

**SUBSTITUTIONS TO INITIAL ANTIRETROVIRAL THERAPY DUE
TO TOXICITY OR CONTRAINDICATION AMONG CHILDREN IN
SOUTH AFRICA**

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Thesis Abstract:**Background:**

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) South Africa 2010 Country Progress report, 81% of South African children in need of antiretroviral therapy (ART) were receiving treatment which is a 20% increment in treatment access from 2008 to 2009. With increase in access to treatment, understanding drug tolerability, safety and durability is important especially among children whose drug options are limited due to few drugs being available in suitable formulations and the need for refrigeration of some drugs. While there are many paediatric studies on ART durability in the developed world, data from the developing world are limited. There is therefore a need to understand the drug-specific probability of and reasons for drug stops or changes among children initiated on ART in South Africa. This knowledge could help in optimisation of use of first-line ART in order to maximise time on first-line therapy and thereby maintain simplicity of programs (program-level benefit) and save alternative drugs for situations of toxicity and virological failure (individual benefit). We determined the probability of and reasons for stopping/changing of antiretroviral drugs in the International epidemiological Databases to Evaluate AIDS Southern Africa (IeDEA-SA) paediatric data.

Methods:

This study was a secondary analysis of cohort data which are routinely collected from all paediatric HIV clinic sites in South Africa that contribute data to the IeDEA-SA Collaboration. The study population included all HIV infected children ≤ 16 years of age at ART initiation with a documented date of birth and initial regimen of ≥ 3 antiretroviral (ARV) drugs, and attending any one of 7 South African paediatric HIV clinic sites that contribute data to the IeDEA-SA database. The time from initiation of ART to first treatment change both for the entire regimen (mainly due to treatment failure) and for individual drugs was described using the Kaplan-Meier method. Competing risks analysis was used to determine the reasons for drug-specific changes. Predictors of specific drug substitutions due to toxicity were determined using Cox-proportional hazards models stratified by site.

Results:

Data from 5517 children with median [IQR] age at ART start of 42 [15-82] months were included in the analysis. By 3 years on ART, 81% of children alive and in care were still taking their initial regimen. Drug stops/changes for reasons other than treatment failure were mainly due to potential drug interaction in the 1st year on therapy (2.9%) while in the 3rd year toxicity (3.1%), potential drug interaction (2.6%), treatment simplification (e.g. changing from syrup to tablet formulations) (2.3%) and other unspecified reasons (4.1%) were the main contributors. Nevirapine, zidovudine and stavudine were responsible for most treatment-limiting toxicity by 2 years on ART i.e. n=10/259 (4%), n=11/602 (2.8%) and n=45/4883 (1.4%) respectively. Nevirapine toxicity occurred almost entirely in the first six months whereas stavudine toxicity occurred mostly after 1 year of therapy. Half of the zidovudine toxicity occurred in the first 3 months with the remainder evenly spread over the following 21 months.

Conclusion

Paediatric ART durability in resource-limited settings is good but complex, with treatment changes not only due to toxicity, treatment failure and drug interactions, but also treatment simplification. NVP, AZT and d4T are responsible for most of the treatment-limiting toxicity in children in resource-limited settings.

Dedication

This dissertation is dedicated to my family who stood by me through three years of studying and encouraged me to reach for the stars.

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Abbreviations:

ABC	Abacavir
aHR	Adjusted hazard ratio
AIC	Aikaikes Information Criterion
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
CI	Confidence Interval
ddI	didanosine
d4T	Stavudine
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IAS	International AIDS Society
IeDEA-SA	International Epidemiologic Database to Evaluate AIDS-Southern Africa
IQR	Interquartile range
LPV/r	Lopinavir/ritonavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OASIS	Observational Antiretroviral Studies in South Africa
PI	Protease inhibitor
PMTCT	Prevention of mother to child transmission
RTV	Ritonavir
SQV	Saquinavir
TB	Tuberculosis
WAZ	Weight-for-age z-score
WHO	World Health Organisation
3TC	Lamivudine
UNAIDS	Joint United Nations Programme on HIV/AIDS

PART A: PROTOCOL

SUBSTITUTIONS TO INITIAL ANTIRETROVIRAL THERAPY DUE TO TOXICITY OR CONTRAINDICATION IN CHILDREN IN SOUTH AFRICA

I. INTRODUCTION

Southern Africa has a high burden of paediatric HIV, and despite recent massively expanded access to antiretroviral therapy (ART), coverage remains low. By the end of 2009, 81% of South African children in need of ART were receiving treatment which is a 20% increment in one year from 2008 [1]. However, these data do not account for children lost to follow-up, transferred out of care or who had died or remained undiagnosed.

With increased access to ART, many children in South Africa and other parts of the world may have one or more drugs in their initial antiretroviral (ARV) regimen changed during therapy. Regimen changes can be considered as either **(i)** one or more drug substitutions for reasons other than treatment failure while keeping the same overall regimen, e.g. a change from stavudine (d4T) to zidovudine (AZT) in a child with lipodystrophy, with all other drugs in the regimen remaining the same (which will be referred to as “substitutions”) or **(ii)** a complete switch of the regimen due to treatment failure in which there is a change from a non-nucleoside reverse transcriptase inhibitor (NNRTI) to a protease inhibitor (PI) or vice versa together with a change of at least one of the nucleoside reverse transcriptase inhibitors (NRTI) (which will be referred to as “switches”). Reasons for regimen or drug change reported by previous studies of paediatric ART outcomes include serious adverse events, treatment failure, co-treatment for tuberculosis (TB), policy/guideline changes and drug stock outs [2-7]. In these studies, the median time to treatment change regardless of whether this was a substitution or a complete regimen switch varied between 5 and 17 months after ART initiation.

II. PROBLEM IDENTIFICATION:

Understanding regimen durability is particularly important in resource-limited settings with limited drug options [8]. This is especially so for children [9] due to limited palatable paediatric formulations, the need for refrigeration of liquid formulations which may not be feasible in resource-poor settings and lack of incentive for pharmaceutical companies to manufacture paediatric ARV drugs due to a small market especially in resource rich countries [10].

While the frequency and determinants of regimen switch in children with virological failure in South Africa have been examined [11], there is very little data from South Africa or other developing countries on the frequency of drug substitutions for reasons other than treatment failure.

III. LITERATURE REVIEW:

We aim to review all paediatric observational studies from resource limited settings reporting on regimen changes in children on ART. Selected key articles from the adult literature on regimen changes in developing countries as well as studies from developed countries will also be reviewed for comparison with and to contextualise the paediatric studies. In addition, selective randomised controlled trials reporting on toxicity of ART will also be included as determining drug safety is one of the main reasons for studying regimen changes.

ART regimen changes are fairly common in routine HIV care albeit less common in developing countries compared to developed countries [8, 9] probably due to fewer alternative regimens in the developing countries, hence the importance of determining the frequency and reasons for them. Alternatives to the first-line ART recommended in national guidelines are limited and should ideally be preserved for situations of virological failure or serious adverse events. This is a particular concern in children for whom ART options are limited due to the need for palatable formulations of ART in which small dosing increments are possible. In addition, prior exposure to prevention of mother to child transmission (PMTCT) regimens predisposes these children to resistance to the drugs used i.e. nevirapine (NVP) and AZT [12] and consequent treatment failure [11] further

reducing the options available for use as first-line regimens and/or alternative regimens among children.

3.1 ART drug substitution in adults

In Africa and elsewhere in the world, most large cohort studies done to determine the tolerability and reasons for first-line ART change have been conducted in adults. Boulle et al (2007), in a study conducted to determine the probability of substitutions due to ARV toxicity or contraindication in the first three years of therapy in 2 South African cohorts reported that 72% of 2679 adults remained on their initial NNRTI-based regimen after 3 years of treatment. Substitutions of d4T were the most common and accumulated over time, with patients having a 21% cumulative probability of having their treatment substituted by 3 years on ART. In contrast, cumulative probabilities of substitutions due to toxicity of NVP (8%), efavirenz (EFV) (2%) and AZT (8%) were less frequent and occurred early on after starting ART. Another prospective cohort of 559 adult patients in Uganda, most of whom were started on NVP-based (74%) or EFV-based first-line ART, reported that about a quarter of the cohort had at least one treatment change after a median follow-up time of 33 (IQR, 24 to 34) months on ART. Drug toxicity accounted for the majority of first treatment changes (62%) followed by treatment failure (16.2%) with the remainder of the regimen changes being due to TB/HIV co-infection and pregnancy [13]. d4T toxicity was found to be the main reason for drug substitution due to toxicity and was associated with being female and WHO stage 3 or 4 and this concurs with Boulle et al (2007). The median time to substitution was 2 (IQR, 0.45 to 1.09) years. In addition, other developing country adult studies assessing initial response to ART, its durability and tolerability have also found that toxicity contributed most to both inter and intra-class single drug substitutions [14-16].

3.2 ART drug substitution in children

In comparison to adult studies, data on the durability and tolerability of ARVs in children are restricted as there are few large paediatric cohort studies that have been conducted and most data come from cohort studies conducted in the developed world. While different drugs may have

overlapping toxicities; there are also drug and class-specific toxicities [17, 18] hence the need to clearly document the drug limiting toxicities associated with ART in children as extrapolating results from adult studies to children may be inaccurate. A cohort study conducted to describe outcomes of ART-naïve severely immune suppressed children less than 5 years old and receiving ART in resource limited settings, 90% of whom were in Africa and the rest in Asia; showed that after a median time of 1.5 (IQR, 0.7-5.7) months on highly active antiretroviral therapy (HAART), 3.8% of these children had one or more of their first-line ARV drugs changed mainly due to toxicity. The first-line regimen was d4T/3TC/NVP for children aged between 12 to 59 months with AZT replacing d4T for those who were 12 months and younger. In African children, AZT toxicity was more frequent while in Asian children, toxicity was mainly due to NVP. Switching to second-line drugs was more common in African children (87.9% of all switches) after about 27 months on ART [19].

In contrast, Davies et al (2011), in a study designed to determine the probability of virological failure and switching to second-line ART in children in South Africa found that ART-naïve South African children aged less than 16 years had a 19% probability of failing treatment by 36 months on therapy with a 38% switch rate in those with at least 1 year of follow-up after failure. The switches occurred a median of 5.7 (IQR, 2.9-11.0) months after treatment failure was diagnosed. This study, however, did not aim to examine reasons for ARV regimen substitution which may include toxicity, contraindication and change of eligibility criteria e.g. a child turning 3 years of age and changing from lopinavir/ritonavir (LPV/r) to EFV.

A small number of studies report on reasons for ARV drug substitution including toxicity, treatment failure, initiation or completion of TB treatment and change due to increasing age [6, 20-23]. However, many of these cohorts are small with limited follow-up duration and the majority of children started on NNRTI-based treatment. Tolerability of PI-based regimens in children has not been studied. In addition, only the overall proportion of changes has been described with descriptions of the time to regimen change and reasons for change being limited.

3.3 Studies from the developed world

Most of the cohort studies done in the developed world have shown that the main reasons for ARV regimen changes in children are toxicity and treatment failure [24-28] and this is similar to findings from developing countries. For example, a retrospective cohort study of 110 HIV infected children in routine care in London, 83% of whom were not ART-naïve, found that the commonest cause of treatment change was virological failure (60%) and durability of first-line therapy was better (46 weeks) compared to that of second (42 weeks) and third-line therapy (40 weeks) [29]. Tolerability of ART among children reduced as the treatment became more complex highlighting the importance of achieving maximum utility from standard first-line drugs before changing to an alternative drug to prevent situations where alternative regimens may run out. Other reasons for treatment change were toxicity and immunological failure in 10% and 6% of the children respectively [29] and this is consistent with findings from other cohort studies done in similar settings [24-28].

IV. JUSTIFICATION:

With the scale up of ART in sub-Saharan Africa, knowledge of the tolerability and durability of first-line ART is increasingly important as there are very few alternatives to standard first-line ARV regimens for children. Due to the few available alternative drugs, if the durability of standard first-line regimens is short, children may be placed on sub-optimal regimens increasing their risk of treatment failure and/or resistance. Furthermore, substitution of single drugs in the first-line regimen for reasons other than failure, may limit the options for an effective second-line regimen when the child ultimately fails therapy. A number of observational studies on tolerability, safety and durability of first-line ART have been done in adult patients both in the developed and developing countries [8, 13-16]; however, there is still a paucity of information about the same in paediatric patients especially in low income settings such as South Africa.

There are few available options for ART for use in HIV infected children, especially in Sub-Saharan Africa, due to lack of suitable formulations for children. There is thus a huge need to try to prevent early and frequent substitutions and/or switches in order to optimise the use of standard first-line

therapy and save the few alternatives for situations of virological failure and/or drug resistance. This involves understanding the durability and tolerability of different ARV regimens and individual drugs. In addition, studying treatment-limiting toxicities will give us information about drug safety in clinical practice. In situations where drugs are changed or stopped for reasons of toxicity, studying such treatment-limiting toxicities will allow us to determine the rate of clinically important adverse events. Where standardized ART regimens are used, a change of a single drug due to toxicity indicates that the adverse event was severe enough for a clinician to stop the drug thought to have caused it. Accurate recording of all reasons for regimen changes ensures that under-ascertainment of event rates is minimized.

V. RESEARCH QUESTION:

What is the probability of and reasons for substitution of one or more drugs in an initial antiretroviral (ARV) regimen among South African children during the first three years on antiretroviral therapy (ART)?

VI. RESEARCH AIM, OBJECTIVES AND HYPOTHESIS

6.1 Aim:

To determine the drug-specific probability of and reasons for drug change/stop among children initiated on ART in South Africa.

6.2 Objectives:

- To determine the cumulative probability of changing or stopping one or more drugs from an initial ARV regimen for each first-line drug among children on ART in South Africa.
- To describe the reasons for changing or stopping one or more drugs from an initial ARV regimen for each first-line drug among children on ART in South Africa.
- To determine characteristics of children associated with requiring particular drug changes or stops.

6.3 Hypothesis:

- a) There is an association between child characteristics and probability of and reasons for change of one or more ARV drugs in a regimen among children on ART.
- b) Drug substitutions will be rare in the leDEA-SA cohort.

VII. METHODS

7.1 Study design:

This will be a secondary analysis of cohort data routinely collected from children attending different paediatric HIV clinic sites in South Africa that contribute data to leDEA-SA. These children are followed up routinely as part of standard HIV care and their response to ART is monitored. Treatment changes are made according to the South African National HIV Treatment Guidelines [30].

7.2 Population and sampling:

7.2.1 Study Population:

This will include all HIV infected children who were below 16 years of age at the time of ART initiation and attend any of the South African paediatric HIV clinic sites that contribute data to the leDEA database. These are Tygerberg Academic Hospital, Red Cross War Memorial Children's Hospital, McCord Hospital, Rahima Moosa Mother and Child Hospital, Harriet Shezi Children's HIV Clinic, Khayelitsha Community Health Centre and Gugulethu Community Health Centre. The points of entry for the children into these cohorts include referral from other medical facilities and/or hospital wards, or being a family member of someone already attending the clinic. These patients attend these routine government clinics free of charge with the exception of McCord Hospital where patients contribute a small co-payment for screening and/or routine consultations. As recommended by the South Africa National Treatment Guidelines [30], these patients are followed up 1-2 monthly for the first 3-6 months on ART and 3 monthly thereafter especially if the patient is stable on treatment i.e. if the viral load is undetectable.

The standard first-line regimens across all the sites are d4T/3TC/ (LPV/r) for children 6 months to 3 years of age or d4T/3TC/EFV if over 3 years of age and > 10kgs. The second-line regimen for children less than 3 years of age and commenced on a PI-based first-line regimen is AZT/ddI/NVP with EFV replacing NVP in children > 3 years of age. A second-line of AZT/ddI/ (LPV/r) is used for children commenced on an NNRTI-based first-line. Viral load and CD4 percentages are measured at least 6 monthly across all sites.

7.2.2 Sampling:

This study will include all children less than 16 years old with complete data i.e. date of birth, gender, ART start date, initial ARV regimen, reasons and dates of regimen change or stop and from all paediatric HIV treatment sites in South Africa that contributed data to the leDEA database up to March 2008.

7.2.3 Inclusion criteria for cohorts:

Only cohorts that initiated ART in at least 25 ART-naïve HIV-infected children will be included in the analysis.

7.2.4 Inclusion criteria for children:

- Children who commenced ART at <16 years of age
- HIV-infected children who were ART-naïve at the time of ART initiation.
- HIV-infected children who initiated ART with a documented initial regimen of at least 3 ARV drugs.

7.2.5 Exclusion criteria for children:

- All children with any missing information on key variables e.g. date of birth, gender and initial ARV regimen used will be excluded from the analysis.

7.2.6 Sample size calculation:

We will assume 90% power at a 0.05 level of significance for a two-sided test and a 0.2% overall probability of a child having either their whole ARV regimen changed or a single drug substitution

which is slightly less than the 0.3% probability observed in resource rich settings [9]. Therefore, given a 20% anticipated censoring due to loss to follow-up from the study [31], entering the cohort immediately before database closure and transfer out of the cohort, the sample size will include at least 365 children [32].

7.3 Measurement:

7.3.1 Instruments:

Data are routinely collected from children during every clinic visit at the clinic sites. These data are kept in folders that are identified by unique patient numbers. Each site has a site-specific data collection form and data have been entered into a site-specific electronic database. Anonymised data are then transferred to the leDEA database in various formats which include Access, XML, STATA and SAS where the data are converted to the SQL format and stored on the local server. While these data are void of any patient personal information (e.g. patient names), each patient has a unique and anonymous patient identifier that can easily be cross referenced by individual sites with the site database.

Data from all seven cohorts that will be included in this analysis will be checked for completeness. Where data are found to be missing, for example, reasons for regimen substitution and the corresponding dates when the substitution was done; the sites will be contacted and requested to provide these data through folder review, and the combined leDEA database updated accordingly. In addition, data on laboratory investigations done and opportunistic infections recorded during follow-up will be cross-checked to identify possible reasons for regimen change.

7.3.2 Validity and Reliability:

Validity and reliability of this study's data collection tools is contingent upon that of the tools used at the HIV clinic sites for routine data collection. In order to check accuracy of these data, initial manual checking will be done to ensure that for every drug stopped, there is an appropriate stop reason and that drug start and stop dates are complete and coherent. Where inconsistencies are noticed or data are missing, this will be checked and sourced directly from the respective sites.

7.3.3 Variables:

The dependent variables will include:

- Drug change –binary
- Reasons for individual drug change- categorical e.g. toxicity, treatment simplification, potential drug interaction, treatment failure.

The independent variables will include:

- Age of the child at ART initiation-categorical i.e. <3years versus ≥3years
- Gender- binary
- CD4 percentage at ART initiation-continuous
- WHO disease stage at ART initiation -categorical i.e. WHO stage 1 and 2 versus WHO stage 3 and 4
- Viral load at ART initiation -continuous
- Initial ARV regimen used-nominal
- Weight-for-age at baseline –categorical i.e. weight-for-age <-1 versus weight-for-age>=-1
- Haemoglobin at ART initiation- categorical i.e. Haemoglobin <7g/dl versus haemoglobin ≥7g/dl
- Liver function tests values (e.g. alanine aminotransferase (ALT)) at ART initiation -continuous

Data on potential confounders e.g. age, gender will be extracted from the leDEA database and these will be adjusted for in the analysis using multivariate regression methods.

