine-efavirenz. [6]

A recently published retrospective case-cohort study conducted in Soweto from 2005 to 2013 reported no significant difference in virological suppression comparing children under 3 years using abacavir and stavudine. [10] However, the analysis was limited by a very small sample size, as only 57 children using abacavir were included. The observed differences in virological suppression at 6 months (54% versus 67%, Chi-squared *p* value 0.12) would have been statistically significant if they had used a larger sample size and would be congruent both with our results and with the IeDEA SA collaboration. [6]

WHO guidelines for ARV initiation in children have evolved over time, from only initiating children with advanced clinical or immunological disease in 2010, [11] to recommending treatment for all HIV-infected children irrespective of age or WHO staging. [7] At the time of introduction of abacavir, African children on abacavir were found to possess better pre-initiation characteristics than their predecessors initiated on other regimes prior to this. This is most likely because it coincided with the change in initiation criteria guidelines. [5] Furthermore, evidence suggests better outcomes in children who are initiated earlier; [12] and one would have expected to find better outcomes in those children with less severe immune suppression who were commenced on abacavir compared to those children with more severe disease who were commenced on stavudine.

There are a number of possible reasons for the unexpected lower rate of virological suppression of children using abacavir in this study. The CHAPAS-3 study, a parallel-group randomised controlled trial conducted in Zambia and Uganda, compared stavudine, zidovudine or abacavir in combination with lamivudine and nevirapine or efavirenz, and found children had good clinical, immunological and virological response regardless of backbone NRTI. [13] They also found no major differences in any adverse event or toxicity endpoint during the nearly 2.5 years follow up of 480 ART-naive and ART-experienced children from November 2010- December 2011. [13] Notably, there was a very high

retention in this intensively-monitored clinical trial: less than 5% were lost to follow up. In this context, unlike our study and in the IeDEA collaboration of routinely-collected clinic data, [6] where adherence was not necessarily optimised, and retention was not ideal, the CHAPAS-3 trial did not find abacavir to be poorer in its virological response when compared to stavudine [13]. It is also important to note only 24 of the ART-naïve children were younger than 1year, in contrast to our study, where 392 (58%) were younger than 1year, with associated high viral loads. This suggests that the differences we observed may not be due to intrinsic virological properties of the medications, but rather reflect the changing context of the expanding paediatric ART program.

The extensive PMTCT roll out in South Africa during the study period decreased the overall number of vertically transmitted HIV cases [14] . We observed fewer children initiating ART in the later years of our cohort, figure 2. In addition to decreased burden of new infections, this also shows the effect of expanding access to community ART over time, as more children initiated ART at community sites, which has been a hallmark of the paediatric ART rollout.[15] As more children with uncomplicated disease were initiated at community sites, over the course of the study children with complex or severe disease, co-morbidities or social problems would have remained at the hospital-based clinic. This may have contributed to poorer adherence and virological suppression in the later abacavir era compared to the earlier years.

Furthermore, as the PMTCT program led to marked decreases in peripartum and breastfeeding-acquired infections, the relative proportion of intrauterine infected children has increased. [12] The effect on virological suppression on children with *in utero* infection may be different to children who are infected later, as the long-term impacts of HIV infection occurring in a foetus at a stage with a very immature immune system are not fully understood.

Our study also displayed poorer virological suppression among children using LPV/r-based regimes compared to efavirenz-based regimes, in both abacavir and stavudine groups. As efavirenz was used in older children, the lower virological suppression among children using LPV/r may due to higher baseline viral loads in younger children and infants, making suppression more difficult. Furthermore, administration of LPV/r is problematic, as each dose comprises a small volume of very unpalatable syrup. Children may be more prone to spit out or vomit a dose of LPV/r than efavirenz, which results in under-dosing, and may have contributed to lower suppression in this age group.

