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Regimen durability in HIV-positive children andd adolescents initiating first-line art in a large public sector HIV cohort in South Africa

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REGIMEN DURABILITY IN HIV-POSITIVE CHILDREN AND ADOLESCENTS INITIATING FIRST-LINE ART IN A LARGE PUBLIC SECTOR HIV COHORT IN SOUTH AFRICA

by

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ABSTRACT

Introduction: In April 2010 tenofovir and abacavir replaced stavudine in public-sector first-line antiretroviral therapy (ART) for children under 20 years old in South Africa. The association of both abacavir and tenofovir with fewer side-effects and toxicities compared to stavudine could translate to increased durability of tenofovir or abacavir-based regimens. We evaluated changes over time in regimen durability for pediatric patients 3 to 19 years of age at 8 public sector clinics in Johannesburg, South Africa.

Methods: Cohort analysis of treatment naïve, non-pregnant pediatric patients from 3 to 19 years old initiated on ART between April 2004-December 2013. First-line ART regimens before April 2010 consisted of stavudine or zidovudine with lamivudine and either efavirenz or nevirapine. Tenofovir and/or abacavir was substituted for stavudine after April 2010 in first-line ART. We evaluated the frequency and type of single-drug substitutions, treatment interruptions, and switches to second-line therapy. Fine and Gray competing risk regression models were used to evaluate the association of antiretroviral drug type with single-drug substitutions, treatment interruptions, and second-line switches in the first 24-months on treatment.

Results: 398 (15.3%) single-drug substitutions, 187 (7.2%) treatment interruptions and 86 (3.3%) switches to second-line therapy occurred among 2602 pediatric patients over

24-months on ART. Overall, the rate of single-drug substitutions started to increase in 2009, peaked in 2011 at 25%, then declined to 10% in 2013, well after the integration of tenofovir into pediatric regimens; no patients over the age of 3 were initiated on abacavir for first-line therapy. Competing risk regression models showed patients on zidovudine or stavudine had upwards of a 5-fold increase in single-drug substitution vs. patients initiated on tenofovir in the first 24-months on ART. Older adolescents also had a 2-3-fold increase in treatment interruptions and switches to second-line therapy compared to younger patients in the first 24-months on ART.

Conclusions: The decline in single-drug substitutions is associated with introduction of tenofovir. Tenofovir use could improve regimen durability and treatment outcomes in resource-limited settings.

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LIST OF ABBREVIATIONS

3TC……………………………………………………………………………Lamivudine

ABC……………………………………………………………………………….Abacavir

ART…………………………………………………………….. Antiretroviral Therapy

AZT…………………………………………………………………………… Zidovudine

BMI……………………………………………………………………Body Mass Index

d4t……………………………………………………………………………….. Stavudine

EFV………………………………………………………………………………. Efavirenz

HIV……………………………………………………Human Immunodeficiency Virus

LMIC…………………………………………………….. Lower Middle Income Country

NNRTI…………………………………...Non-nucleoside Reverse Transcriptase Inhibitor

NRTI…………………………………………Nucleoside Reverse Transcriptase Inhibitor

NVP…………………………………………………………………………..Nevirapine

PMTCT……………………………Prevention of Maternal to Child Transmission of HIV

SDS……………………………………………………………… Single Drug Substitution

TB………………………………………………………………………….Tuberculosis

TDF…………………………………………………………………………… Tenofovir

USAID…………………………...United States Agency for International Development

WHO………………………………………………………….. World Health Organization

CHAPTER ONE: INTRODUCTION

In 2015, there were an estimated 1.8 million children under age 15 living with HIV globally, with 150,000 new pediatric infections annually (1). Despite prevention of mother to child transmission (PMTCT) programs, large numbers of children are still perinatally infected. In South Africa, approximately 370,000 children under age 15 are currently living with HIV, and in 2012, there were an estimated 166,000 children receiving antiretroviral therapy (ART) (2). As the pediatric ART program has matured, numerous changes were made to South African national guidelines regarding first-line ART for pediatric patients. Prior to 2010, standard first-line ART for children under age 3 included a protease-inhibitor and two nucleoside reverse transcriptase inhibitors (NRTIs); after age 3, children were transitioned to a non-nucleoside reverse transcriptase inhibitor (NNRTI) backbone regimen. In 2010, the South African National Guidelines recommended either abacavir or tenofovir for children under 14, and tenofovir for adolescents over 14, as preferential NRTIs over stavudine for initiation regimens (3, 4) in accordance with World Health Organization (WHO) guidelines (5, 6) (Table 1).