In South African paediatric ART programs, laboratory monitoring (including CD4 testing, viral load testing, alanine transaminase (ALT) and haemoglobin testing) is available at all sites (either on-site or off-site) and the turnaround time for results varies between one day to 1 week. Patients are assessed clinically for adverse events at each clinical visit. Clinical visits are scheduled 1-2 monthly for the first 3-6 months on ART and approximately 3-monthly thereafter. In most programs, CD4 monitoring, ALT and haemoglobin monitoring was done routinely every 6 months as recommended in national treatment guidelines during this period [30]. Lactate measurements were performed if there was clinical suspicion of hyperlactataemia.

VIII. DATA ANALYSIS

8.1 Data management:

All the patient folders are kept at the different paediatric HIV sites. During data transfer from the paediatric HIV sites, the data are encrypted and compressed using WinZip9 and the password is given to the leDEA data manager either by fax or telephone (Appendix A). All patients have unique anonymised identifiers and no personal patient information e.g. names will be used for patient identification in the database. All electronic data are kept securely and managed by the leDEA data manager and will be transferred into a STATA statistical package for the analysis. I will not have access to the main leDEA database.

Variables in the data set include but are not limited to: patient identifiers, cohort name, age, gender, first-line ART regimens, ART start and stop dates, alternative ART regimens given, visit dates, weight, height, laboratory tests done to monitor progress on treatment and any opportunistic infections (e.g. TB) suffered by children when on treatment.

Using the data in STATA, I will manually check for missing data on dates of and reasons for regimen substitution, inconsistencies on regimens given, for example, patients on >4 ART drugs at any one time and duplicate drug records with identical start dates but different stop dates. A list of patients (using the leDEA anonymous unique identifier) for whom there is missing or inconsistent data will be created for each site, and sites will be asked to provide the missing data and correct any inconsistencies by cross-checking with the site-level patient identifier and referring to original data collection forms and patient records. This will be followed by correction of data in the main leDEA database which will only be done by the designated leDEA data manager.

8.2 Analysis plan:

For all analyses, techniques will be used that account for between cohort variation. Data will be analysed on an intention-to-treat basis in order to avoid an over estimation of treatment changes e.g. Children who had drug interruptions with the same drugs being re-started at a later date will be considered to still be at risk of having a drug changed until such a time as it was changed or when

follow-up ended. Follow-up will be censored at the first of: first drug stop/change, date of death, date of transfer out, date of last visit if lost to follow-up or still in care at database closure. Analysis will be done using both univariate and multivariate methods. Characteristics of children at baseline and at time of treatment change will be described using univariate analysis i.e. medians and interquartile ranges if numerical but skewed, means and 95% Confidence Intervals (CIs) if numerical and normally distributed and proportions and 95% CIs for categorical variables. Multivariate analysis will be done to explore any associations between child-specific characteristics and specific drug treatment changes due to toxicity after adjusting for potential confounding variables.

The Kaplan Meier method will be used to describe the time to first ART change for individual drug substitutions. For changes to the overall regimen, description of drug changes for each year will be done with the denominator being the number of children still in care at the end of that year. Survival curves will be plotted to show the different regimen change or single drug substitution events and risk tables will be included to show the number of children at risk of having a regimen or single drug substitution at different time intervals. Competing risks analysis will be used to determine the incidence of drug changes for specific reasons (e.g. d4T change due to lipodystrophy) in the sub-population of children exposed to each specific drug. The competing risks methods takes into account the fact that if a patient changed d4T for a competing reason (e.g. lactic acidosis) before the reason of interest (lipodystrophy), this drug could no longer be changed due to lipodystrophy. In other words, the competing risk is an event (changing d4T due to lactic acidosis), the occurrence of which precludes or alters the probability of the main event (d4T substitution due to lipodystrophy).

Cox proportional hazards models will be used to identify independent predictors of individual drug changes due to toxicity for specific drugs in the initial ARV regimen (e.g. predictors of change of d4T due to toxicity). The Cox proportional hazards method will be used because it takes into account any losses to follow-up which a cohort study such as this one is vulnerable to and, stratification by site will be done to account for between site heterogeneity. These models will also be used to adjust for any confounders and/or effect modifiers in these paediatric cohorts. Confounders known to be biologically associated with ART drug substitution in children e.g. age at ART initiation; viral load at

ART initiation, CD4 count at ART initiation will be included in the model *a priori*. Interaction between some confounding variables and risk factors for ART drug substitution due to toxicity and between different risk factors will be investigated and any variables that are found to have interaction (i.e. which make a significant contribution to the model by significantly lowering the Aikaikes Information Criterion (AIC) and which are biologically plausible) will be included in the final model, while still maintaining parsimony. The final model will be chosen based on biological plausibility and will have the lowest AIC and largest log-likelihood. All analyses will be done using Stata 11.0 [32].

IX. ETHICS AND COMMUNICATION:

9.1 Ethics:

The primary ethical issues that are likely to arise from this analysis will include beneficence, autonomy and justice.

Beneficence implies that patients are not intentionally harmed and that benefits to patients are maximised and possible harms are minimised [33]. This analysis will pose no direct foreseen risk or harm to the patients since no further human subjects' research will be done and only data routinely collected in the clinics will be used.

Collection of these data was formally approved by the University of Cape Town Health Sciences Human Research Ethics Committee (Appendix B).

Since this analysis will use data that do not contain personal patient identifiers e.g. names, confidentiality will be assured.

A concept paper describing the type of analysis that will be done using these data will be circulated among the different leDEA-SA sites and data will only be included in this analysis upon receiving permission from the participating sites to have their data used for this study (Appendix C).

The concept of justice implies that patients' rights should be considered when conducting any study. Despite the fact that this study will not directly benefit the children whose data will be used in this analysis, the results will be disseminated to the respective paediatric HIV clinics so as to inform and improve patient management with regard to substitution of individual ARV drugs and switching ART.

The results will also be widely disseminated to other health centres within and outside South Africa in order to improve management of HIV in children who need ART with regard to changing therapy. The results from this study will be aimed at informing policy regarding management of paediatric HIV and specifically concerning ART changes as this is a dilemma that is faced by health workers during the day to day routine care of children on ART.

9.2 Stakeholders:

The stakeholders will include all the paediatric HIV clinic sites whose data will be used in this analysis, the children who attend these clinics, the policy makers in the field of HIV and the wider community. The researchers at the leDEA both locally and internationally have a direct interest in this study since this analysis will use data from their database.

9.3 Dissemination of study results:

The results will be distributed electronically with the opportunity for an oral presentation at sites being offered. Abstracts will be submitted to relevant conferences (e.g. International AIDS Society (IAS) conference) to disseminate study results at the national and international level. Findings will be made available to other researchers in the field of infectious diseases by publishing results in the form of a manuscript in a peer-reviewed journal that will be identified.

X. LOGISTICS

10.1 Budget:

As this will be a retrospective analysis of routinely collected data, the study will not incur any foreseeable costs.

10.2 Timeline:

year	activity	protocol development	protocol submission for approval	literature review	data cleaning	data analysis	discussion	write up	journal manuscript	
2010	Mar				[purple bar]					
	Apr									
	May									
	June									
	July									
	Aug									
	Sept									
	Oct									
	Nov									
	Dec	[black bar]								
	2011	Jan	[black bar]							
		Feb	[black bar]							
Mar		[black bar]								
Apr		[black bar]								
May		[black bar]								
June				[red bar]						
July				[red bar]						
Aug				[red bar]						
Sept				[red bar]						
Oct				[red bar]						
Nov				[red bar]						
Dec				[red bar]						
2012	Jan									
	Feb		[blue bar]			[teal bar]				
	March						[purple bar]	[olive bar]		
	April						[purple bar]	[olive bar]		
	May						[purple bar]	[olive bar]		
	June						[purple bar]	[olive bar]		
	July						[purple bar]	[olive bar]		
	August						[purple bar]	[olive bar]		
	Sept						[purple bar]	[olive bar]		
	Oct						[purple bar]	[olive bar]		
	Nov						[purple bar]	[olive bar]		
	Dec						[purple bar]	[olive bar]		
2013	Jan						[purple bar]	[olive bar]		
	Feb						[purple bar]	[olive bar]		

XI. STUDY LIMITATIONS:

- As this will be a retrospective analysis of routinely collected cohort data, the validity of this study's results is contingent upon that of the data collected during a routine patient visit at the clinic sites.
- Selection bias might affect our results if the children who are lost to follow-up or transferred out of the sites are different from those who are retained with regard to disease severity and ARV regimen changes or single drug substitutions.
- This analysis will exclude all children with missing first-line regimens and if these children's characteristics e.g. age, disease severity at treatment start are different from those whose data is available with regard to ARV regimen changes or single drug substitutions; this might introduce selection bias into the results.
- The study is dependent on how well the data on regimen changes and/or drug substitution are collected and the variability in completeness of reasons for regimen substitution. While reasons for all recorded drug changes will be sought, if the drug is completely unrecorded we will have no trigger to seek a reason for the change at the site where the child was being followed up.

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PART B: STRUCTURED LITERATURE REVIEW

Definition of regimen changes, substitutions and switches:

For the purpose of this review, regimen changes were considered as either **(i)** one or more drug substitutions for reasons other than treatment failure while keeping the same overall regimen, e.g. a change from stavudine (d4T) to zidovudine (AZT) in a child with lipodystrophy, with all other drugs in the regimen remaining the same (which will be referred to as “substitutions”) or **(ii)** a complete switch of the regimen due to treatment failure in which there is a change from a non-nucleoside reverse transcriptase inhibitor (NNRTI) to a protease inhibitor (PI) or vice versa together with a change of at least one of the nucleoside reverse transcriptase inhibitors (NRTI) (which will be referred to as “switches”). Collectively all drug changes will be referred to as “changes” where there is no distinction being made between “substitution” and “switch”.

I. INTRODUCTION

1.1 Aim:

The aim was to review all published observational studies conducted on ART regimen changes (i.e. ART tolerability and durability) of ART in children both in developed and developing countries in order to evaluate the available evidence and identify gaps for further research. Selected key articles from adult literature on regimen changes from developed and developing countries were also reviewed for comparison with and to contextualise the paediatric studies. The review also draws upon paediatric studies on drug toxicity (including toxicity that did not lead to a drug change or stop) as toxicity is one of the main reasons for drug changes among children taking ART both in developed and developing countries. Included studies were appraised for validity regarding selection of the study sample, sample size and methods used to monitor patients on treatment. Any discrepancies in the literature regarding reasons for individual drug change among children on ART were highlighted.

1.2 Search strategy

1.2.1 Search engines: Articles were searched for from the following online search engines: Pub med, Google Scholar, EBSCOhost and Science Direct.

1.2.2 Search terms: Key search terms were: ["substitution" OR "change" OR "durability" OR "tolerability" OR "toxicity" OR "switch"] AND ["ART" OR "HAART" OR "antiretroviral therapy" OR "antiretroviral treatment" OR "highly active antiretroviral therapy"].

1.2.3 Search strategy: The literature search was done using the search terms above and the articles found in the bibliographies of the chosen articles were examined and included if found to be relevant. Only articles in English were reviewed due to lack of resources to have non-English articles translated.

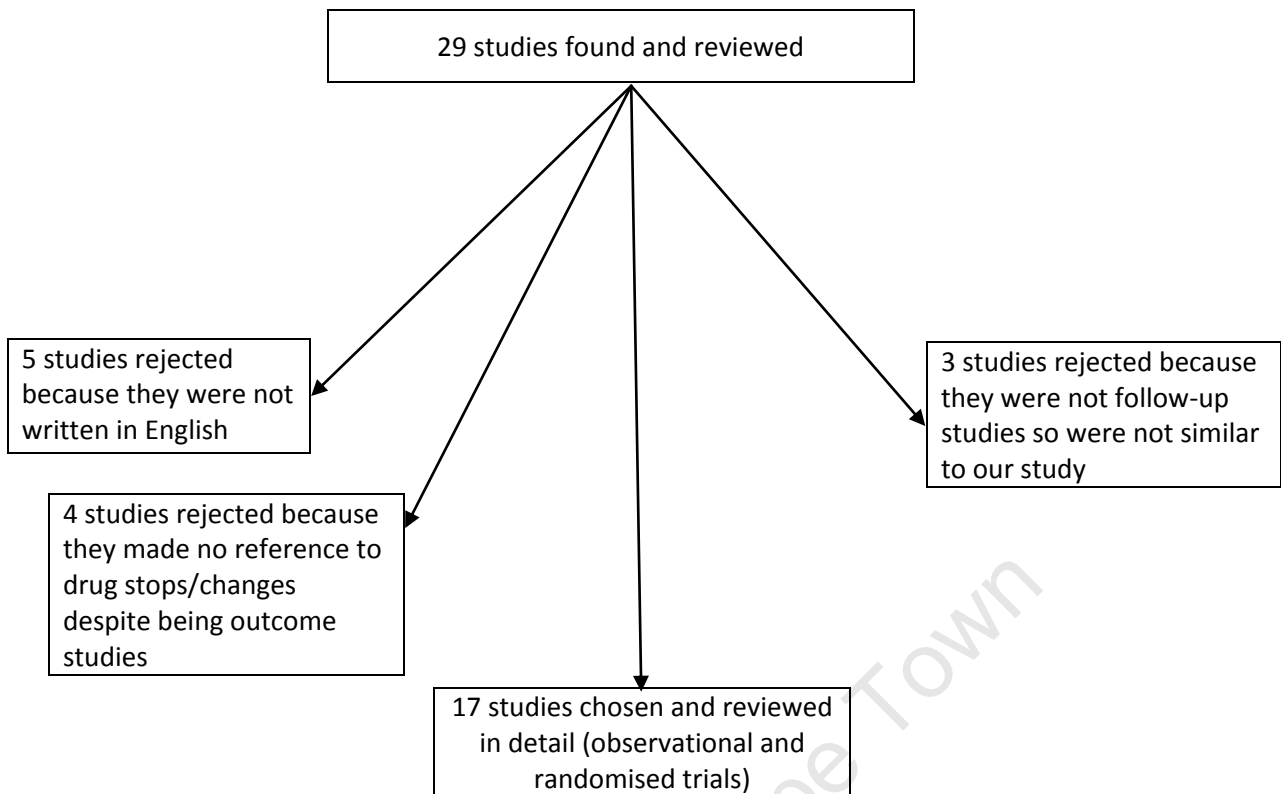
1.2.4 Inclusion criteria for studies:

All studies written in English from peer-reviewed journals whose primary objective was to investigate ART drug substitutions, stops, changes and/or switches in children and adults from both developing and developed countries published prior to 2012 were included. Any ART outcome studies among children in developing and developed countries that reported on ARV drug changes/stops as one of the outcomes were also included. Only observational studies e.g. cohorts and relevant systematic reviews were included as these are similar to our study and are likely to have similar criteria for drug change/stop. In addition, the purpose of the review was to focus on drug changes in routine clinical practice rather than study settings in which toxicity monitoring and criteria for change/stop might be different. Nevertheless, selective randomised controlled trials reporting on toxicity of ART were also included as determining drug safety is one of the main reasons for studying regimen changes.

1.2.5 Exclusion criteria for studies:

Any studies investigating ART outcomes but which made no reference to drug changes/stops were excluded.

FLOW DIAGRAM OF STUDIES CHOSEN



1.3 Quality and relevance criteria of included studies

A summary of the included studies is shown in the appended tables (Appendix D). Some studies were repeats on the same cohort [1, 2]. Studies were appraised for biases like selection bias (e.g. due to systematic error in selection of study participants or due to differential loss to follow-up with respect to both the exposure and outcome) and information bias, specifically detection bias in determining whether or not a child's regimen needed to be changed. Differential loss to follow-up might have led to under-reporting of drug substitutions especially those due to toxicity if the children who were lost to follow-up experienced more toxicities than those retained but could not return because they were very ill.

Studies included were both from developed and developing countries as the outcomes might be different given the difference in available resources e.g. laboratory monitoring of toxicity and response to treatment, classes and formulations of ARVs used as first-line therapy and availability of alternative regimens. These factors could affect the time taken to and reasons for change/stop of

drugs. Studies from developing countries are especially important as these have the largest burden of people living with HIV yet resources are limited with frequently poorer access to laboratory monitoring and ARV drugs; hence the need to optimise use of available first-line regimens.

II. LITERATURE REVIEW:

Since the launch of the comprehensive ART program in South Africa, the number of children receiving ART has increased from 4200 to 152,000 between 2004 and 2011 [3]. This scale up of ART has led to a marked reduction in morbidity and mortality of children due to HIV; however, it has also been associated with increased incidence of toxicities [4] and treatment failure [5] which have in turn led to substitution and switching of therapy respectively. The World Health Organisation (WHO), in a bid to simplify care of HIV infected patients, has developed guidelines for the management of both adult and paediatric patients on ART including when their treatment should be changed and/or switched [6]. However, the available evidence to inform paediatric guidelines is limited because of limited data on long term toxicity and durability of paediatric ARV regimens in routine clinical practice. A fairly large number of cohort studies have been conducted to determine tolerability of ART among adults both in the developed and developing world but this remains an under-studied area among children on ART especially in developing countries.

2.1 Studies dedicated to assessing ART regimen substitution/changes:

Only one of 17 paediatric studies from the developing world [7] and none from the developed world were primarily focused on measuring the probability of ART regimen change/stop. A few of the adult studies, from both the developing and developed world [8-12] were dedicated to assessing the tolerability and durability of ART. The rest of the reviewed studies were aimed at investigating outcomes of ART, however, they reported on regimen changes/stops as one of their outcomes, but not in detail.

2.2 Sample size:

The paediatric observational studies had variable sample sizes ranging from 32 to 6151 participants with two of the large cohorts being multi-regional [4, 13]. Both the adult and paediatric cohorts from developed countries were generally much smaller than those from developing countries. Small

numbers may mean that estimates of risk of drug changes are not precise, one may not detect a difference in risks of different drug changes where there is one, and rare causes of drug change may not be observed. While collaborative cohorts may have large numbers of participants, data quality may not be as good. For example, some cohorts might have missing data, definitions of changes and coding of reasons for changes may differ between cohorts and some changes or reasons for change may be missed leading to under-reporting of results.

2.3 Study participant characteristics:

The paediatric cohorts from developed countries have relatively younger children [14-18] compared to those from developing countries [1, 2, 4, 7, 13, 19-21] with the median age of children ranging from 2-7 years in the former and from 4-10 years in the latter. This could be a result of the fact that in developed countries children are likely to initiate ART soon after being diagnosed with HIV rather than waiting until they meet ART initiation criteria that restrict ART to those with particular clinical or immunological criteria as is the case in most resource-limited settings. In addition, access to HIV care may be better in developed than developing countries. In some developing countries like South Africa, immediate treatment of all HIV infected infants has only been recently included in the HIV treatment guidelines [22].

2.4 Sample selection:

Most studies enrolled all the eligible children who were taking ART during the duration of the study. Some used data from paediatric HIV registers [18] and others from cohorts of HIV-infected children on ART who regularly attended HIV/AIDS clinics or ART programs in hospitals [13, 14, 19, 23]. These studies were not affected by selection bias since they enrolled all eligible children into their cohorts at ART initiation, however, validity and reliability of data from registers is reliant on good record keeping. In situations where the registers are incomplete, there might be over or under-estimation of ART durability.