Adherence in this retrospective study was difficult to measure, with variable subjective and objective comments recorded. Missed visits served as a more objective inference of adherence. Similar to a 10-year cohort analysis from a rural hospital in South Africa, [16] abacavir was noted to have higher attrition rates than stavudine. Substantial attrition within the first 6 months was observed in this study. Viral load testing amongst both groups was also poor, with only 145 (33%) of children using stavudine and 91 (50%) of children using abacavir having a documented viral load at 6 months. Other South African paediatric studies have documented viral load testing of 60 – 80% in urban centres and 40-45% in rural facilities. [14,16-18] It was reported that implementation of VL testing was particularly poor at facilities with large catchment populations (district or regional hospitals) compared to primary healthcare facilities. [16,19] It is uncertain whether this is due to temporal

changes in health-seeking behaviour, higher transportation costs and waiting times to accessing an urban facility, or decreased time spent counselling patients during busy clinics by overworked staff. In our cohort, it was also not clear whether the attending clinician deliberately deferred viral load testing if poor adherence or tolerability was reported. The lack of uniform follow-up testing guidelines within the clinic may have also contributed to infrequent or inconsistent testing.

Cape Town, has a high incidence of tuberculosis. In 2000, the incidence was 562 new cases per 100 000 population, with children under 15 years of age forming between 15% and 20% of this TB burden. [20] In our study the presence of TB was found to be unusually low; we suspect this was systematically under-reported, but we could not confirm this.

Most deaths occurred within the first 3 months on treatment; this may reflect the baseline clinical severity of participant at initiation, rather than specific ART regimen. The decline in early deaths (within 6 months of initiation of ART) with abacavir regimes in the latter part of this study may reflect increased and earlier access to ART.

There were several limitations in this analysis. This data is not that of a clinical trial, but of a busy public-sector clinic with high staff turnover and large patient numbers. Due to resource constraints, there were many missing variables, limiting statistical analysis of some outcomes. The groups compared were not randomised, but were initiated over different temporal periods, and initiation criteria and social environments varied markedly, making direct comparisons of the participants at baseline as well as the regimens used difficult. The study was also conducted at a single centre and with limited follow-up, only 6 months, with suboptimal and infrequent rates of viral load testing. This unique setting makes it difficult to extrapolate our results to the other paediatric populations at other time periods. However, use of routine program data rather than dedicated clinical trial databases may have enhanced representativeness, as it is likely to be a better reflection of the “real world” state of paediatric ART clinics.

Conclusion

The overall rate of virological suppression we observed for all regimens was lower than that reported in the IeDEA collaboration [6] and in a recent analysis from Soweto. [10] Although of small sample size and limited by substantial missing data, this study offered an opportunity to describe an urban ART facility and contextualize our outcomes to current local and international data.

Our analysis again raises concerns about virological suppression in the abacavir era of paediatric ART, compared to the previous stavudine era, particularly in combination with LPV/r in the younger, more vulnerable children. Whether this is because of intrinsic properties of the different medications or is a marker of the evolving complexity of the South African ART rollout, may never be resolved. However, this is of concern as abacavir and LPV/r appear to be entrenched as first-line paediatric ART in a setting where attrition is high, many children are lost to follow up and virologic

surveillance is not always optimal. Clinicians need to optimize retention strategies, especially of young infants, to ensure that children are retained in care, have viral load testing timeously, so that those virologically unsuppressed can be detected and treated early and appropriately.

The authors declare no conflicts of interest

Acknowledgments

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Tables and figures

Table 1: Characteristics of children commenced on ART

	Stavudine-containing regimen (n=437)	Abacavir-containing regimen (n=181)	Neither abacavir nor stavudine in initial regimen (n=54
Age in months at initiation, median (Interquartile Range)	8.9 (4.1; 24.1)	11.0 (3.5; 29.9)	3.1 (0.8; 10.0)
Male sex, (%)	219 (50%)	88 (49%)	19 (35%)
TB diagnosis: Never, (%) Before ART, (%) At ART, or within 6 months, (%) >6 months after ART, (%)	 407 (93%) 11 (3%) 16 (4%) 3 (1%)	 152 (84%) 5 (3%) 24 (13%) 0	 53 (98%) 1 (2%) 0 0
Outcomes Transferred out, (%) Died, (%) Lost to follow up, (%) Retained in care, but no 6-month viral load, (%) Had 6-month viral load, (%)	 64 (15%) 15 (3%) 49 (11%) 174 (40%) 145 (33%)	 1 (0.5%) 1 (0.5%) 2 (1%) 87 (48%) 91 (50%)	 4 (7%) 1 (2%) 3 (6%) 23 (43%) 23 (43%)
Poor adherence to medication noted, (%)	15/111 (13%)	2/163 (1%)	0
Poor tolerability of medication noted, (%)	17 /108 (16%)	4 /162 (2%)	1/33 (3%)
Missed visits noted, (%)	31/109 (28%)	79/161 (49%)	14/33 (42%)

Table 2: Comparison individual ART (anti-retroviral therapy) regimens

	Number of children	Age (months) at initiation Median (IQR)	Number with 6-month viral load result, n (%)	Virological suppression at 6 months
Stavudine / Lopinavir-ritonavir	318	6.9 (3.6; 15.4)	102/318 (32%)	57/102 (56%)
Abacavir / Lopinavir-ritonavir	125	7.0 (3.0; 16.8)	57/125 (46%)	22/57 (39%)
Stavudine / Efavirenz	109	39.4 (9.4; 82.7)	40/109 (37%)	29/40 (73%)
Abacavir / Efavirenz	47	54.0 (29.3; 96.5)	30/47 (63%)	15/30 (50%)

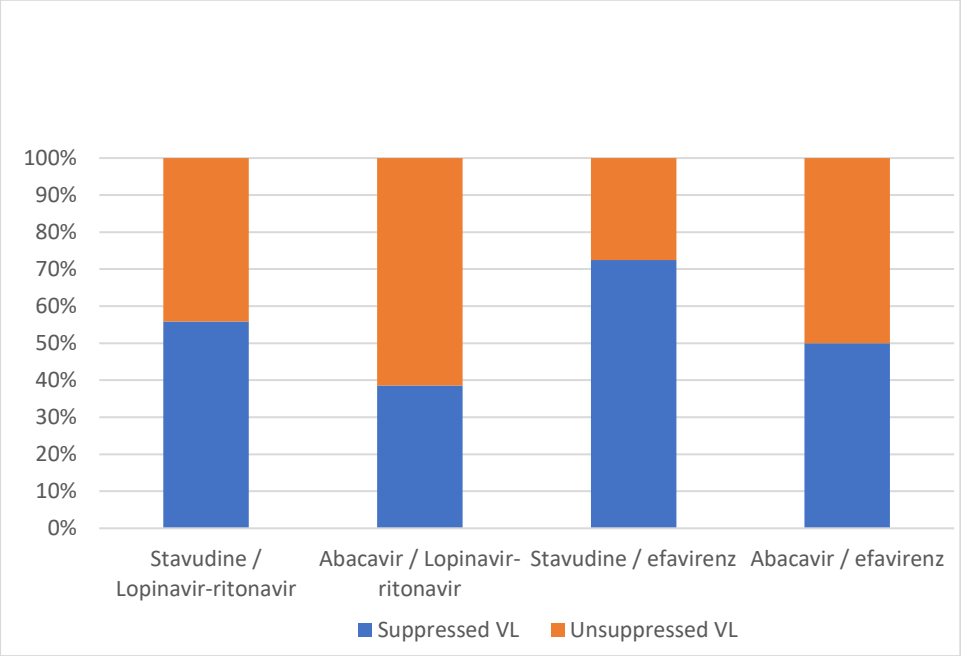

Figure 1: Virological suppression at 6 months, by initial ART regimen

Table 3: Risk of virological unsuppression at 6 months, using different antiretroviral regimens and tuberculosis treatment, from modified Poisson regression