Most of these children were referred to these clinics from either public hospitals or centres of excellence with some research capacity [1, 2, 4, 16, 24-26] therefore the private sector is not well represented. We could assume, however, that in developing countries especially; most children

would be accessing HIV care in public health facilities or centres of excellence which would be affiliated with government hospitals. Being at a centre with research capacity means that there is better access to laboratory monitoring of toxicity and to alternative drugs and formulations hence there might be more frequent changes compared to more poorly resourced settings. All of the study participants in the adult cohorts were enrolled from routine ART programs both in developing and developed countries. In some of the adult studies, all the patients attending these programs were enrolled into the cohort study [9-11, 27, 28] while for the rest, consecutive sampling was used to enrol patients into the study until the desired sample size was attained [8, 12].

2.5 First-line ART regimens used:

Patients in cohorts from developed countries initiated therapy using NNRTI and/or PI-based ART regimens [14-18] while those in developing countries initiated therapy using mainly NNRTI-based ART [13, 19, 20, 23, 29] with the exception of South African and some West African cohorts where children initiated therapy using PIs [1, 2, 24, 26, 30]. Therefore changes made to NNRTI-based regimens have been better studied than PI-based treatment in resource-limited settings.

2.6 Monitoring of study patients:

There was a difference between monitoring of children in developed and developing country settings. While most developed country paediatric cohorts monitored their patients using 6 monthly absolute CD4 count/percent, viral load measures and/or clinical improvement; those in developing countries mainly used CD4 count and/or clinical improvement [7, 13, 19, 21, 23]. There was a lot of variability in the reported median duration of treatment before drug change. Reasons for this might include different overall follow-up durations [2, 13, 23], different monitoring practices [2, 13, 23], different methods of reporting i.e. it is not explicitly stated if this median time to drug change only included children who had a regimen change or all children who initiated therapy in the denominator. Most children had clinical evaluations every 1-3 months [1, 7, 19, 21, 23], however, only the Kenyan children had extensive laboratory tests done e.g. complete blood counts and alanine aminotransferase (ALT) at baseline and every 3 months after ART initiation [19]. This may have led to under-reporting of drug toxicities (e.g. nevirapine (NVP)-associated liver toxicity) in some

cohorts since they were not being actively monitored. With the exception of Hawkins et al (2007); all the adult cohorts monitored their patients using both viral load and CD4 counts [8, 9, 12, 27].

2.7 ART drug substitution:

ART drug changes occurred more frequently in resource-rich settings [14-18] compared to resource-poor settings [1, 2, 4, 7, 13, 16, 19-21, 23-26, 29-31] with virological failure and toxicity being the main reasons for change in both settings. For example, in a prospective cohort study in South Africa among 80 children starting therapy, 2 had a treatment change by a total follow-up time of 29.3 child years after ART initiation (24), while in another cohort study in the Netherlands, 8 of 32 children changed therapy by a median (range) of 1 (0.04-1.5) years on ART [15]. Reasons for this difference might include the fact that resource-rich settings have more drugs available, more regular and comprehensive monitoring both for toxicity and failure, lower thresholds for switching therapy (e.g. lower viral load thresholds used to define treatment failure) and individualized care rather than public health approach to regimen choice. The common treatment-limiting toxicities included: NVP-associated skin rashes, AZT-induced anemia and ABC hypersensitivity. Other reasons for drug change included: concomitant TB treatment, drug dosing issues, treatment simplification (e.g. when a drug was not palatable, a child needed to change from a syrup to tablets or vice versa or changing to a PI-sparing regimen in order to save PIs for second-line therapy), poor adherence, structured treatment interruption, drug shortages and NVP resistance due to previous exposure to monotherapy (i.e. single dose NVP for PMTCT) or dual therapy in the private sector. ART for children is thus complex with several factors to consider e.g. appropriate formulations for young children, drug palatability, need for small doses and small dose increments for infants and the challenge of storage requirements such as refrigeration of syrups and exposure to PMTCT regimens that may cause resistance. This also means that pharmaceutical companies have to manufacture different paediatric drugs in various formulations to meet the demand of different settings. However, because some formulations have short shelf lives, there is little financial incentive for companies to make them as production may not be profitable and demand may be low and erratic. This means that there isn't always an adequate supply of the required drugs [32].

2.7.1 Time to first drug substitution:

None of the paediatric cohorts report on the cumulative probability of drug substitution. They only report the drug changes that were made and the median or mean time to these changes. This justifies the need to investigate the tolerability and durability of the initial ART regimen given to HIV infected children in developing countries, in this case, South Africa.

2.8 Toxicity of HAART among children in resource limited settings:

Toxicity has been identified as one of the main causes of treatment changes among children on HAART in both resource rich and resource poor settings and understanding toxicity is an important reason for studying drug changes. Common toxicities in children include AZT-induced anemia; d4T-induced lipodystrophy, peripheral neuropathy, lactic acidosis; NVP-induced hepatotoxicity and hypersensitivity, LPV/r-induced electrolyte abnormalities, gastrointestinal toxicities; ABC hypersensitivity and EFV associated psychiatric disturbances [33-39].

2.8.1 Lipodystrophy:

Lipodystrophy has been identified as one of the main toxicities associated with NRTIs especially d4T and didanosine (ddI) and while this is usually dependent on dosing and duration of therapy, d4T has been found to cause this toxicity even in standard paediatric doses [34] and there is no evidence about its reversibility [40].

A cross-sectional study done in Uganda among 364 children aged 2-8 years who had been on ART for ≥ 6 months found that 34% had metabolic abnormalities with 27% having lipodystrophy [35]. These children had been on ART for a longer duration compared to those who did not have lipodystrophy (mean (SD) duration of 3.5 (± 1.3) and 3.1 (± 1.2) years respectively) and were slightly older. Children's adherence might be adversely affected as the physical features of lipodystrophy might identify a child as being HIV-infected with consequent HIV-related stigma [34].

2.8.2 Anemia:

Unlike d4T; AZT toxicity (especially anemia) has not been widely studied in children in resource-limited settings. In a retrospective cohort of 78 children in Thailand who had no haematological abnormalities at ART start, changing from d4T to AZT at 48 weeks of therapy was associated with a

slight decline in haemoglobin [33]. These children had experienced immune recovery by the time of drug change, suggesting that the anemia was AZT-induced and not disease-associated. In addition, in a Jamaican cohort of 121 children 64% of whom were on ART; there was increased severity of anemia among those who were on AZT-based therapy (93%) [54]. A Nigerian cohort found a non-significant increase in incidence of anemia among children taking AZT-based regimens compared to d4T-based ones. This was more pronounced among children who received cotrimoxazole prophylaxis and AZT. However, the numbers of those who did not get the prophylaxis for both d4T and AZT were too small to detect a difference between the groups so it is difficult to discern if this toxicity was a result of a synergistic effect between AZT and cotrimoxazole or only associated with AZT [41]. Results from the Anti-Retroviral Research for Watoto (ARROW) randomised trial in Uganda and Zimbabwe which is comparing AZT vs. no AZT toxicities in children might contribute to the limited evidence base when they are published [36].

2.8.3 Hepatotoxicity:

NVP has been found to be the leading cause of hepatotoxicity among patients on ART. Chu et al (2010) showed that after a median of 32 (IQR: 28-63) days on therapy, 1.4% of patients who had been taking NVP for ≥ 1 month developed hepatotoxicity. Those who had complete ALT monitoring had significantly higher incidence of hepatotoxicity (incidence rate (IR): 7.6 (95% CI: 4.8–12.1) per 100 person-years) compared to those who did not (IR: 3.6 (95% CI: 1.8–7.2) per 100 person-years). This suggests that in settings where regular liver function monitoring is not available, there might be under-reporting or late diagnosis of NVP-associated hepatotoxicity. However, other studies have shown that regular hepatic function monitoring does not improve detection of clinically significant ART-induced hepatotoxicity [42, 43]. Incidence of liver toxicities may be increased by co-treatment of opportunistic infections like TB where Isoniazid use may increase the risk of hepatotoxicity [43].

2.8.4 Hypersensitivity:

Hypersensitivity is associated with ABC and NVP therapy.

- NVP hypersensitivity: While NVP-induced hypersensitivity has been found to be less common among children than adults [44, 45], it remains an important cause of toxicity

especially if there is no slow dose escalation at ART initiation e.g. in a phase I trial to determine NVP safety among children, 1 in 21 children experienced a NVP-related rash [44]. This may complicate ART initiation in children as certain fixed dose combinations are not available in the doses needed for paediatric dose escalation, requiring the use of individual drugs at the start of therapy.

- Abacavir hypersensitivity: Studies have shown that the incidence of ABC hypersensitivity is low ranging between 0.3-3.3% [46, 47] and mostly occurring within a month of initiating therapy among children aged less than 17 years. Misclassification of children on ABC as having hypersensitivity is common [47] emphasising the need for alerting caregivers to possible symptoms and frequent clinical monitoring especially during the first few months of ART initiation. Studies have shown that ABC hypersensitivity is associated with HLA-B57 [48], a marker that is more common among western populations than African ones explaining the higher incidence of ABC hypersensitivity in the former compared to the latter [49, 50].

2.8.5 Lactic acidosis:

Lactic acidosis caused by d4T exposure in adults has been widely studied, but very little is known about it among children. Fielder and Rambiki (2010) describe a case of a family of 3 that developed lactic acidosis following therapy with d4T. The child developed it 2 years after initiating therapy (one year later than the parents); however, this was reversed when therapy was stopped. It is important that tests for blood lactate levels are available for patients who take d4T and clinicians should be aware of the relevant symptoms in order to change this drug as soon as the toxicity is detected.

2.8.6 Peripheral neuropathy:

Peripheral neuropathy is thought to be infrequent in young children but may also be under-reported as children may not self-report about reduced sensation in their extremities. So, despite it being one of the common d4T-induced toxicities there is very limited data about it in children. A prospective study in Kolkata, India found that only 1 of 100 children developed peripheral neuropathy after 2.5 years of follow-up. Children were frequently clinically monitored (i.e. every 2, 4, 8, 12 and 24 weeks after ART start and every 6 months thereafter) [51]. None of the reviewed paediatric studies report

on treatment change due to peripheral neuropathy, while this is commonly reported as a reason for treatment change in adults [8, 9, 27].

2.8.7 Psychiatric disturbances:

Psychiatric disturbances are commonly reported among patients taking EFV-based regimens. None of the reviewed paediatric or adult studies report on EFV-induced psychiatric disturbances. However, a review of neuropsychiatric effects of EFV in adults reveals contradictory evidence with some studies showing that $\geq 50\%$ of patients experience temporary effects especially after the first dose, while others report long term effects [28, 52] with symptoms reducing with time [28]. While there are lots of studies about EFV-associated psychiatric effects in adults, paediatric data are lacking.

2.8.8 Toxicity associated with PIs:

Like d4T, PIs have also been found to be associated with abnormal fat redistribution. Other toxicities associated with PIs include: gastrointestinal e.g. liver and pancreatic toxicities; nervous system, endocrine toxicities, cardiovascular, hypersensitivities, dyslipidaemias and haematological abnormalities e.g. thrombocytopenia [38].

2.8.9 Dyslipidaemias:

While dyslipidaemias may occur in ART naïve patients, they have been found to be common among children receiving ART. In a before and after sub study of the NEVEREST I trial of 195 South African children aged < 2 years initiating ART with LPV/r-based regimens, there was a significant increase in all lipid profiles after 9 months on ART. This was, however, reversed for all but high density lipoproteins (HDL) in the NVP group after randomisation to either take NVP or maintain the PI [53].

2.9 Summary and interpretation of literature:

The reviewed literature shows that there are limited data on the tolerability and durability of ART in children. The outcome studies reviewed, which report on drug changes, reveal that initial ART drug changes are more frequent in developed countries compared to developing countries with the main reasons in both being virological failure and toxicity. This could be due to the fact that monitoring practices differ in resource-rich and resource-poor settings and therefore toxicities are detected

early on during treatment and the offending drugs changed. In addition, there are more alternative first-line drug options in developed countries compared to developing countries hence the higher frequency of ART changes in the former. Furthermore, the initial ART regimens used in developed countries are different than those used in developing countries and this could further explain the difference in the frequency of drug changes in the two settings.

Unlike adult therapy, paediatric ART is complicated by the fact that there is reduced access to alternative drugs when toxicities occur especially in settings where most available drugs are given as fixed dose combinations. Paediatric programs have to work closely with their supply chain departments in order to ensure that there is adequate supply of alternative first-line drugs. This would also require that pharmaceutical companies increase production of different paediatric ART drugs in child-friendly formulations.

2.10 Identification of needs for further research:

There is a need for larger paediatric cohort studies dedicated to examining the tolerability and durability of first-line ART in developing and developed countries in order to identify drugs that are best tolerated by children so that these are considered for first-line therapy, adequately stocked and their use optimised. It is also important to identify the incidence of and risk factors for toxicity to inform guidelines for monitoring ART and to improve patient care.

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Part C: Journal Manuscript

Title: Substitutions to initial antiretroviral therapy due to reasons other than treatment failure in children in South Africa

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ABSTRACT

Background: Knowledge of the tolerability, safety and durability of first-line paediatric antiretroviral therapy (ART) regimens is vital to scaling up and maintaining children on therapy. We determined the probability of and reasons for stopping/changing of antiretroviral drugs in children from 7 South African sites in the International epidemiological Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration.

Methods: All ART-naïve children (< 16 years at ART initiation) with a documented initial regimen of ≥ 3 antiretroviral drugs and ≥ 1 follow-up visit after initiation were included. The proportion of patients changing/stopping one or more drugs and the reasons for drug changes/stops were determined. The time from ART initiation to first treatment change/stop of ≥ 1 drug for toxicity was described using the Kaplan-Meier method. Competing risks analysis was used to determine the reasons for specific drug changes. Predictors of drug substitution due to toxicity were determined using Cox-proportional hazards models stratified by site.

Results:

Data from 5517 children with median [IQR] age at ART start of 42 [15-82] months were included in the analysis. By 3 years on ART, 81% of children alive and in care were still taking their initial regimen. Drug stops/changes for reasons other than treatment failure were mainly due to potential drug interaction in the 1st year on therapy (2.9%) while in the 3rd year toxicity (3.1%), potential drug interaction (2.6%), treatment simplification (e.g. changing from syrup to tablet formulations) (2.3%) and other reasons (4.1%) were the main contributors. Nevirapine (NVP), zidovudine (AZT) and stavudine (D4T) were responsible for most treatment-limiting toxicity by 2 years on ART i.e. $n=10/259$ (4%), $n=11/602$ (2.8%) and $n=45/4883$ (1.4%) respectively. NVP toxicity occurred almost entirely in the first six months whereas d4T toxicity occurred mostly after 1 year of therapy. Half of the AZT toxicity occurred in the first 3 months with the remainder evenly spread over the following 21 months.

Conclusion:

Paediatric ART durability in resource-limited settings is good but complex, with treatment changes not only due to toxicity, treatment failure and drug interactions, but also treatment simplification. NVP, AZT and d4T are responsible for most of the treatment-limiting toxicity in children in resource-limited settings.

Key words: children, antiretroviral therapy, substitution, South Africa

University of Cape Town

Background:

World Health Organisation (WHO) and developing country national Paediatric HIV treatment guidelines increasingly recommend universal antiretroviral therapy (ART) for infants and young children and/or commencement of ART at higher CD4 thresholds [1, 2]. This means that an increasing number of children in resource-limited settings are likely to initiate ART earlier in their disease course, with lower mortality and longer time spent on ART. It is thus important to understand the tolerability, durability and safety of paediatric ART. This can be used to optimise the use of drugs in first-line ART regimens and inform toxicity monitoring guidelines. While a number of adult studies describe the tolerability of ART regimens in both developed and developing countries [3-6], there are few paediatric studies that have specifically studied ART regimen changes in developing countries [7-9]. These studies report between 4.5%, and 19.4% of children changing ≥ 1 drug in their non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART regimen, mainly due to toxicity and tuberculosis (TB) co-treatment. However, none of these studies report on the duration of therapy before treatment change. As these studies were conducted in small cohorts with limited follow-up duration, less common reasons for regimen change and those that only occur after longer ART durations may not have been described. A large number of cohort studies of paediatric ART outcomes report reasons for ART regimen modification. These include: starting/ending TB treatment while on ART, toxicities (e.g. stavudine (d4T)-induced lipodystrophy, zidovudine (AZT)-induced anemia and nevirapine (NVP) hypersensitivity), treatment simplification (e.g. changing from syrups to tablets when a child is old enough to swallow them, changing drug or formulation when refrigeration requirements cannot be met), dosing issues, poor adherence and treatment failure. These studies were mostly done in children on NNRTI-based ART, so there are limited data on durability of protease inhibitor (PI)-based ART [8, 10-25].

The International epidemiologic Database to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration includes relatively complete programmatic data on ART drug changes/stops from 7 South African paediatric ART programs with approximately 30% of children commencing PI-based first-line ART.

The aim of this study was to determine the probability of and reasons for change/stop of

antiretroviral drugs at South African leDEA-SA paediatric sites, with a focus on drug changes due to toxicity. Risk factors for treatment –limiting toxicity were examined for each of the drugs most commonly stopped/substituted due to toxicity.

Methods:

Study design and population:

Data was collected prospectively at each collaborating site and transferred anonymously to the leDEA Data centers at the Universities of Bern and Cape Town. The study was approved by the University of Cape Town Health Sciences Human Research Ethics Committee.

All ART-naïve children <16 years of age at ART commencement with ≥ 1 follow-up visit after treatment initiation and initiated ART with a documented regimen of ≥ 3 antiretroviral drugs prior to March 2008 were included. As recommended by the South Africa National Treatment Guidelines [26], patients were followed up 1-2 monthly for the first 3-6 months on ART and 3 monthly thereafter.

Treatment regimens used:

At the time of data collection, the standard first-line regimens used were d4T/lamivudine (3TC)/lopinavir/ritonavir (LPV/r) for children 6 months to 3 years of age or d4T/3TC/ efavirenz (EFV) if over 3 years of age and >10kgs [26]. Children <6 months of age were given RTV alone (due to lack of dosing recommendations for children <6 months of age) which was replaced with LPV/r when the child reached the age of 6 months while those who developed TB while on treatment had their treatment changed from LPV/r or NVP to RTV or RTV-boosted LPV/r if <3 years or weighed <10kgs while those who were ≥ 3 years and weighed >10kgs would be given EFV in place of NVP.

Frequency of clinical and biological monitoring:

While 2 of the clinics had paediatricians specifically providing HIV care, most of the clinics have physicians giving HIV care.

Children are followed up clinically 1-2 monthly during the first 3-6 months after ART initiation, and, if stable, 2-3 monthly thereafter. While 2 of the clinics had paediatricians specifically providing HIV care, most of the clinics have medical officers providing care. Laboratory monitoring including CD4

testing, viral load testing, alanine transaminase (ALT) and haemoglobin testing was available at all sites (either on-site or off-site) and the turnaround time for results varied from one day to 1 week in all clinics. In most clinics, CD4 measurement was done every 6 months except for Gugulethu where they were done 4 monthly. ALT and haemoglobin monitoring was done 6 monthly at all clinics except Khayelitsha where complete blood counts were done 12 monthly.

Key Variables:

Socio-demographic and clinical characteristics of children at baseline were described using means and 95% confidence intervals (CIs) for normally distributed numerical variables, medians and interquartile ranges for skewed numerical variables and proportions for categorical variables. Child characteristics included age, sex, first-line regimen and measures of disease severity (WHO Clinical Stage, CD4 percentage and absolute counts as well as the degree of immune suppression determined using the worst of CD4%/absolute according to WHO criteria) [27].

Age and sex-standardized weight-for-age z-scores (WAZ) were calculated using the WHO 2006 reference standards [28]. Age was included as a binary variable with a cut-off at 3 years because of different regimens being prescribed for children <3 yrs and ≥3 yrs. Severe anemia at ART start was defined as baseline haemoglobin (Hb) <7g/dl and age >21 days) as per the Division of AIDS grading of adverse events [28]. Lipodystrophy was defined as a disorder of fat metabolism characterised by loss of fat from or deposition of fat in tissue.

Outcomes:

The main outcomes included the time to the first drug change or stop for reasons other than non-adherence and reasons for the change. Drug changes were considered as either **(i) “Substitutions”**: one or more drug substitutions/stops for reasons other than treatment failure while keeping the same overall regimen (e.g. a change from d4T to AZT in a child with lipodystrophy, with all other drugs in the regimen remaining the same; or **(ii) “Switches”**: a complete switch of the regimen due to treatment failure in which there is a change from an NNRTI to a PI or vice versa together with a change of at least one of the nucleoside reverse transcriptase inhibitors (NRTI).

Analysis:

Data were analysed on an intention-to-treat basis in order to avoid an over estimation of treatment changes/stops e.g. children who had drug interruptions most likely due to missed appointments with the same drugs being re-started at a later date were therefore considered to still be at risk of having the drug changed until such a time as it was changed or when follow-up ended. Follow-up was censored at the first of: first drug stop/change, date of death, date of transfer out, date of last visit if lost to follow-up or still in care at database closure. The time from initiation of ART to first treatment change/stop was described using the Kaplan-Meier method. Only children with at least one follow-up visit were included in the time-to-event analyses as a follow-up visit is needed for treatment to be change or stopped. Competing risks analysis was used to determine the incidence of drug changes for each specific reason (e.g. d4T change due to lipodystrophy) in the sub-population of children exposed to each specific drug. The competing risks method takes into account that if a patient changed d4T for a competing reason, the competing reason (e.g. lactic acidosis) led to the change of d4T before the reason of interest (lipodystrophy), this drug could no longer be changed due to lipodystrophy. In other words, the competing risk is an event (changing d4T due to lactic acidosis), the occurrence of which precludes or alters the probability of the main event (d4T substitution due to lipodystrophy). Cox-proportional hazards models stratified by site were used to determine the predictors of particular drug substitutions due to toxicity e.g. d4T substitutions due to toxicity. Potential confounders like age at ART initiation; viral load, CD4 count, and immune suppression at ART initiation were included in the multivariate model *a priori*. WAZ was included as baseline fatness may confound lipoatrophy and lipohypertrophy assessment. The covariates were chosen based on previous literature showing their association with regimen-specific and/or drug-specific changes in ART delivery. For example, WAZ was included as a covariate as in adult studies a high body mass index at ART initiation is a risk factor for stavudine toxicity [4]. The best model was the one that was biologically plausible and had the lowest Aikaikes Information Criterion while maintaining parsimony. All statistical analysis was done using Stata version 11.0 [29].

Results:

The study population included all HIV infected children who were below 16 years of age at the time of ART initiation with a documented date of birth, gender and initial regimen of at least 3 ARV drugs. A total of 5517 children that initiated ART with a documented regimen prior to March 2008 at the 7 South African paediatric ART programs were included in this analysis. Median age was 42 (15-82) months. Most were severely ill at ART initiation (i.e. 75% WHO stage 3/4 disease; 80% severely immune suppressed) (Table 1). First-line regimens including d4T were used by 89% of children, with the most common regimens being d4T/3TC/EFV (49%) followed by d4T/3TC/LPV/r (24%). NVP/EFV was the “third drug” in the regimen for 60% of children. Most of the children were still in follow-up by the time of database closure, with 5% lost to follow-up, 6% dead and 16% transferred out on treatment.

Treatment durability:

Among the children still in active follow-up by the end of the 1st, 2nd and 3rd years of treatment, 92.8%, 87.7% and 80.9% respectively were still taking their initial regimen (Figure 1). In the first year on therapy, drug substitution was mainly due to potential drug interaction (2.9%) (e.g. changing from LPV/r to either LPV/r boosted with ritonavir or ritonavir alone due to co-treatment with anti-TB drugs or vice versa when TB treatment was stopped). By the third year on therapy, the main reasons for drug substitutions other than treatment failure were toxicity (3.1%), potential drug interaction (2.6%), treatment simplification (2.3%) and other unspecified reasons (4.1%). Treatment simplification was due to: changes in treatment protocols especially during the early years of ARV roll-out (e.g. changing from AZT to d4T in first-line regimens when national guidelines recommending d4T-based first-line were introduced in 2004), child initiating on ART including LPV/r at < 3 years of age and changing to EFV after their third birthday to facilitate better adherence and preserve LPV/r for later use, lack of refrigeration facilities required for certain syrups/solutions and receiving more effective treatment where this was previously unavailable (e.g. children previously on ritonavir alone as a 3rd drug being changed to LPV/r when this became widely available in 2004).

Reasons for substitution of different drug classes:

Protease inhibitors:

When competing risks analysis for different causes of drug substitution was undertaken, the main reason for changing LPV/r in the first year of therapy was potential drug interaction with TB therapy with a cumulative incidence of 2.8% by one year. After the first year on ART, LPV/r was mainly changed due to treatment simplification (Figure 3). Like LPV/r, RTV was changed mainly due to potential drug interaction and treatment simplification (Figure 3).

Nucleoside reverse transcriptase inhibitors:

Apart from treatment failure, the main reasons for d4T changes were toxicity, simplification of treatment and potential drug interaction (cumulative probabilities: 1.4%, 0.5% and 0.1% respectively by the second year of ART) with the latter occurring only in the first 6 months on therapy (Figure 4). Changes due to d4T toxicity were analysed in more detail as this drug has been found to be one of the main causes of toxicity among patients on ART [30] prompting the change in WHO treatment guidelines from d4T to abacavir (ABC) as first-line therapy. Toxicity was mainly due to hyperlactataemia (cumulative incidence: 0.45% after 2 years on ART), lipodystrophy (abnormal fat redistribution) (cumulative incidence: 0.41%) and peripheral neuropathy (Figure 5).

AZT changes in the 1st 2 years were mainly due to toxicity and treatment simplification with treatment failure being more important after 1.5 years on ART (Figure 4). The cumulative probability of changing AZT due to toxicity was 2.8% by 2 years on ART (i.e. n=11/602 children who initiated therapy with AZT) (Figure 2) with the main reason being anemia.

Non-nucleoside reverse transcriptase inhibitors:

NVP was mainly changed due to potential drug interaction with TB therapy and toxicity (cumulative probabilities: 12% & 4.5% by 2 years on therapy) (Figure 3). NVP had the highest incidence of changes due to toxicity among children initiating therapy (i.e. n=10/259) mostly occurring early with the probability of a change being 2% by 6 months on ART. Toxicity was mainly due to hypersensitivity reactions and liver toxicity. Changes to EFV were due to toxicity and treatment failure with most occurring after the second year on ART. Changes due to toxicity were low with a

cumulative probability of 0.7% by 2 years (i.e. n=17/3031 children who initiated therapy with EFV) (Figure 2) and were mainly due to hypersensitivity reactions, gastrointestinal and neuropsychiatric toxicities.

Predictors of treatment-limiting toxicity:

Multivariate models showed that the probability of d4T toxicity increased with age (adjusted hazard ratio (aHR): 3.80 for ≥ 3 years compared to < 3 years; 95% CI=1.04-13.85), baseline viral load (aHR: 2.25 for each log increase compared to < 400 copies/ml; 95% CI=1.11-4.57) and baseline WAZ (aHR: 3.64 for each unit decrease in z-score; 95% CI=1.27-10.39). Additional adjustment for baseline liver function and WHO stage did not change the results. There was a reduced risk of treatment-limiting AZT toxicity among children who were not anaemic at ART start (aHR=0.09; 95%CI=0.02-0.55) and those in WHO stage 3 or 4 (aHR=0.14 compared to stage 1 or 2; 95% CI=0.03-0.77), after adjusting for baseline age. There were no predictors of NVP toxicity.

DISCUSSION:

Durability of initial ART in the first 3 years of treatment:

ART durability among children on treatment in South Africa is good with about 80% of children who were in active follow-up continuing with their initial regimen after 3 years of therapy. This is slightly higher than that of adults; in South Africa 72% of adults remained on their initial regimen after 3 years [4] and 51% of the Swiss HIV adult cohort after 1 year of ART [31]. This may in part be due to the lack of alternative first-line drugs, especially when compared with adult studies. By 2 years on ART; NVP, AZT and d4T were responsible for the most treatment-limiting toxicity (n=10/259 (4%), n=11/602 (2.8%) and n=45/4883 (1.4%) respectively). Our findings are similar to those from some paediatric cohorts in developing countries which report ART durability between 80%-99% [7, 8, 24] although having fewer children and shorter durations of follow-up than our study.

Reasons for drug changes:

Overall, reasons for drug substitution changed with duration of therapy. In the first year, the main reason was potential drug interaction while in the second year treatment failure, drug interaction and treatment simplification were the commonest reasons for drug substitution.

Toxicity was a small, but important cause of treatment changes early on, but became more important by the 3rd year on treatment. NVP, AZT and d4T were the main causes of changes due to toxicity, while EFV, 3TC and the PIs were relatively well tolerated. This agrees with findings from adult studies that showed a higher risk of NVP changes due to toxicity compared to EFV [4, 34]. NVP toxicity occurred almost entirely in the first six months whereas d4T toxicity occurred mostly after 1 year of therapy e.g. lipodystrophy only started occurring after 1 year. Half of the AZT toxicity occurred in the first 3 months with the remainder evenly spread over the following 21 months. The largest cause of toxicity late in therapy was lipodystrophy due to d4T as was the case in other studies conducted in similar settings [25, 35]. The timing of toxicity is similar to findings in a Ugandan study by Tukei et al (2012) except that more children (i.e. one third) developed toxicities in that study. A number of reasons may account for this difference: our study only focuses on treatment-limiting toxicity, not all toxicity which might result in finding lower incidences especially in the context of limited alternative drugs. In addition, in the Ugandan study physicians actively assessed children for toxicity especially in the first 3 months of treatment, whereas our study is based on routine programmatic data. In the busy clinics where our data is collected, laboratory tests to detect toxicity may not have been done as frequently or completely as in a dedicated toxicity study.

Risk factors for stavudine, zidovudine and nevirapine toxicity:

Age \geq 3 years, higher baseline viral load and higher baseline WAZ were predictive of treatment-limiting d4T toxicity. It is plausible that 2 of the major forms of d4T toxicity, namely lipodystrophy and peripheral neuropathy, are difficult to detect or do not occur in very young children. The finding of higher baseline WAZ being predictive of d4T toxicity concurs with adult studies in which higher baseline weight was associated with treatment-limiting d4T toxicity. It is possible that fatter children were more predisposed to uneven distribution of fat after initiating ART with d4T-based regimens. For adult studies also suggest that female sex, advanced WHO stage [4, 6] and weight gain \geq 5kgs in the first 3 months of therapy [4] are predictive of d4T changes due to toxicity. Lack of anemia and advanced WHO stage were protective against treatment-limiting AZT toxicity. It is possible that children who had advanced disease were actively given nutritional supplements including but not

limited to iron and folate hence preventing them from becoming anemic while taking AZT containing ART regimens. Like our study, adult studies found no predictors of treatment-limiting NVP toxicity. In contrast, Tukei et al (2012) found no significant baseline predictors of any ARV toxicity despite the children in their cohort being of similar age to ours.

Unique challenges of paediatric ART:

We found some unique reasons for treatment change that are not reported in adult studies, but have been reported from paediatric studies in settings similar to ours, and which increase the challenge of scaling up ART for children. Unlike adults, children's ART drugs may be changed to simplify their treatment e.g. when a child grows older and can take tablets instead of syrups or when a child grows to >3 years or 10kg and can take EFV instead of other drugs [8, 12, 20]. In certain situations it may be safe to substitute PIs with NNRTIs after initial viral suppression, thus saving PIs for second-line treatment [33]. In clinical practice in South Africa, LPV/r is sometimes changed to EFV when children reach 3 years of age especially in children with difficulty adhering to LPV/r. In this study, 7.3% of all changes made to LPV/r were a result of children growing older than 3 years and thus having their drug changed to EFV.

In addition, liquid formulations may require refrigeration which is frequently unavailable in resource-limited settings. This may necessitate off-label use of adult capsule formulations or syrups not requiring refrigeration for infants and young children (e.g. AZT) even if these are not part of nationally recommended first-line, with drug changes to simplify treatment once children are old enough to be dosed in fractions of tablets. Drug storage requirements together with more frequent drug changes make supply chain management of paediatric ARVs more complex and expensive. For example, while ritonavir boosted LPV/r appears to be the best treatment approach for children on LPV/r based regimens co-treated for TB, ensuring sufficient quantities of RTV is difficult since it has a short shelf-life [32]. Further, it is not used in any standard regimen, making supply-chain management difficult.

The burden on the procurement system of any paediatric ART program may be substantial and, as recommended first-line regimens change, it is important to monitor child-specific reasons for ART change to inform treatment and monitoring guidelines and drug procurement plans [37].

Parents and guardians also may have to frequently learn about different storage requirements for the new drugs, the different dosing of each drug and different administration methods, which may adversely affect adherence.

Strengths and limitations:

This is the largest longitudinal dataset of paediatric data evaluating ART durability, tolerability and safety from a programmatic setting in the developing world using WHO recommended drugs over a duration of 3 years, giving enough time and sufficient numbers for relatively long term complications and rarer toxicities to develop e.g. lipodystrophy from d4T only started occurring after 1 year in this cohort and could have been missed if follow-up duration was shorter. Some studies which investigated ART durability over shorter durations were unable to demonstrate metabolic complications of some drugs [36]. In this analysis, diet was not adjusted for and this may have confounded the assessment of drug-related dyslipidaemias.

A substantial number of children were on PI-based first-line therapy which is unusual in resource-limited settings. Competing risks analysis was used to assess the incidence of each reason for changes of a particular drug which prevented over-estimation of drug changes. This analysis was limited to children whose data in the leDEA database was complete. It is possible that children with incomplete data or who were not captured may have had different outcomes.

These data were routinely collected in busy HIV clinics where there may be inconsistencies in recording of data and different thresholds for drug changes due to toxicity between clinicians in the same site or across sites. Some reasons for drug substitution remained unascertained therefore there may be underestimation of various drug change reasons. In addition, there might be some differences in monitoring patients on ART and this may impact on frequency of and reasons for treatment changes, however, the clinics included in this analysis had similar frequencies of clinical and laboratory monitoring of patients on ART so this might not have been the case. Different sites

might have varying alternative drug options leading to differences in their treatment change protocols. Furthermore, the absence of paediatricians specifically providing HIV care at most of the clinics might have contributed to the heterogeneity in changing regimens or individual drugs across cohorts. Differential loss to follow-up of children with versus without toxicity may have biased our results.

A fairly large proportion of children were transferred out and censored at their last visit. This might have affected estimates of ART durability if treatment changes in these children differed from those retained in the cohorts. However, there is no reason to suspect that this was the case as standard South African national paediatric ART guidelines are generally followed at all down-referral sites. Using competing risks analysis limits the generalizability of the reasons for individual drug substitution to populations without similar competing risks/reasons for drug substitution. We specifically excluded examining treatment stops due to non-adherence in this study as it was difficult to distinguish in this routine monitoring data the difference between passive treatment interruptions due to missed visits and active stopping of treatment by the treating clinician due to non-adherence. A detailed study assessing the impact of poor adherence on treatment durability would be valuable. Similarly, as this study only looked at the first treatment change, it would be useful to examine subsequent treatment changes particularly after routine changes due to potential drug interactions and treatment simplifications.

Conclusion:

These findings suggest that paediatric ART durability in resource-limited settings is good but complex, with treatment changes not only due to toxicity, treatment failure and drug interactions, but also treatment simplification. Clinicians treating children need to be aware of the drugs commonly causing toxicity, notably NVP, AZT and d4T in order to specifically monitor for them and ensure timely substitution of the drugs.

Abbreviations:

ABC-abacavir; aHR-adjusted hazard ratio; ART-Antiretroviral therapy; AZT-zidovudine;

CIs-confidence intervals; D4T-stavudine; EFV-efavirenz; Hb-haemoglobin; leDEA-SA- International epidemiologic Database to Evaluate AIDS-Southern Africa; IQR-interquartile range; LPV/R-lopinavir/ritonavir; NNRTI-Non-nucleoside reverse transcriptase inhibitors; NRTI-nucleoside reverse transcriptase inhibitors; NVP-nevirapine; PI-protease inhibitors; RTV-ritonavir; TB-tuberculosis; WHO-World Health Organisation; WAZ-weight-for-age z-score; 3TC-lamivudine.

Competing interests:

The authors state that they have no competing interests.

Author's contributions:

LK and MD conceived and designed the study. DG, JG, HR, RW, HM, KT, BE had the data collected at the different clinic sites that contribute data to the leDEA-SA database. LK carried out the statistical analysis of the data with supervision from MD. OK and AB provided critical advice with the data analysis. All authors read and approved the manuscript.

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Tables:

Table 1: Patient characteristics of children at ART initiation in routine HIV care programs in South Africa (N=5517)

	Number of children*	Median (IQR)
Age (months)	5517	42(15-82)
CD4 count (cells/mm ³)	4498	388(174-723)
CD4 Percent	4270	12(7.1-17.4)
Weight-for-age z score	3838	-1.94(-3.24 to -0.97)
log ₁₀ viral load	3757	5.3(4.7-5.9)
	Number of children*	Percent
Gender (Males)	2825/5517	51%
WHO stage 3 or 4	2911/3857	75%
Severe immune suppression	3705/4594	80%
Severe anemia at ART start	263/1365	19%
"First" drug in regimen **		
AZT	602/5517	10.9%
d4T	4883/5517	88.5%
ABC	32/5517	0.6%
"Third" drug in regimen **		
EFV	3035/5517	55%
NVP	259/5517	4.7%
RTV / LPV/r	2223/5517	40.3%
*Not all variables were measured on all children		
**Most regimens are of the form: NRTI + 3TC + (NNRTI OR PI)		

Table 2: Predictors of D4T changes due to toxicity over 3 years using Cox-proportional hazards regression among South African children on ART in routine HIV Programs (only children with at least one follow-up visit were included)

Variable	D4T (n=4623)					
	Unadjusted HR ^a	p-value	95%CI ^b	Adjusted HR ^a	p-value	95%CI ^b
Weight-for-age-z score <-1 (N=2387)	1					
Weight-for-age z-score >=-1 (N=2236)	4.40	0.001	1.78-10.87	3.64	0.016	1.27-10.39
Baseline log ₁₀ viral load (median=5.61)	1.69	0.093	0.92-3.12	2.25	0.025	1.11-4.57
Age < 36 months (N=1987)	1					
Age >=36 months (N=2636)	2.62	0.24	1.14-6.06	3.80 (n=3165)	0.043	1.04-13.85
^a Hazard Ratio, ^b Confidence Interval						

Weight-for age-z score, viral load and age were measured at baseline. Age and sex-standardized weight-for-age z-scores (WAZ) were calculated using the WHO 2006 reference standards ; age was included as a binary variable with a cut-off at 36 months because of different regimens being prescribed for children <36 months and ≥36 months; increase in viral load copies was compared to <400copies/ml which is considered undetectable viral load in clinical care.