Regimen and comparison	Risk ratio (95% confidence interval)	P value
Age at ART initiation:		
Under 1 year (comparator)	1	
1 to 3 years	0.97 (0.70 – 1.34)	0.83
Over 3 years	0.89 (0.60 – 1.31)	0.54
TB treatment[1] vs no TB treatment[2]	1.36 (0.95 – 1.95)	0.09
Using LPV/r[3]:		
ABC[4] vs d4t[5], unadjusted	1.39 (1.03 – 1.88)	0.03
ABC vs d4T, adjusted for TB treatment	1.36 (1.00 – 1.86)	0.049
Using EFV[6]:		
ABC vs d4t, unadjusted	1.82 (0.98 – 3.39)	0.06
ABC vs d4T, adjusted for TB treatment	1.82 (0.96 – 3.44)	0.07

1. Tuberculosis, diagnosed at ART initiation or within 6 months after ART initiation
2. Never treated for TB, or not within 6 months of ART initiation

ART: Anti-retroviral therapy
LPV/v: Lopinavir-ritonavir
ABC: Abacavir
d4T: Stavudine
EFV: Efavirenz

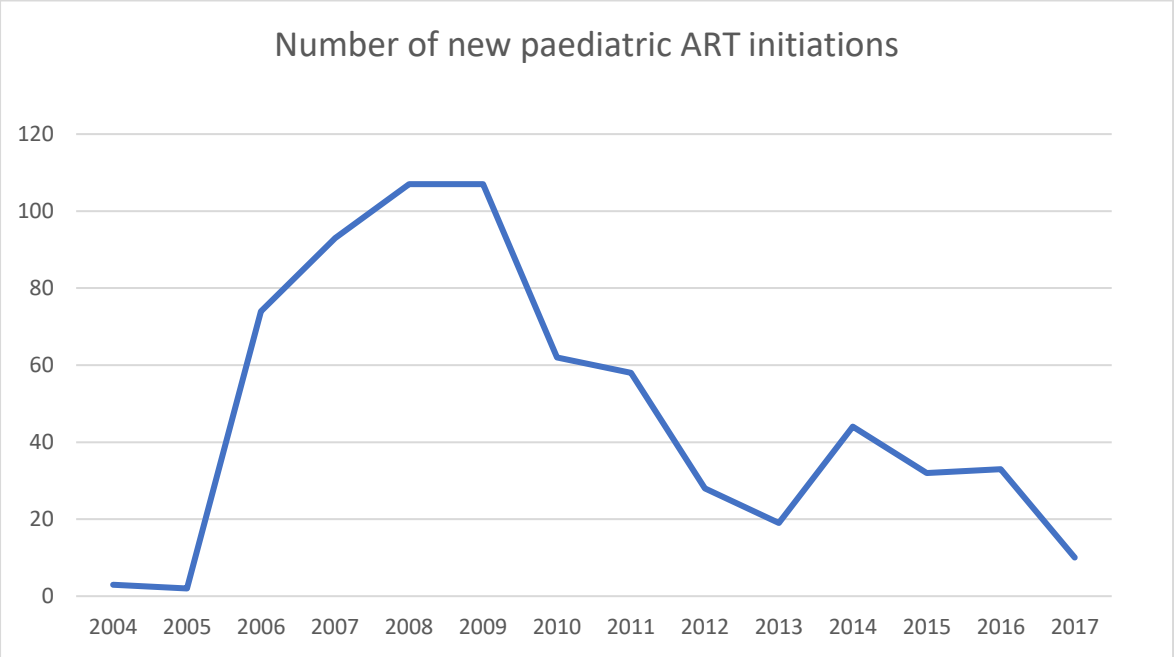

Figure 2: Temporal evaluation of new paediatric ART initiations at New Somerset Hospital

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For attention: Dr Zeenat Gaibee

Re: **Effect of initial antiretroviral regime on virological suppresion in children in a Southern African urban population: a retrospective record review.**

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact following people to assist you with any further enquiries in accessing the following sites:

New Somerset Hospital	**Dr Donna Stokes**	**021 402 6408**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).