Table 3: Predictors of AZT changes due to toxicity over 3 years using Cox-proportional hazards regression among South African children on ART in routine HIV Programs (only children with at least one follow-up visit were included)

Variable	AZT (n=592)					
	Unadjusted HR ^a	p-value	95%CI ^b	Adjusted HR ^a	p-value	95%CI ^b
WHO 3 or 4 (vs. 1 or 2) (N=441)	0.35	0.150	0.08-1.46	0.14	0.024	0.03-0.77
Severe Anemia (N=262)	1					
No severe anemia (N=76)	0.12	0.013	0.02-0.64	0.09	0.009	0.02-0.55
Age less than 36 months (N=408)	1					
Age in months (≥36) (N=184)	1.69	0.416	0.48-5.99	1.22	0.848	0.13-11.55
^a Hazard Ratio, ^b Confidence Interval						

WHO stage, degree of anemia and age were measured at baseline; severe anemia was defined as baseline haemoglobin (Hb) <7g/dl and age >21 days) and age was included as a binary variable with a cut-off at 36 months because of different regimens being prescribed for children <36 months and ≥36 months.

Figures:

Figure 1: Proportion of children who had drug stops/substitutions having remained in follow-up at 1, 2 and 3 years of therapy in routine HIV care programs in South Africa.

Among the children still in active follow-up by the end of the 1st, 2nd and 3rd years of treatment, 92.8%, 87.7% and 80.9% respectively were still taking their initial regimen. The main reasons for treatment change other than treatment failure were drug interaction in the 1st and 2nd years of therapy while in the 3rd year of therapy; the main contributors were drug interaction, toxicity and treatment simplification.

Figure 2: Drug substitution due to toxicity by drug over 2 years among South African children in routine HIV care programs (only children with at least one follow-up visit were included).

Nevirapine had the highest probability of being changed due to toxicity followed by zidovudine and stavudine. Efavirenz caused the least toxicity. LPV/r and RTV are not on this graph due to almost no treatment-limiting toxicity (i.e. even less than EFV which is the lowest on the graph).

Figure 3: LPV/r, RTV & NVP substitution over 2 years by reason among South African children in routine HIV care programs.

The main reasons for changing lopinavir/ritonavir and ritonavir apart from treatment failure were potential drug interaction and treatment simplification while nevirapine was mainly changed due to toxicity and drug interaction with anti-tuberculosis drugs.

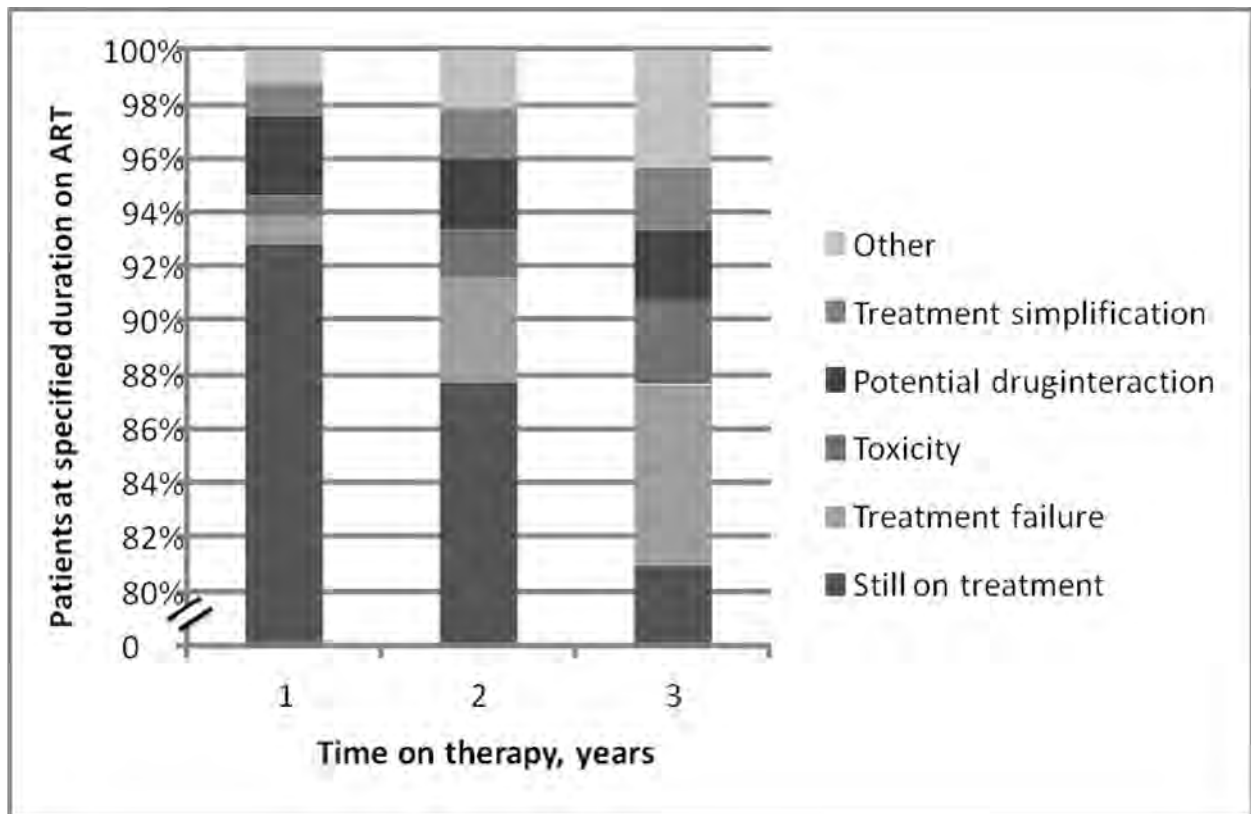
Figure 4: d4T & AZT substitution over 2 years by reason among South African children in routine HIV care programs.

Apart from treatment failure, the main reasons for stavudine changes were toxicity, simplification of treatment and potential drug interaction while zidovudine changes were mainly due to toxicity and treatment simplification.

Figure 5: d4T substitution due to toxicity over 2 years by reason among South African children in routine HIV care programs.

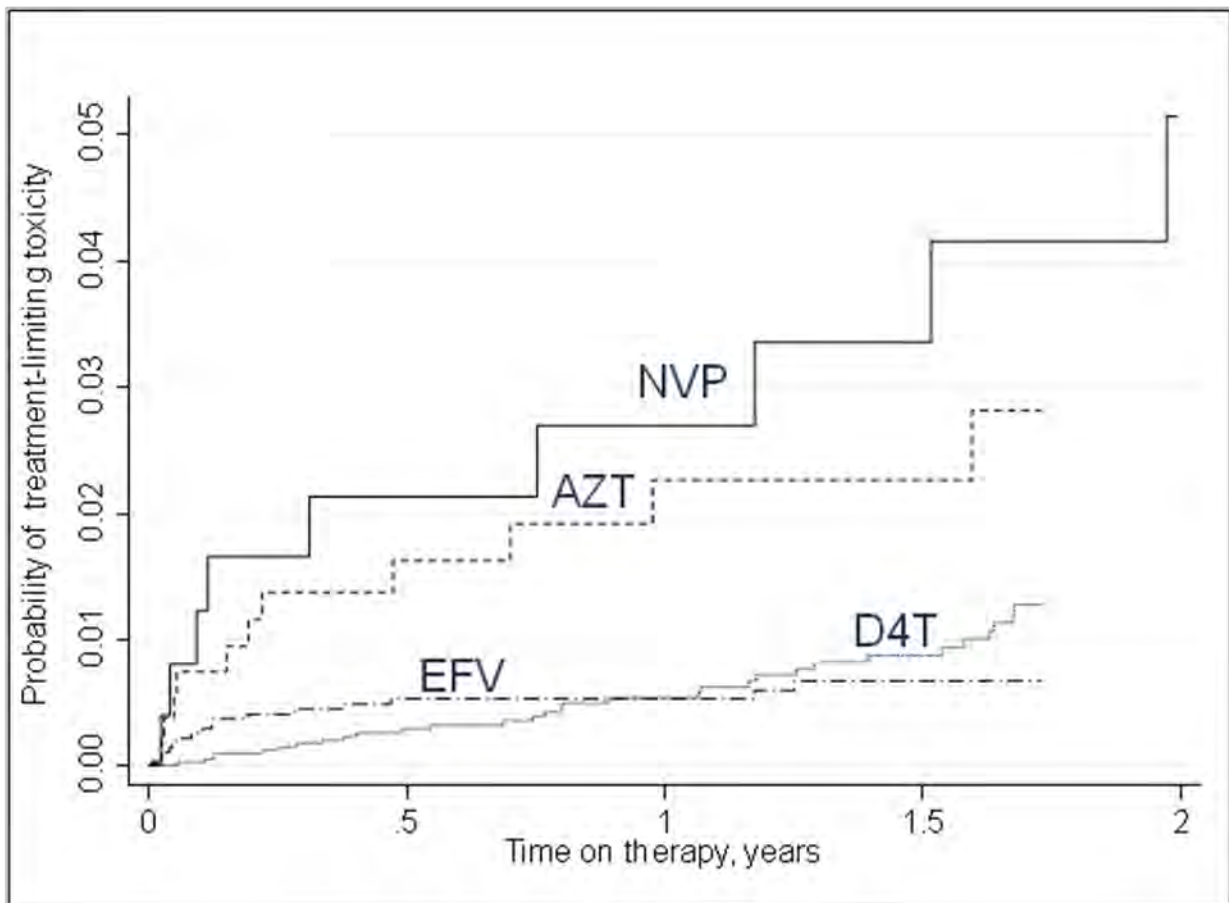
Treatment changes due to stavudine toxicity were mainly due to hyperlactataemia, lipodystrophy (abnormal fat redistribution) and peripheral neuropathy.

Figure 1



Year of treatment	1	2	3
Number followed	3226	1434	1065
Substitution due to other reasons%	1.3	2.2	4.4
Substitution due to treatment simplification%	1.2	1.9	2.3
Substitution due to potential drug interaction%	2.9	2.6	2.6
Substitution due to toxicity%	0.8	1.7	3.1
Substitution due to treatment failure%	1.0	3.9	6.7
Still on initial treatment%	92.8	87.7	80.9

Figure 2



Time on therapy, years	0	0.5	1.0	1.5	2.0
NVP	256	192	156	121	95
AZT	592	419	317	233	166
d4T	4623	3489	2653	1948	1383
EFV	2898	2374	1871	1423	1044

Figure 3

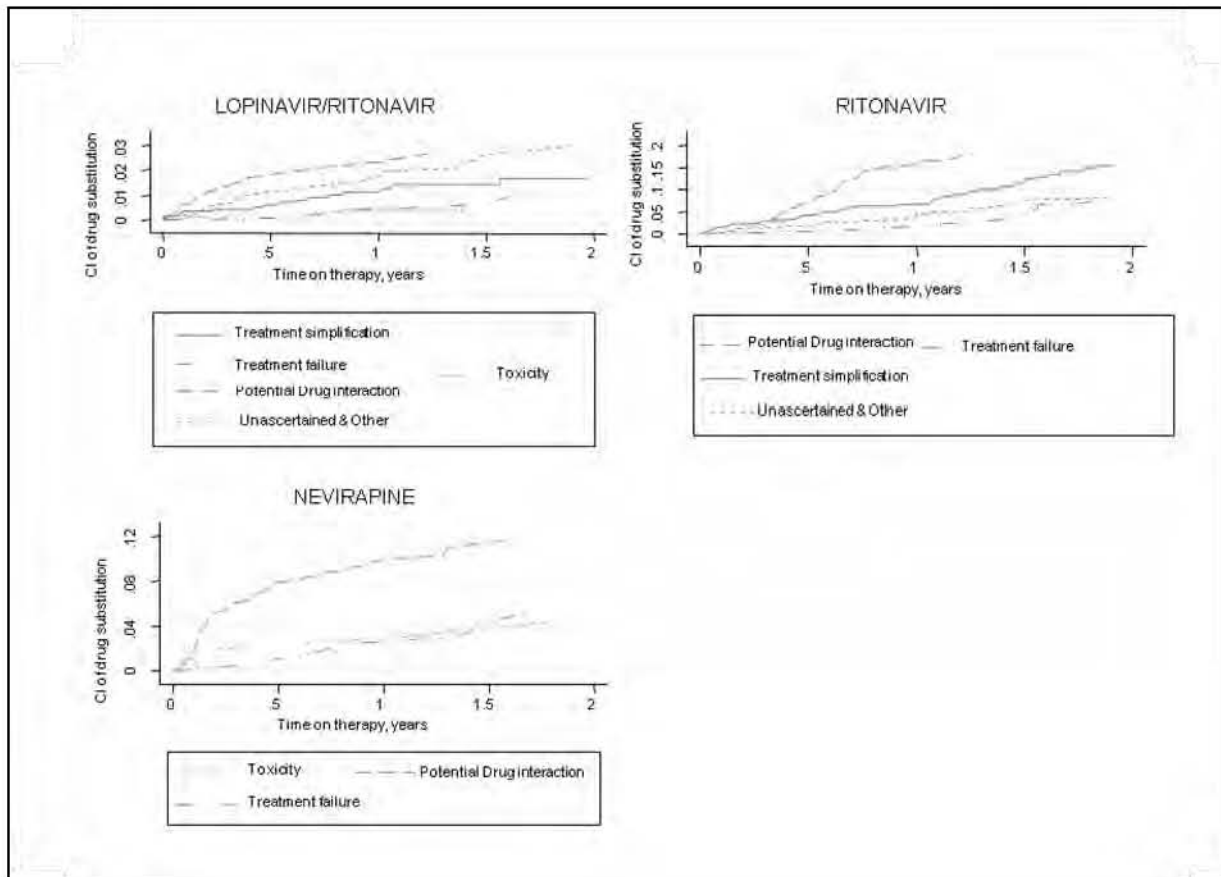


Figure 4

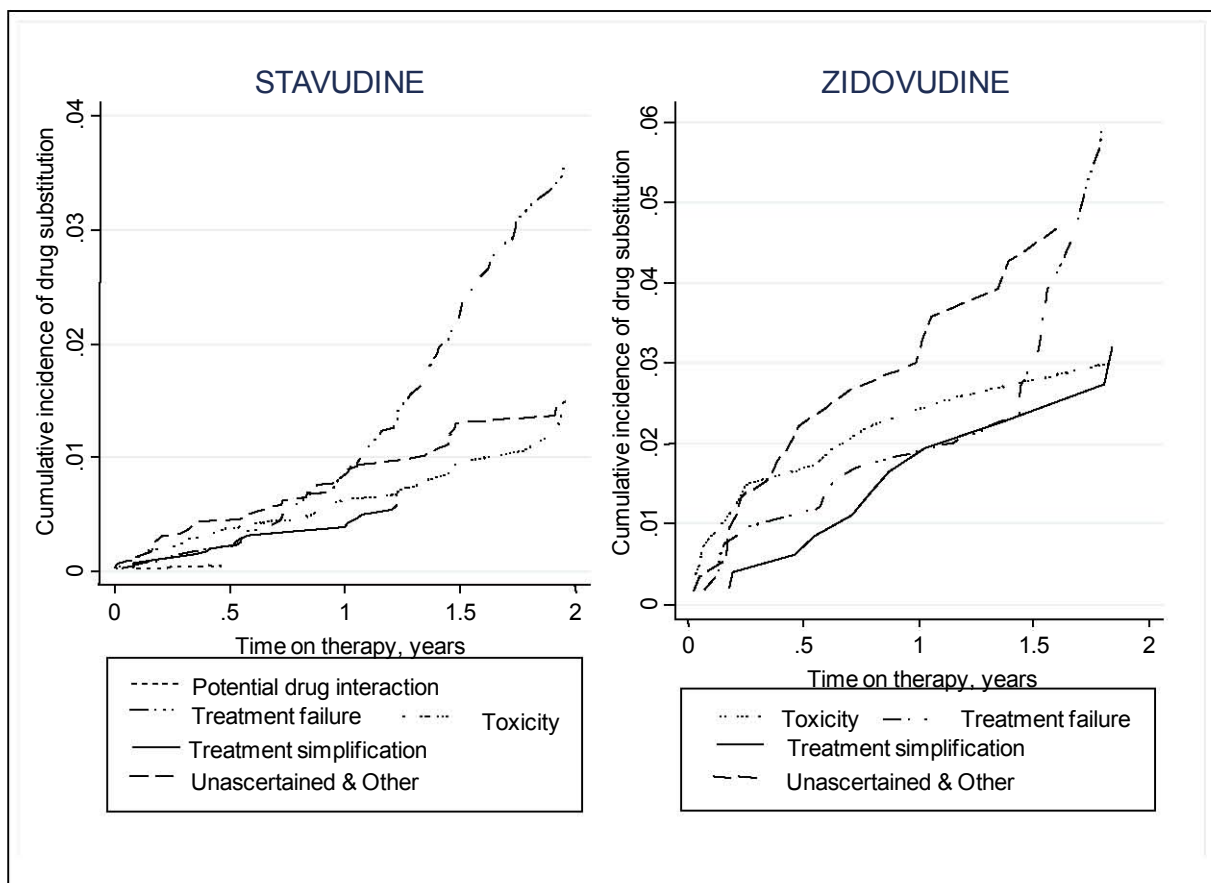
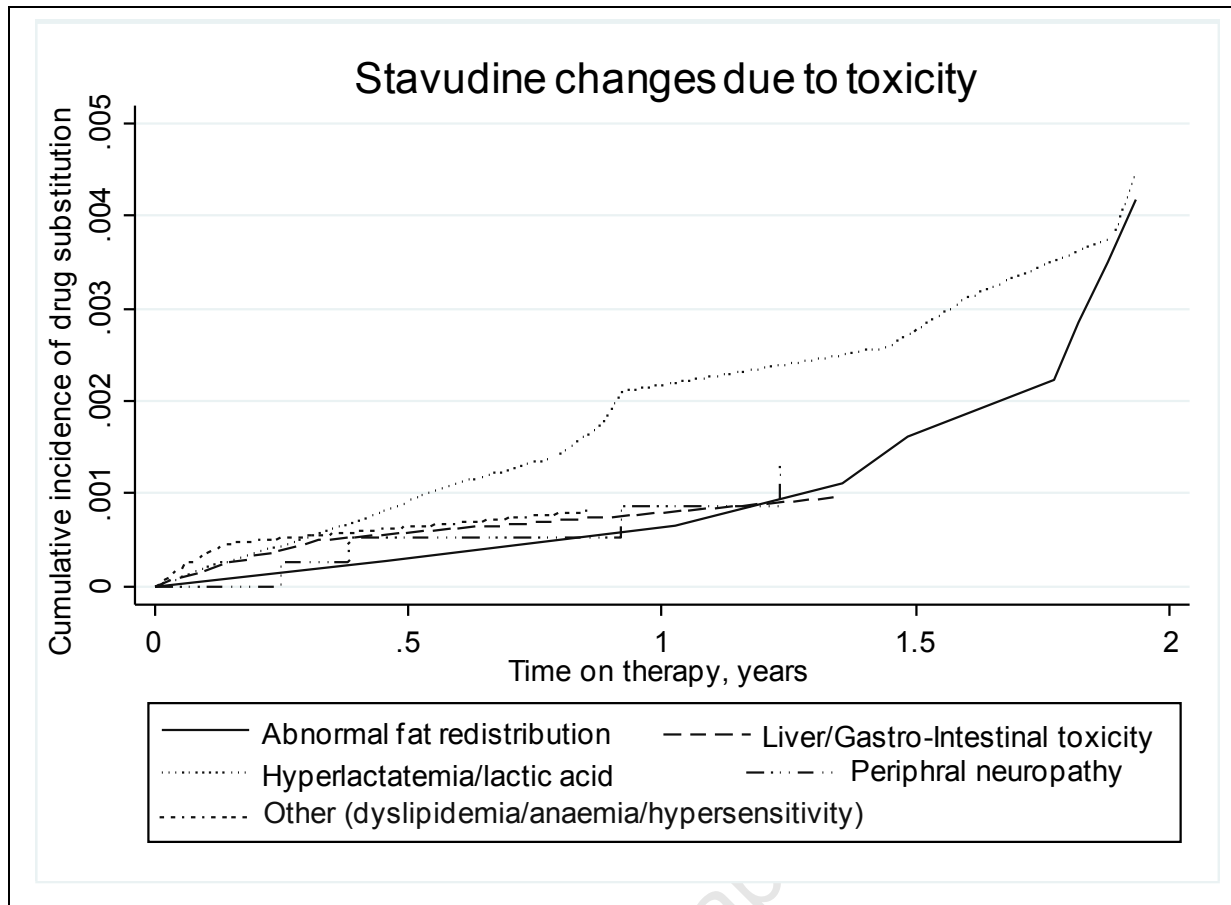


Figure 5



The liver toxicity, dyslipidaemias and peripheral neuropathy lines do not go up to 2 years because these toxicities occurred very early on during therapy and there were no further events beyond 1.5 years on therapy.



APPENDIX A: IeDEA Standard procedures for data transfer

IeDEA Southern Africa

STANDARD PROCEDURE FOR DATA TRANSFER

Version 2.0/August 2010

Contact: idea-info@ispm.unibe.ch

www.iedea-sa.org / www.iedea-hiv.org

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University of Cape Town

Introduction

General remarks

- This document provides guidance on the preparation of data tables for the transfer of data for the leDEA Southern Africa Collaboration.
- It is requested that each clinic prepares **ten separate tables** with the new data, as described in detail below. While 6 of these tables should be submitted by all sites, tables 7 -10 will only be applicable to certain sites (see below).
- The tables can be sent in the format that is most convenient for the site, including MS Excel, MS Access, ASCII etc. Please contact the leDEA data manager if you have any queries.
- **It is appreciated that for some clinics it may be easier to send their data as they stand (for example in Excel) and to leave the data management and preparation of the ten tables to the data centre. This is not a problem, but it is requested that a separate document be included with a list of the variables in the dataset and brief descriptions/definitions.**
- It is accepted that there will be missing data for some patients, and even entire missing tables from some sites who simply do not have that data in electronic format.
- It is requested that for security purposes, data tables be encrypted and compressed with WinZip 9 or higher using the AES encryption algorithm prior to sending. The encryption password (minimum of 10 characters long, including upper/lower case, numbers and special characters) should be communicated to the relevant data centre contact person by fax or by telephone.
- The use of UCT's Vula site is encouraged; this is an open-source tool allowing for the secure transfers of data from sites to the Data Centre. Vula is open and accessible 24 hours a day, 7 days a week.
- Please ensure that the dataset has been stripped of personal identifying information prior to sending.
- Please include a unique anonymous identifier for each patient (PATIENT) for cross-reference with your own database. It can be the identifier you are using or a special identifier you create for leDEA Southern Africa. This anonymisation key must be maintained by the site under secure conditions.
- Sites treating children should please send the date at which they changed from using the WHO 3-stage clinical staging system to the 4-stage clinical staging system.
- Thank you very much for your contribution to this collaborative project!

Inclusion criteria for patients

Please include all patients with the following characteristics:

- Documented HIV-1 infection
- Patients in care at the facility for whom the date of first visit at the facility is known exactly.

Notes:

- Where possible, it is intended that data be transferred on HIV-infected patients followed-up at the facility irrespective of whether or not they received highly active antiretroviral therapy (HAART).
- When transferring data just on patients who received HAART, it is preferable to include patients irrespective of whether or not they were exposed to antiretrovirals before the recorded HAART start date. In other words treatment-naïve and treatment-experienced patients are included.
- Sites should send all information on all patients (adults and/or children) in a single dataset. For adult patients (those whose **first visit at your facility was after their 16th birthday**) the paediatric specific fields (highlighted in blue) do not need to be completed (i.e. enter code 88 – not applicable). Paediatric specific fields must be entered as completely as possible for all patients whose **first visit at your facility is before their 16th birthday** even if their follow-up extends beyond the age of 16 years.
- Some patients will have been in care at another facility prior to commencing care at your facility. These patients should be included in the dataset, noting against the relevant field that they have been transferred in. All treatment and opportunistic infection (OI) history prior to commencing care at the facility should be reconstructed as far as possible and entered in the appropriate tables, with unknown codes for dates of start and end date of OIs/antiretroviral drugs where necessary.

Dates

- The term baseline will not be used as this creates confusion. We will rather make use of a set of key dates that will be entered into the first table, the **PATIENT** table. These are:

Variable name	Definition of key date
FRSVIS_DMY	Date of first visit at your facility
HIVP_DMY (HIVP_Y (year) and HIVP_M (month) if exact date unknown)	Date of first positive HIV-1 test
HAART_DMY	Date of HAART initiation

- For all fields that require a date, the precise date should be entered in the format dd-mm-yyyy if it is known. If the precise date is not known, the month and year should be entered separately as far as possible in the separate dedicated fields provided for these, and the precise date field should be left blank.
- If month or both the year and month are unknown, the precise date field should be left blank and unknown codes should be entered into the year field (9999) and the month field (99) as appropriate.
- For certain date fields a precise date is obligatory e.g. date of first visit at your facility (FRSVIS_DMY) and date of HAART initiation (HAART_DMY). In patients who commenced HAART at another facility, if the precise date of start of HAART cannot be estimated reasonably accurately, the patient should be entered as treatment experienced and the date of first visit at your facility will be regarded as the date of start of HAART.

Definitions

- HAART is defined as treatment with a combination of at least three drugs from any class or classes.
- “Treatment experienced” is defined as previous exposure to any antiretroviral drug for at least 30 days, **excluding** exposure for prevention of mother to child transmission (PMTCT) or post-exposure prophylaxis (PEP).

Standard codes

Certain codes will appear repeatedly in a number of lists for coded fields. In this instance, the same codes/coding format will be used in all fields where these codes appear as follows:

Codes	Description
0	No
1	Yes
90	Other
95	Not ascertained/Not collected at this facility
99	Unknown despite attempting ascertainment
88	Not applicable

Data tables

For each clinic, the following **five** to **ten** data tables or files should be prepared, depending on data availability.

- Tables 1 to 5 are required by **all** sites.
- Table 6 (LINKAGE DATA) is required only for sites that record information on families

- Table 7 (PREGNANCY) is required only for sites that record information on pregnancy electronically.
 - Table 8 (PAR HEALTH) is required only for patients who commence care before their 16th birthday.
 - Table 9 (TB) is required only from sites that record detailed information on episodes of tuberculosis electronically.
 - Table 10 (TRIAL) is required only for sites where patients may be enrolled on clinical trials or research studies apart from cohort analyses of routinely collected data.
 - In addition, a table summarising with information on the overall cohort or “meta-data” for the transfer, should be included with all transfers.
1. **PAT (Patient data)**: A table containing socio-demographic data on patients, clinical characteristics at start of HAART in HAART-treated patients, as well as information on the **outcomes** of patients. One line will correspond to one patient. In other words, each patient will appear only once in this table. We propose that this table is called **PAT**.
 2. **LAB (Laboratory data at baseline and follow-up)**: This is a single table containing all laboratory data: CD4, HIV viral load, and all other laboratory tests. One line will correspond to one laboratory result. In other words, most patients will have multiple records in this table. We propose that this table is called **LAB**.
 3. **ART (Antiretroviral treatments)**: A table with the data on all antiretroviral drugs that a patient has received or been exposed to including PMTCT (both exposure to mother as well as infant peri- or post-natal) or post-exposure prophylaxis. This includes treatment received at your facility and at other facilities. The table will contain one line for each separate drug, with different fields for the drug name (code), the prescription start dates and stop dates. Most patients will have numerous records in this table. The drug history of patients who commence care at your facility but have previously been treated at another facility should be reconstructed and entered into this table as far as possible. We propose that this table be called **ART**.
 4. **OI (Opportunistic Events)**: A table with the information on all opportunistic infections or incident HIV-associated diagnoses. One line will correspond to one clinical event with different fields for the event type (code), the start dates and stop dates. It is anticipated that stop dates will often not be known. In other words, some patients will have more than one record in this table and some may have no records in this table. History of opportunistic events occurring prior to commencing care at your facility should be reconstructed as far as possible. We propose that this table be called **OI**.

5. **VIS (Visit data):** A table containing information on all clinical visits (including the first visit at your facility). One line will correspond to one visit. Most patients will have more than one record in this table. We propose that this table be called **VIS**.
6. **LINK (Linkage data):** A table containing information on family members (partners, children and siblings) also receiving HIV care either within your cohort or at another site. All family members receiving HIV care should be included whether they are receiving care at an IeDEA collaborative site or at a non-IeDEA site. One line will correspond to one family member receiving HIV care. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table is called **LINK**.
7. **PREGNANCY (Pregnancy data):** A table containing information on all pregnancies, including spontaneous abortions/miscarriages and terminated pregnancies, and their outcomes. One line will correspond to one pregnancy. Multiple pregnancies will each have a record in the table, with the outcome of the relevant foetus recorded. Some patients will have more than one record in this table, while others (including all males and children less than 10 years) will have no records in this table. We propose that this table be called **PREGNANCY**.
8. **PAR_HEALTH (Parental health):** A table with information on parental health status. This table is only required for sites sending data on patients 15 years old and younger at their first visit to the facility. This table is linked to the visit table, so ideally there is an update on parental health status at every visit. Alternatively, this table should be filled in at least once, either for the first visit at your facility or the date of start of HAART.
9. **TUBERCULOSIS (Tuberculosis data):** A table with information on all episodes of tuberculosis (TB). This table is only for sites that record detailed information on TB episodes. Sites that do not collect detailed information on TB episodes should enter the TB episodes in the OI table. One line will correspond to one TB episode. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table be called **TB**.
10. **TRIAL (Enrolment in trials):** A table with information on any trial or research study (apart from cohort analysis of routinely collected data) on which a patient is enrolled. This table is only for sites running trials or research studies. One line will correspond to one trial/research study on which the patient is enrolled. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table be called **TRIAL**.
11. **OUTCOME_REVISIED: (Death registry linkage data)** A table with information on updated death status following linkage to registry systems.
12. **MET (Meta-data):** A table comprising key characteristics of the data that is transferred.

Variables to be included in core tables

Socio-demographic characteristics and outcomes (PAT table)

Table 1 below details the data that should be included in PAT table.

The patient identification variable (PATIENT) must be unique, and it cannot be missing in any of the tables. This field must contain a unique and anonymous patient identifier; the field must NOT contain their name or any other identifying information. It is up to the local collaborator to maintain the key for linking the unique patient identifier with the patient.

Table 1 – Variables to be included in PAT table

Name	Format and definitions	Description
PATIENT	Text & numeric characters (based on cohort/site/patient identifier - FS)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
FACILITY	Text	Text field identifying particular clinic within cohort, if more than facility within the cohort
BIRTH_DMY	DATE (dd-mm-yyyy)	Date of birth Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
BIRTH_Y	Numeric (for example 1960) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of birth
BIRTH_M	Numeric (for example 8) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of birth
GENDER	Numeric with codes: 1 = Male 2 = Female 95 = Not ascertained 99 = Unknown despite	Sex / gender of patient

	attempting ascertainment	
FRSVIS_DMY	DATE (dd-mm-yyyy)	Date of first visit at facility (Note: This date must be entered exactly)
ENTRY	Numeric with codes (see List 1)	Mode of entry to your facility
ENTRY_OTHER	Text	Details of other mode of entry not listed in List 1
MODE	Numeric with codes (see List 2)	Most probable mode of HIV transmission
Name	Format and definitions	Description
HIV_TYPE	Numeric (for example 1) 1 = HIV-1 2 = HIV-2 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Field to distinguish HIV-1 from HIV-2
HIVP_DMY	DATE (dd-mm-yyyy)	Date of first positive HIV test Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
HIVP_Y	Numeric (for example 2001) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of first positive HIV-1 test
HIVP_M	Numeric (for example 8) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of first positive HIV-1 test
HIV_TEST	Numeric with codes (IeDEA SA codes) 1 = Presumptive diagnosis 2 = Serology 3 = PCR 4 = P24 5 = Rapid test 90 = Other	Type of test used for diagnosis

	95 = Not ascertained 99 = Unknown despite attempting ascertainment	
HAART	Numeric 0 = Never started HAART 1 = Started HAART	Conditional: If 1 then go to HAART_DMY
HAART_DMY	DATE (dd-mm-yyyy)	Date of HAART initiation (minimum 3 drugs together) Note: This date must be entered exactly. If patient commenced HAART at another facility and the exact date is not known, the patient should be entered as "Treatment experienced" in the EXP_Y field below and the first visit at your facility will be used as the start of HAART date.
Name	Format and definitions	Description
FHV_STAGE_WHO	Numeric with codes: 1 = Stage I 2 = Stage II 3 = Stage III 4 = Stage IV 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Clinical WHO stage (I to IV) at time of starting HAART (Enter 88 patients who have not commenced HAART)

<p>FHV_SDI_1</p>	<p>Text (for example PCP - see List 3)</p> <p>88 = Not applicable</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite attempting ascertainment</p>	<p>Stage defining illness-1 at time of starting HAART.</p> <p>(Enter 88 patients who have not commenced HAART)</p> <p>Note: At least FHV_S_SDI_1 should be completed in patients commencing HAART; A maximum of 4 stage defining illness can be entered in the 4 fields provided. There is no specific ordering to the entering of stage defining illnesses.</p>
<p>FHV_SDI_2</p>	<p>Text (for example PCP - see List 3)</p> <p>0 = No further stage defining illness</p> <p>88 = Not applicable</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite attempting ascertainment</p>	<p>Stage defining illness-2 at time of starting HAART.</p> <p>(Enter 88 patients who have not commenced HAART)</p>
<p>FHV_SDI_3</p>	<p>Text (for example PCP - see List 3)</p> <p>0 = No further stage defining illness</p> <p>88 = Not applicable</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite attempting ascertainment</p>	<p>Stage defining illness-3 at time of starting HAART.</p> <p>(Enter 88 patients who have not commenced HAART)</p>
<p>FHV_SDI_4</p>	<p>Text (for example PCP - see List 3)</p> <p>0 = No further stage defining illness</p> <p>88 = Not applicable</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite</p>	<p>Stage defining illness-4 at time of starting HAART.</p> <p>(Enter 88 patients who have not commenced HAART)</p>

	attempting ascertainment	
Name	Format and definitions	Description
EXP_Y	<p>Numeric with codes:</p> <p>0 = No (No previous ARV experience)</p> <p>1 = Yes (Treatment experienced, drug history known and recorded in ART table)</p> <p>2 = Yes (Treatment experienced, drug history not known)</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite attempting ascertainment</p>	<p>Patient is treatment experienced prior to starting HAART (HAART_DMY) ?</p> <p>Experienced = Any ARV drug for at least 30 days before starting HAART (PMTCT regimen and PEP excluded)</p> <p>This should be entered for all patients even those who have not commenced HAART.</p>
MTCT_Y	<p>Numeric with codes:</p> <p>0 = No (No MTCT exposure)</p> <p>1 = Yes (MTCT exposed, drug history reconstructed and recorded in ART table)</p> <p>2 = Yes (MTCT exposed, drug history not reconstructable)</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite attempting ascertainment</p>	<p>Patient exposed to MTCT drugs (either mother during pregnancy or infant peri- or post-natally) prior to start of HAART (HAART_DMY)?</p> <p>This should be entered for all patients even those who have not commenced HAART.</p>

PEP_Y	Numeric with codes: 0 = No (No PEP exposure) 1 = Yes (PEP exposed, drug history reconstructed and recorded in ART table) 2 =Yes (PEP exposed, drug history not reconstructable) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient exposed to post-exposure prophylaxis (PEP) drugs prior to start of HAART (HAART_DMY)? This should be entered for all patients even those who have not commenced HAART.
TB_FHV	Numeric with codes 0 = No 1 = Yes 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient was on treatment for TB at start of HAART (HAART_DMY) (Enter 88 patients who have not commenced HAART)
WKS_TB_FHV	Numeric (for example 8) 88=Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Duration in weeks since start of TB treatment when HAART was commenced in patients with TB at start of HAART (Enter 88 for patients who have not commenced HAART or who did not have TB at start of HAART)
Name	Format and definitions	Description
PREG_FHV	Numeric with codes 0 = No 1 = Yes 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Pregnant at start of HAART (Enter 88 for men and children <10 years old AND all patients who have not commenced HAART)
LAST_CONTACT_DMY	DATE (dd-mm-yyyy)	Date of last contact Note: This date must be entered exactly.

LAST_CONTACT_T	Numeric with codes (See List 4)	Type of last contact
OUTCOME	Numeric with codes (See List 5)	Outcome including death and loss to follow-up
OUTCOME_DMY	DATE (dd-mm-yyyy)	Date of outcome (Leave blank if outcome is Alive [in care] or Alive [not in care])
OUTCOME_Y	Numeric (e.g. 2004) 8888 = Not applicable or exact date of outcome entered above 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of outcome Enter 8888 for patients who have not died, or if exact date of outcome entered above.
OUTCOME_M	Numeric (e.g.12) 88 = Not applicable or exact date of outcome entered above 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of outcome Enter 88 for patients who have not died, or if exact date of outcome entered above.
DEATH_C1	Numeric with codes (see List 6)	Cause of death : Enter 88 for patients who have not died
DEATH_N1	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	Note : There are 3 fields for 3 causes of death to be entered in no specific order. If an HIV-related cause of death is recorded, please ensure that the condition is recorded appropriately in the OI table.
DEATH_C2	Numeric with codes (see List 6)	Nature of contribution of cause: For each cause of death, please characterise the contribution of the specific cause.
DEATH_N2	Text with following codes: I = Immediate cause	

	U = Underlying cause/condition C = Contributing cause N = Not available	
Name	Format and definitions	Description
DEATH_C3	Numeric with codes (see List 6)	
DEATH_N3	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	
CAREG	Numeric with codes (see List 7)	Primary caregiver at start of HAART (HAART_DMY) (paediatric patients only – enter 88 for adult patients)
DISCL_CG	Numeric with codes (see List 8)	Person informed of the HIV status of the child (paediatric patients only – enter 88 for adult patients)
DISCL_CHILD	Numeric with codes 0 = No 1 = Yes 2 = In process 88 = Not applicable (adult patient) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Was the child informed of his/her status at HAART_DMY? (paediatric patients only - enter 88 for adult patients)
DELIV_M	Numeric with codes 10 = Vaginal, spontaneous 11 = Vaginal, forceps	Mode of delivery (paediatric patients only - enter 88 for adult patients)

	<p>12 = Vaginal, vacuum</p> <p>20 = Caesarean section – primary/elective (before onset of labour and rupture of membranes)</p> <p>21 = Caesarean section – emergency</p> <p>22 = Caesarean section – type unknown</p> <p>88 = Not applicable</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite attempting ascertainment</p>	
WEIGHT_BIRTH	<p>Numeric (e.g. 3.20)</p> <p>88 = Not applicable</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite attempting ascertainment</p>	<p>Weight at birth in kg (paediatric patients only - enter 88 for adult patients)</p>
Name	Format and definitions	Description
BRSTFD	<p>Numeric with codes</p> <p>10 = breastfeeding, exclusive</p> <p>11 = breast-feeding, exclusivity unknown</p> <p>12 = mixed feeding</p> <p>20 = Formula feeding</p> <p>88 = Not applicable</p> <p>95 = Not ascertained</p> <p>99 = Unknown, despite attempting ascertainment</p>	<p>Main infant feeding option after birth (paediatric patients only - enter 88 for adult patients)</p>
BRSTFD_ED	DATE (dd-mm-yy)	<p>Date of cessation of breast feeding if applicable</p> <p>Leave blank if not applicable, child still being breastfed, date not known, or child not</p>

		breastfed at all.
BRSTFD_EST_DUR	Numeric (e.g. 2) 77 = still breast-feeding, ED unknown 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Estimated duration of breastfeeding in months in children who are exclusively breastfed or mixed fed. (paediatric patients only - enter 88 for adult patients) Enter 88 if child still being breastfed or child not breastfed at all.

Laboratory data (LAB table)

Table 2 details the laboratory data that should be included in the LAB table. All available data from the date of first visit should be included.

Notes:

- Results of laboratory tests must be provided in the units specified
- Results of laboratory tests can be entered in one of two fields – a numeric field (LAB_V) and a coded text field (LAB_T) (for very high and/or undetectable viral loads, and for TB microscopy and culture results).
- TB microscopy and culture results should only be entered in the coded result field (LAB_T) as follows, and not in the numeric field (LAB_V):
- For viral loads, there is an additional field to indicate the lower limit of detection of the assay used. This field should be entered as not-applicable (Code = -88) for other laboratory results.
- For TB sensitivity results, there are 2 additional fields. The first (TB_DRUG) where the drug to which sensitivity testing has been done is entered, and the second (SENS), where the sensitivity is recorded using the standard yes/no format. These fields should be entered as not-applicable (Code = 88) for other laboratory results.
- Both CD4 percentage and absolute count should be included on paediatric patients until they are 16 years old.
- There is no code for unknown values of for laboratory test results as tests of which the result is unknown should not be included in the dataset.
- Only dates in the DMY format are permissible in this table.

Table 2 – Variables to be included in the table LAB

Name	Format	Description
PATIENT	Free (numerical or alphanumeric)	Unique patient identifier
LAB_DMY	Date (for example dd/mm/yy)	

		Date when specimen was taken
LAB_ID	Text (see List 9)	Code representing the measurement
LAB_V	Numeric (for example 44)	Numeric value of measurement Leave blank if result entered as code (LAB_C)
Name	Format	Description
LAB_T	Text Lower than limit of detection for viral loads should be entered as “LDL” TB microscopy and culture results should be entered as follows: - Paucibacillary 1+ 2+ 3+ Unknown +	Text result e.g. “> 6 000 000” or “P+++” Leave blank if result entered as number (LAB_V)
RNA_L	Numeric -88 = Not applicable -99 = Unknown	Lower limit of detection of RNA assay (Enter -88 for laboratory tests other than viral load)
TB_DRUG	Text with codes: INH_L = Isoniazid low dose INH_H = Isoniazid high dose INH_U = Isoniazid – dose unspecified PZA = Pyrazinamide RIF = Rifampicin ETN = Ethionamide ETB = Ethambutol STREP = Streptomycin QUI = Quinolone 88 = Not applicable	TB Drug against which sensitivity has been tested. (Enter 88 for laboratory tests other than viral load)
DRUG_RES	Numeric with codes: 0 = No (Sensitive) 1 = Yes (Resistant)	Is Mycobacterium TB cultured RESISTANT to drug in TB-DRUG field? (Enter 88 for laboratory tests other than viral

	88 = Not applicable	load)
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Antiretroviral drug variables (ART table)

Table 3 details the data on antiretroviral treatment that should be included in the ART table. As previously mentioned, preferably we will receive one line per drug, each with its prescription, start and stop date.

Notes:

All antiretroviral drugs to which a patient has been exposed (including PMTCT exposure of both pregnant women and infants peri- or postnatally) and PEP should be included with either the dates of starting and stopping the individual drugs, **OR** the number of doses **OR** the duration of treatment.

- History of exposure to antiretroviral drugs prior to commencing care at the reporting facility should be reconstructed as far as possible and included in this table, making use of appropriate drug codes for unknown regimens and date/time codes for unknown start and stop dates or unknown durations.

Table 3 – Variables to be included in ART table

Name	Format	Description
PATIENT	Free (numerical or alphanumeric)	Unique patient identifier
ART_ID	ATC (for example NVP – see List 10)	Type of antiretroviral drug
ART_SD_DMY	Date(dd-mm-yyyy)	Date of starting each antiretroviral drug (start date). Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
Name	Format	Description
ART_SD_Y	Numeric (e.g. 2003) 8888 = Exact start date entered in appropriate field 9999 = Unknown despite attempting ascertainment 9995 = Not ascertained	Year of starting drug
ART_SD_M	Numeric (e.g. 7)	Month of starting drug

	<p>88 = Exact start date entered in appropriate field</p> <p>99 = Unknown despite attempting ascertainment</p> <p>95 = Not ascertained</p>	
ART_RS	<p>Numeric with codes</p> <p>(See List 11)</p>	Reason for receiving ART
ART_FORM	<p>Numeric with codes</p> <p>1 = Tablet/capsule</p> <p>2 = Syrup/Suspension</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite attempting ascertainment</p>	Type of formulation
ART_COMB	<p>Numeric with codes</p> <p>1 = Individual drug</p> <p>2 = Part of a fixed dose combination</p> <p>95 = Not ascertained</p> <p>99 = Unknown despite attempting ascertainment</p>	Is drug part of a fixed dose combination?
ART_ED_DMY	Date(dd-mm-yyyy)	<p>Date of stopping each antiretroviral drug (end date)</p> <p>Enter exact date in this field if known.</p> <p>If unknown leave blank and enter EITHER month and year as far as possible in fields below OR number of doses OR duration in weeks in the appropriate fields.</p>
ART_ED_Y	<p>Numeric (e.g. 2004)</p> <p>8888 = exact end date or number of doses or duration in weeks entered in appropriate fields</p> <p>9999 = Unknown despite attempting ascertainment</p> <p>9995 = Not ascertained</p>	Year of stopping drug
ART_ED_M	<p>Numeric (e.g. 7)</p> <p>88 = exact end date or number of</p>	Month of stopping drug

	doses or duration in weeks entered in appropriate fields 99 = Unknown despite attempting ascertainment 95 = Not ascertained	
Name	Format	Description
NO_DOSES	Numeric (e.g. 1) 888 = end date or duration in weeks entered in appropriate fields 999 = Unknown despite attempting ascertainment 995 = Not ascertained	Number of doses of drug e.g. 1 for single dose Nevirapine
NO_WEEKS	Numeric (e.g. 12) 888 = end date or number of doses entered in appropriate fields 999 = Unknown despite attempting ascertainment 995 = Not ascertained	Number of weeks of receiving drug e.g. 12 for AZT from 28 weeks of pregnancy delivering at term
ART_END_RS	Numeric with codes (See List 12)	Reason for stopping antiretroviral drug
INFO_SOURCE	Numeric with codes 1 = Clinical records at this facility 2 = Clinical records/letter from another facility 3 = Patient/caregiver report 4 = Likely protocol in use 90 = Other 99 = Unknown	Source of information about ART

Opportunistic events (OI table)

Table 4 below details the data on opportunistic events or HIV associated conditions diagnosed during follow-up that should be included in table OI.

History of opportunistic events prior to commencing care at the reporting facility should be reconstructed as far as possible and included in this table, making use of appropriate date/time codes for unknown start and end dates. It is anticipated that the end date of OIs will frequently be unknown.

Table 4 – Variables to be included in OI table

Name	Format	Description
PATIENT	Free (numerical or alphanumeric)	Unique patient identifier
OI_ID	Text (for example PCP - see List 3 – Disease codes – under PAT table)	Type of opportunistic event
OI_SD_DMY	Date(dd-mm-yyyy)	Date of start of each opportunistic event. Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
OI_SD_Y	Numeric (e.g. 2001) 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of start of event
OI_SD_M	Numeric (e.g. 11) 88 = Not applicable (Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of start of event
OI_ED_DMY	Date(dd-mm-yyyy)	Date of end of each opportunistic event. Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below

		If OI is ongoing (has not yet ended) leave blank and enter appropriate code in field below
Name	Format	Description
OI_ED_Y	Numeric (e.g. 2001) 8885 = Ongoing 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of end of event
OI_ED_M	Numeric (e.g. 11) 85 = Ongoing 88 = Not applicable (Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of end of event
DIAG_METH	Numeric (see List 13)	Method of diagnosis

Follow-up clinic visits (VIS table)

Table 5 below details the information to be included in the **VIS table**. Please include all visits for each patient since the first visit at the reporting facility, and where possible visits at previous facilities. Weight, height and head circumference left blank will be assumed to have not been ascertained.

Table 5 – Variables to be included in VIS table

Name	Format and definitions	Description
PATIENT	Free (numerical or alphanumeric)	Unique patient identifier
VISIT_DMY	Date (for example dd/mm/yy)	Date of visit patient
VISIT_FAC	Numeric with codes 1 = Visit at this cohort's facility	Facility at which visit took place

	2 = Visit at another facility 99 = Site of visit unknown	
WEIGHT	Numeric (for example 75)	Weight in kilos (kg)
HEIGHT	Numeric (for example 75)	Height in centimeters (cm)
CTX	Numeric with codes : 1 = yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Cotrimoxazole status
INH	Numeric with codes : 1 = Yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Isoniazid status
FLU	Numeric with codes : 1 = Yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Fluconazole status
HEADC	Numeric (for example 75)	Head circumference in centimeters (cm)
SCHOOL_Y	Numeric with codes 0 = No school 1 = At school 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Schooling for children >5 years. For adults and children less than 5 years, enter 88.
LINK_REL	Numeric with codes (See List 14)	Relationship of family member to patient

LINK_COHORT	Text with codes (See List 15)	Cohort within which family member is receiving HIV care
LINK_ID	Free (numerical or alphanumerical) -88 = Not applicable -95 = Not ascertained -99 = Unknown despite attempting ascertainment	Unique patient identifier of family member Enter -88 if family member in care at non-leDEA site.

University of Cape Town

Appendix B: Ethics approval



UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
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Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
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31 May 2011

HREC REF: 084/2006

Dr A Boule
Infectious Disease Epidemiology Unit
Public Health & Family Medicine
Falmouth Building
Medical School

Dear Dr Boule

PROJECT TITLE: THE OBSERVATIONAL ANTIRETROVIRAL STUDIES IN SOUTHERN AFRICA (OASIS) COLLABORATION

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 05 May 2011

It is a pleasure to inform you that the Ethics Committee has granted annual approval for the above-mentioned study

Approval is granted for one year until 15 June 2012.

Please send us an annual progress report (website form FHS 016) if your research continues beyond the approval period. Alternatively, please send us a brief summary of your findings so that we can close the research file.

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

Please quote the REC. REF in all your correspondence.

Yours sincerely

A handwritten signature in black ink, appearing to be 'M Blockman', written over a horizontal line.

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

temjedi

APPENDIX C: Concept paper

The International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA)

Proposed analysis: Substitutions to initial antiretroviral therapy due to toxicity or contraindication in children in South Africa.

Title:	Substitutions to initial antiretroviral therapy due to toxicity or contraindication in children in South Africa.
Lead author:	Leatitia Kambiire
IeDEA senior investigator:	Mary-Ann Davies
Other data centre staff involved	Andrew Boulle, Olivia Keiser
Collaborators:	Representative from each site contributing data
Statisticians:	Leatitia Kambiire
Target journal:	Paediatric Infectious Diseases Journal/JAIDS
Milestones:	<p><i>Circulation of concept sheet: May 2011</i></p> <p><i>Circulation of early draft paper: December 2012</i></p> <p><i>Circulation of mature draft paper: January 2013</i></p> <p><i>Submission to target journal: February 2013</i></p>
Abstract: (about 100 words)	<p>With the scale up of antiretroviral therapy (ART) for children in sub-Saharan Africa, there are important concerns about its tolerability and durability. There is a paucity of information about the frequency of and reasons for single drug or whole regimen changes for reasons other than treatment failure in children. There are few available and palatable options of ART for HIV-infected children. There is therefore a need to understand the probability of and reasons for drug substitutions among children on ART to inform treatment and monitoring guidelines and prevent early and frequent substitutions, thus saving the few alternative and second-line drugs for situations of treatment failure. We aim to use data from South African IeDEA collaborating sites which includes approximately 6000 children initiated on ART, with 30% on protease inhibitor (PI)-based first-line therapy, to determine the drug-specific probability of and reasons for individual drug and regimen substitution.</p>

Outline:

(about 1000 words)

1. Background

Southern Africa has a high burden of paediatric HIV, and, despite recent massively expanded access to antiretroviral therapy (ART), coverage remains low [1]. The 2010 Joint United Nations Programme on HIV/AIDS (UNAIDS) South Africa Country progress report showed that there were 86, 270 children on ART by November 2009.

Tolerability, safety and durability of first-line ART regimens are vital to scaling up ART and maintaining children on therapy. Regimen durability is particularly important in resource-limited settings with limited drug options [2], especially in children [3].

Prospective cohort studies done in the developed world show that the main reasons for ART regimen change in children are toxicity and treatment failure [4-8]. For example, in a nine year cohort of 49 perinatally infected children on highly active antiretroviral therapy (HAART) 50% of the children had their regimen changed by 24 months on treatment [7]. The reasons for treatment change were toxicity in more than half of the children and virological failure (22% of regimen changes), with reasons for the remainder of changes being unspecified [7]. In contrast, a five year cohort study of 40 perinatally-infected children receiving early HAART showed that 47.5% of these children were still receiving their first HAART regimen five years later and the main reasons for regimen change included virological failure (40%), simplification to a PI-sparing regimen (45%) and toxicity (5%) [8]. In many studies from developed country settings, however, children have had pre-HAART ART with either monotherapy and/or combined therapy [4-6] which is different from the cohort that will be used in this analysis in which all children will be HAART naive.

While there are no dedicated studies of ART safety and durability in children from developing countries, paediatric ART cohort outcomes studies from Sub-Saharan Africa have reported on frequency and reasons for drug substitutions. All of these studies report low numbers of treatment changes with the reasons for drug changes including antiretroviral (ARV) toxicity, treatment failure, initiation or completion of tuberculosis treatment and change due to increasing age [9-13]. For example, an open cohort assessment of children

receiving ART at primary health care centres in Lusaka, Zambia; found that of the 2938 children who started ART, 17.6% had a single-drug substitution of their nucleoside reverse transcriptase inhibitor due to toxicity, intolerance or problems with dosing. The median time to substitution was 132 days after ART initiation. Children on an AZT-based regimen were more likely to have a substitution compared to those on a d4T-based regimen (Hazard Ratio, 2.8; 95% CI 2.3-3.3). NVP-based regimens were substituted at a rate of 7.9/100 patient years (median time to substitution, 103 [IQR, 43 to 262] days) [11].

Many of these cohorts are small with limited follow-up duration and the majority of children started on NNRTI-based treatment. In addition, only the overall proportion of changes has been described, with descriptions of the time to regimen change and reasons for change being limited [14]. We therefore aim to use data from South African IeDEA collaborating sites which includes approximately 6000 children initiated on ART, with 30% on PI-based first-line therapy, to determine the drug-specific probability of and reasons for substitution. While this analysis will report on all treatment changes, the focus will be on **drug substitutions** defined as changes in single drugs or whole ART regimens for reasons other than treatment failure. An analysis of failure and switching to second-line therapy in this cohort has already been published [15].

2. Objectives and hypotheses

- To determine the cumulative probability of changing one or more drugs from an initial ARV regimen for reasons other than treatment failure for each first-line drug among children on ART in South Africa.
- To describe the reasons for changing one or more drugs from an initial ARV regimen for each first-line drug among children on ART in South Africa.
- To describe the alternative regimen options available for use among children on ART and the proportions of children taking these regimens in South Africa.
- To determine characteristics of children associated with receiving

particular drug substitutions.

3. Study design

3.1 Eligibility criteria

The analysis will only include children with complete data merged from collaborating South African paediatric leDEA sites.

3.3.1 Eligibility criteria for children

- Children who commence ART at <16 years of age.
- HIV-infected children who are ART-naïve (except for PMTCT) at the time of joining the cohort.
- HIV-infected children who initiate ART with a documented regimen of at least 3 ARV drugs.

3.3.2 Eligibility criteria for paediatric cohorts

Cohorts that initiated ART in at least 25 ART-naïve HIV-infected children.

3.2 Key variables and definitions

3.2.1 Brief description of children at commencement of ART

These will include:

- Gender and age.
- Measures of disease severity e.g. WHO stage, CD4 percent or count, viral load.
- Social variables – primary caregiver.
- First-line regimens actually used.
- Previous PMTCT exposure.

3.2.2 Characteristics of children at time of treatment change

These will include:

- Gender and age.
- CD4 cell count and viral load at the time of treatment change.
- First-line treatment regimen used.

3.3 Outcomes

- Treatment change.
- Reasons for treatment change.

3.4 Statistical methods

Analysis of pooled retrospective data from South African leDEA paediatric ART sites using the agreed leDEA Southern Africa data transfer format. For all analyses, techniques will be used that

account for between cohort variation and the hierarchical structure of the data.

Where there is missing or inconsistent information about ART regimen and/or reasons for substitution, additional information will be sought from the individual treatment sites.

- Characteristics of children at baseline will be described.
- Characteristics of children at time of ART regimen change will be described.
- The Kaplan-Meier method will be used to estimate the time from initiation of ART to first treatment change both for all regimen changes not due to failure and for individual drug changes e.g. changing from d4T to an alternative NRTI.
- Cox-proportional hazards models stratified by site will be used to determine the predictors of particular regimen changes e.g. d4T changes. Where there is more than one cause of a particular regimen change, competing risk regression will be used to estimate the cumulative probability of each cause.

3.5 Sample size considerations

No calculation done. We will include all children with available data.

3.6 Ethical considerations

The data to be used for this analysis are anonymised and will be obtained from individual leDEA sites each of which has existing Institutional Review Board (IRB) approval for contribution of data to leDEA collaborative analyses.

4. References – see below

References

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APPENDIX D: Summary of reviewed studies Table 1: Paediatric studies from resource limited settings

Study	Eley B. et al, SAMJ 2004 [24]	Fassinou P. et al, AIDS 2004 [1]	Puthanakit T. et al, Clinical Infectious diseases 2005 [25]	Jooste J. P. et al, SAMJ 2005 [26]
Countries	South Africa	Cote d'Ivoire (ANRS1244/1278 Children's cohort (Abidjan, Cote d'Ivoire))	Thailand (Northern)	South Africa (Northern Cape)
Number of participants	80	78	107	100
Ages of participants	Mean 4.2 years	Median (range) 6.5 (0.7-15.2) years	Mean (SD) 7.7 (2.7) years	Mean (range) 5.5 (0.25-13) years
Gender	61% males	56% males	43% males	Not reported
Follow-up duration	Total follow-up time: 23.9 child-years	Total follow-up time:160.58 child-years	Total follow-up time:143.9 child-years	Total follow-up time:6 months
ARVs used	d4T/ lamivudine (3TC)/ritonavir (RTV) if child < 10 kg or < 3 years old or Efavirenz (EFV) if child > 10 kg or > 3 years old	2 NRTIs with either nelfinavir (NFV) (n=61) or EFV (n=17)	d4T/3TC/EFV or Nevirapine (NVP)	d4T /3TC/ + NVP (n=14) or EFV (n=48) or lopinavir/ritonavir (LPV/r) (n=38)
Treatment changes made	RTV changed to EFV	Not reported	5 children changed from NVP-based to EFV-based regimens	1 changed to Abacavir (ABC), ddI, 3TC, LPV/r, 3 NVP to EFV, 1 LPV/r to EFV, 1 NVP to LPV/r
Reasons for initial regimen substitution or switch	1 child had gastrointestinal (GI) disturbances i.e. persistent nausea and vomiting, 1 had treatment simplified due to failure to tolerate the taste	12 changed once; 5 changed twice. 2 TB treatment, 2 drug shortage, 5 prescription simplification, 1 poor response to ART, 7 adverse effects: pancreatitis, persistent diarrhoea, hepatotoxicity, EFV hypersensitivity, AZT-induced anemia	5 severe adverse reactions: hypersensitivity, drug fever, grade 2 elevated liver enzymes and grade 3 neutropenia	1 patient resistant to treatment due to previous exposure to NVP monotherapy and dual therapy in private sector; other reasons not reported
Median time to change after ART initiation	Not reported	Not reported	Not reported	Not reported
Dedicated to ART regimen changes	NO	NO	NO	NO

Table 2: Paediatric studies from resource limited setting continued

Study	Hansudewechakul R. et al, Vulnerable Children & Youth Studies 2006 [7]	Rouet F. et al, AIDS 2006 [2]	Nyandiko W. M. et al , JAIDS 2006 [19]	O'Brien D. P. et al, AIDS 2006 MSF cohort [13]
Countries	Thailand	Cote D'Ivoire (ANRS1244/1278 Children's cohort (Abidjan, Cote d'Ivoire)	Kenya	Cambodia, Kenya, Malawi, Mozambique, Thailand, Uganda, Burkina Faso and Zimbabwe
Number of participants	110	78	1353 enrolled, 279 received ART	6151
Ages of participants	Median age (IQR) 9.3 (7.2-10.7) years	Median age (range) 6.5 (0.7–15.2) years	Median age (95% CI) 6 (0.4 - 13.7) years	Median (IQR) 7 (4.6-9.3) years
Gender	42% males	56.4% males	51% males	52% males
Follow-up duration	All followed up for 12 months	Median (IQR) 36 (30-42) months	Median 34 months (95% CI: 4.8 months to 13.7 years).	Median (IQR) 6 (2-12) months
ARVs used	10% EFV-based triple therapy, 90% NVP-based triple therapy (89% as fixed-dose combination)	2NRTIs/EFV (17children) or NFV (61 children)	d4T or AZT/3TC/NVP	d4T/3TC/NVP
Treatment changes made	5 from NVP to EFV	9 from NFV-based to EFV-based & 1 from NFV-based to LPV/r-based	Alternative regimens- not reported	Alternative first-line regimen- not reported
Reasons for initial regimen substitution or switch	One had severe hypersensitivity, 4 TB treatment with rifampicin	NFV toxicity (6 children); treatment failure (4 children). No details provided regarding the toxicity	3 changed due to clinical and immunological failure	Side effects (4%-46% children) across the different cohorts; no details reported about side effects
Median time to change after ART initiation	Not reported	Med (IQR) 33 (16.5-36) months	Not reported	Median (IQR) 1.4 (0.5-3.2) months
Dedicated to ART regimen changes	YES	NO	NO	NO

Table 3: Paediatric studies from resource limited settings continued

Study	Bolton-Moore et al, JAMA 2007 [23]	Ble C., Acta Paediatrica 2007 [31]	Reddi A. et al, BMC-Paeds 2007 [4]	Wamalwa D. et al, JAIDS 2007 [20]
Countries	Zambia	Tanzania	South Africa	Kenya
Number of participants	4270 enrolled, 2938 started ART	103	151	67
Ages of participants	Median 2.2 (IQR, 0.77 -3.8) years	Range: 0.1-4.2 years	Median(range) 5.7(0.3-15.4) years	Median(IQR) 4.4 (2.4-6.0) years
Gender	47.9% males	59% males	49% males	51% males
Follow-up duration	Median (IQR) 12.6(4.6-23) months	12 months (no loss to follow-up)	Median (IQR) 8(3.5-13.5) months	Med (IQR) 9(3-15) months
ARVs used	50.6% d4T/3TC/NVP 38.1% AZT/3TC/NVP 4.2% AZT/3TC/EFV 7.1% d4T/3TC/EFV	36% AZT/3TC/NFV 32% AZT/3TC/NVP	d4T/3TC plus either NVP/EFV /LPV/r/ RTV	AZT/3TC/NVP or EFV ; d4T/3TC/ NVP or EFV, 2 children on TB therapy were given d4T/3TC/ABC 1 child who had failed NVP perinatal prophylaxis was given AZT/3TC/ NFV
Treatment changes made	10.1% on d4T changed to AZT; 27.8% on AZT changed to d4T; 8.6% on NVP changed to EFV	59.3% had a treatment change (no details reported)	11.3% (17 patients) had regimen changes to AZT/ddI plus EFV or LPV/r	10 children changed at least one drug-not specified
Reasons for initial regimen substitution or switch	Drug intolerance, toxicity, dosing issues	Concomitant anti-TB treatment; Toxicity (4 neutropenia, 11.4%, 2 anemia, 5.7%); low CD4 count in one (2.6%).	2 due to drug toxicity (AZT-induced anemia; d4T-induced lactic acidosis); 7 due to treatment failure; 6 due to start or stop of TB treatment; 2 from LPV/r to EFV due to increasing age (<3 years)	7 adverse effects e.g. NVP associated rash, AZT-induced anemia, ABC hypersensitivity; 2 treatment failure; 1 to prevent interaction with TB treatment
Median time to change after ART initiation	6.1 [IQR, 2.7 to 12.6] months for d4T to AZT; 3.7 [IQR, 1.4 to 9.0] months for AZT to d4T; 3.4[IQR, 1.4 to 8.7] months for NVP to EFV	5.5 months (IQR not reported)	Not reported	Not reported
Dedicated to ART regimen changes	NO	NO	NO	NO

Table 4: Paediatric studies from resource limited settings continued

Study	Prendergast A. et al, AIDS 2008 [30]	Kumarasamy N. et al, Tropical Paediatrics 2008 [21]	Sauvegeot D. et al, Paediatrics 2009 [29]
Countries	South Africa	India	Africa, Asia
Number of participants	53	67	3936
Ages of participants	Median (range) 0.12 (0.02–1.09) years	Mean (SD) 6.28 (4.18) years	Median (IQR) 2.6 (1.7-3.7) years
Gender	53.3% males	61% males	52.9% males in both regions
Follow-up duration	49 children followed up for one year; 4 died	Minimum 18 months	Median 10.5 (3.7-20.6) months
ARVs used	94% AZT/3TC/NVP/NFV 3 infants were not given NVP due to abnormal liver function at baseline	41.8% 3TC/ d4T/ NVP 16.2% 3TC/AZT/NVP 20.9% 3TC/d4T/EFV	16.2 % d4T/3TC/NVP 41.8% AZT/3TC NVP 20.9% d4T/3TC/EFV
Treatment changes made	Changed to ddi, ABC, LPV/r	The alternative first-line regimens given not reported; 19.4% changed to 2 ND line protease-inhibitor regimens	3.8% changed ≥1 first-line regimens
Reasons for initial regimen substitution or switch	5 Starting TB treatment, 3 AZT toxicity, 4 Virological failure	25.4% of all children due to toxicity e.g. anemia, rash, lipoatrophy, diarrhoea, nausea, pruritus, headache	Toxicity: AZT toxicity more frequent than d4T toxicity in African children while in Asian children, NVP toxicities were more frequent
Median time to change after ART initiation	Not reported	Not reported	Median (IQR) 1.4 (0.7–5.7) months
Dedicated to ART regimen changes	NO	YES	NO

Table 5: Paediatric studies from resource rich settings

Study	Doerholt K. et al, HIV Medicine 2002 [14]	Van Rossum A.M.C. et al, Clinical Infectious diseases 2002 [15]	Resino S. et al, Clinical Infectious diseases 2006 [16]	Bracher L. et al, Scandinavian Journal of Infectious Diseases 2007 [17]	Chiappini E. et al, BMC Infectious Diseases 2009 [18]
Countries /continents	England	Netherlands	Spain	Denmark	Italy
Number of participants	110	32	113 (not ART-naïve)	49	40
Ages of participants	Median (range) 6.3 (0.6-16) years	Median (range) 5.4 (0.25-16.4) years	By CD4 count: Mean (SD) years: <5%: 7.4 (0.5); 5-15%: 7.7 (0.6); 15-25%: 6.9 (0.8); >25%: 4.9 (0.7)	Median (range) 6.7 (0.1-15.6) years	Median (IQR) 2.21 (1.37-4-76) years
Gender	50% males	56% males	44.2% males	47% males	Not reported
Follow-up duration	Not reported	Minimum of 54.2 children-years	Not reported (lasted until early teens)	245 patient-years	Median [IQR] 5.96 (4.21–7.62) years
ARVs used	60% HAART i.e. 2NRTIs & 1PI or 2 NRTIs & 1NNRTI	(17 naïve, 15 non-naïve); AZT/3TC/NFV (n=27); AZT/3TC/indinavir (IDV) (n=3); NFV/d4T/ddi (n=2)	d4T/3TC/NFV or RTV or EFV	d4T/AZT+3TC+NVP/EFV or one of RTV/(LPV/r)/NFV/Saquinavir(SQV)/IDV	AZT or d4T/3TC or ddi / NVP or NFV or LPV/r or RTV
Treatment changes made	Alternative first-line regimens not reported.	IDV to RTV for 8 children	49.6% had treatment changes to their initial regimen (no details reported)	50% had regimens modified (no details reported)	52.5% had treatment changes (no details reported)
Reasons for initial regimen substitution or switch	10% drug toxicity; 16% poor adherence, 66% treatment failure	6 virological failure, 1 toxicity (interstitial nephritis), 1 reluctance to swallow drug	Not reported	22% virological failure, 57% toxicity, 7% non-compliance, 17% other reasons	1 liver toxicity, 3 structured therapy interruption, 9 simplification to a PI sparing regimen, 8 virological failure
Median time to change after ART initiation	Mean (SD) 11.5 (9.5)months	Median (range) 12 (0.5-18) months	Not reported	50% by 2 years on therapy while only 25% remained on initial regimen after 6 years of therapy	Median (IQR) 3.77 (1.71–5.71) years
Dedicated to ART regimen changes	NO	NO	NO	NO	NO

Table 6: Adult studies from the developing world

Study	Wester C. W. et al, JAIDS 2005 [27]	Boulle A. et al, Antiviral Therapy 2007 [9]	Hawkins C. et al, JAIDS 2007 [28]
Countries	Botswana	South Africa	Kenya
Number of participants	153	2679 (2 primary care sites)	1286
Ages of participants	Median (IQR) 36 (30-42)years	Median 32 (28-38) years	Median (range) 36 (18-70)years
Gender	41% males	29% males	40.9% males
Follow-up duration	Median 54 weeks for clinical outcomes; 63 weeks for laboratory data	Median (IQR)11.1 (6.9-18.6) months	Median (range) 11.6 months (0.03-24months)
ARVs used	64%ddl + d4T with EFV/NVP	44% d4T/ 3TC/ EFV 31% d4T/ 3TC/ NVP	98.9% initiated with an NNRTI-based regimen
Treatment changes made	Changed to unused NNRTIs and NFV	28% had treatment changes (no details reported)	54.5% had treatment changes (no details reported)
Reasons for initial regimen substitution or switch	Virological failure, opportunistic infections, poor adherence, toxicity: 31 due to severe peripheral neuropathy, with all patients on ddl + d4Tcontaining ART; 6% due to hepatotoxicity, with 2 patients on NVP-containing ART; 4% were for pancreatitis, with both patients on ddl-containing ART; 7 due to NVP-induced hypersensitivity; 4% due to severe anemia;	8% toxicity; d4T toxicity was mainly due to hyperlactataemia, lipodystrophy & peripheral neuropathy 11% contraindication	40.6% Toxicities, 28.1% TB treatment interaction
Median time to change after ART initiation	Not reported	3 years	Median (range) 2.7 (0.17-20.8) months
Dedicated to ART regimen changes	NO	YES	NO

Table 7: Adult studies from the developing world continued

Study	Zhou J. et al, HIV Medicine 2007 [8]	Castelnuovo B. et al, JAIDS 2011 [12]
Countries	Asia, Pacific region	Uganda
Number of participants	404	559
Ages of participants	50% aged 31-40 years	Median (IQR) 38 (33-44) years
Gender	74% males	30% males
Follow-up duration	586.9 person-years	Median(IQR) 33 (24-34) months
ARVs used	3 or more drugs containing at least one NNRTI & one NRTI but no PI. About 50% received d4T/3TC/NVP	74% d4T/3TC/NVP; 34% AZT/3TC/EFV
Treatment changes made	Most changed to AZT/3TC/NVP and <3% to PI-based regimens	26.5% had treatment changes (no details reported)
Reasons for initial regimen substitution or switch	Virological failure; patient's decision; non-compliance; toxicity including lipodystrophy, hepatitis, rash, pancreatitis, peripheral neuropathy, lactic acidosis, insomnia; others like pregnancy, financial problems, doctor's decision, hospitalisation	Drug toxicity especially due to d4T; treatment failure; TB concomitant treatment, pregnancy
Median time to change after ART initiation	Median (range) 8.7 (0.07–50.6) months for patients on d4T/3TC/NVP who changed one drug. Rate of change was lower in patients on NNRTI-based triple or more combination therapy than on PI-based treatment or on treatment containing three or more NRTIs	Median (IQR) time to substitution due to toxicity was 21.9 (13.4–32.8) months
Dedicated to ART changes	YES	YES

APPENDIX E: Manuscript instructions to authors

BMC Pediatrics

Instructions for authors

Preparing main manuscript text

General guidelines of the journal's style and language are given below.

Overview of manuscript sections for Research articles

Manuscripts for Research articles submitted to *BMC Pediatrics* should be divided into the following sections (in this order):

- Title page
- Abstract
- Keywords
- Background
- Methods
- Results and discussion
- Conclusions
- List of abbreviations used (if any)
- Competing interests
- Authors' contributions
- Authors' information
- Acknowledgements
- Endnotes
- References
- Illustrations and figures (if any)

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The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

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Title page

The title page should:

- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided

Abstract

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections:

Background, the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your research article reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. **Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

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The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

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This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

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A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

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Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who

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All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Please avoid excessive referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

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In press article

Kharitonov SA, Barnes PJ: **Clinical aspects of exhaled nitric oxide.** *Eur Respir J*, in press.

Published abstract

Zvaifler NJ, Burger JA, Marinova-Mutafchieva L, Taylor P, Maini RN: **Mesenchymal cells, stromal derived factor-1 and rheumatoid arthritis [abstract]**. *Arthritis Rheum* 1999, **42**:s250.

Article within conference proceedings

Jones X: **Zeolites and synthetic mechanisms**. In *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore*. Edited by Smith Y. Stoneham: Butterworth-Heinemann; 1996:16-27.

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Schnepf E: **From prey via endosymbiont to plastids: comparative studies in dinoflagellates**. In *Origins of Plastids. Volume 2*. 2nd edition. Edited by Lewin RA. New York: Chapman and Hall; 1993:53-76.

Whole issue of journal

Ponder B, Johnston S, Chodosh L (Eds): **Innovative oncology**. In *Breast Cancer Res* 1998, **10**:1-72.

Whole conference proceedings

Smith Y (Ed): *Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore*. Stoneham: Butterworth-Heinemann; 1996.

Complete book

Margulis L: *Origin of Eukaryotic Cells*. New Haven: Yale University Press; 1970.

Monograph or book in a series

Hunninghake GW, Gadek JE: **The alveolar macrophage**. In *Cultured Human Cells and Tissues*. Edited by Harris TJR. New York: Academic Press; 1995:54-56. [Stoner G (Series Editor): *Methods and Perspectives in Cell Biology*, vol 1.]

Book with institutional author

Advisory Committee on Genetic Modification: *Annual Report*. London; 1999.

PhD thesis

Kohavi R: **Wrappers for performance enhancement and oblivious decision graphs**. *PhD thesis*. Stanford University, Computer Science Department; 1995.

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The Mouse Tumor Biology Database [<http://tumor.informatics.jax.org/mtbwi/index.do>]

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- File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)
- Title of data
- Description of data

Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.
University of Cape Town

Additional file formats

Ideally, file formats for additional files should not be platform-specific, and should be viewable using free or widely available tools. The following are examples of suitable formats.

- Additional documentation
 - PDF (Adode Acrobat)

- Animations
 - SWF (Shockwave Flash)
- Movies
 - MP4 (MPEG 4)
 - MOV (Quicktime)
- Tabular data
 - XLS, XLSX (Excel Spreadsheet)
 - CSV (Comma separated values)

As with figure files, files should be given the standard file extensions.

Mini-websites

Small self-contained websites can be submitted as additional files, in such a way that they will be browsable from within the full text HTML version of the article. In order to do this, please follow these instructions:

1. Create a folder containing a starting file called index.html (or index.htm) in the root.
2. Put all files necessary for viewing the mini-website within the folder, or sub-folders.
3. Ensure that all links are relative (ie "images/picture.jpg" rather than "/images/picture.jpg" or "http://yourdomain.net/images/picture.jpg" or "C:\Documents and Settings\username\My Documents\mini-website\images\picture.jpg") and no link is longer than 255 characters.
4. Access the index.html file and browse around the mini-website, to ensure that the most commonly used browsers (Internet Explorer and Firefox) are able to view all parts of the mini-website without problems, it is ideal to check this on a different machine.
5. Compress the folder into a ZIP, check the file size is under 20 MB, ensure that index.html is in the root of the ZIP, and that the file has .zip extension, then submit as an additional file with your article.

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Abbreviations

Abbreviations should be used as sparingly as possible. They should be defined when first used and a list of abbreviations can be provided following the main manuscript text.

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- Please use double line spacing.
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- Use the *BMC Pediatrics* [reference format](#).
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- Please do not format the text in multiple columns.
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Units

SI units should be used throughout (liter and molar are permitted, however).