Regimen durability, defined as the time from initiation of an ART regimen until first modification of that regimen, is a crucial aspect of pediatric HIV treatment given the necessity of conserving ART regimens for a lifetime. Pediatric first-line regimens may be affected by single-drug substitutions, treatment interruptions, or switches to second-line therapy. There have been limited data from LMICs regarding regimen durability for pediatric patients. Previous data from a single pediatric ART facility in South Africa showed that 83% of pediatric patients remained in care over four years, 65% stayed on their initiating regimen, and 26% had a single-drug substitution for ART-related toxicities (7). This evidence from a single pediatric site was published prior to the 2010 South African guidelines change. More recent data from two pediatric programs in South Africa post-2010 have shown that 26% of children remained on their initial regimen over 5 years, with toxicity to stavudine being the most common reason for discontinuation (8).

Preservation of ART regimens in the pediatric population is essential for children who will survive to adulthood and require ART for many years. Because HIV-infected children must have good adherence to ART, better understanding of factors associated with regimen instability is needed to strengthen pediatric ART programs and ensure survival of successive generations of children. Research on adult patients in LMICs has demonstrated a decline in single-drug substitutions in the first 12 months on ART with the introduction of tenofovir after 2010 (9-15). However, large-scale examinations of ART regimen durability in children in light of changing guidelines, with respect to the inclusion of both tenofovir and abacavir replacing stavudine for pediatric patients, is needed. We sought to assess the association of first-line NRTI and regimen durability in a large pediatric cohort in South Africa.

Age group (years)	Pre 2010	Post 2010
3 to 5	d4T + 3TC + EFV	ABC + 3TC + EFV TDF + 3TC + EFV
5 to <14	d4T + 3TC + EFV	ABC + 3TC + EFV TDF + 3TC + EFV
14 to <20	d4T + 3TC + EFV d4T + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP	TDF + 3TC + EFV TDF + 3TC + NVP

Table 1. 2004 and 2010 South African National Treatment Guidelines for first-line ART for children and adolescent HIV-positive patients
*Table adapted from South African National Antiretroviral Treatment Guidelines 2004[2] and 2010[3]
d4T, stavudine; 3TC, lamivudine; EFV, efavirenz; NVP, nevirapine; AZT, zidovudine; ABC, abacavir; TDF tenofovir

CHAPTER TWO: METHODS

Cohort description

This was an analysis of prospectively collected cohort data. Patients included in the cohort are ages 3 to 19 years old initiating antiretroviral (ARV) drugs at one of eight HIV clinics in Gauteng and Mpumalanga provinces, South Africa (16). These are primary healthcare sites, supported by Right to Care, a South African non-governmental organization funded by the Unites States Agency for International Development (USAID) (16). All clinical data are entered into an electronic clinical database (TherapyEdge-HIV™) in real-time by either a clinician or data entry clerk at the clinic. Since the wide-scale rollout of ART in April 2004, clinic staff at these eight sites have provided pediatric HIV care according to South African National Department of Health Guidelines (3-5).

Standard first-line ART prior to April 2010 for children 3-14 years old was stavudine, lamivudine, and efavirenz. First-line ART for adolescents >14 years old included lamivudine, and the second NRTI was either stavudine or zidovudine, with either efavirenz or nevirapine for NNRTI. After 2010, the South African National Guidelines recommended either abacavir or tenofovir for children 3-14 years old, or only tenofovir for adolescents >14 years old, as the preferential NRTIs in first-line ART (3-5) (Table 1).

Routine laboratory tests (CD4 counts, hemoglobin, liver function tests, creatinine clearance), with exception of HIV viral load, are conducted at the time of ART initiation. Additional testing (TB microscopy and culture results, lactate levels, glucose, lipid profiles) is performed when clinically indicated. Prior to 2010, CD4 counts and viral loads were repeated at three and six months post-initiation and then every six months, but the 2010 guidelines recommended them at 6 and 12 months after initiation and then yearly thereafter (4,5).

Eligibility Criteria:

All non-pregnant, ART-naïve patients over 3 years of age and younger than 20 years of age initiating a standard public-sector first-line ART regimen at one of these eight clinics between April 2004 and December 2013 were included in this analysis. All patients had the potential for 24-months of follow-up.

Study Variables:

Primary outcomes for this analysis were: (1) single-drug substitutions, defined as changing the NRTI only, excluding lamivudine, within first-line ART; (2) treatment interruptions, defined as stopping ART for at least one week before resuming a regimen; and (3) switch to second-line therapy, defined as a new NRTI substitution and replacement of the NNRTI for a protease inhibitor. All outcomes were measured in the first 24-months on ART. Loss to follow-up is defined as loss to follow-up 3 months after last-scheduled visit (4 months from last actual clinic visit). All outcomes were calculated individually.

Statistical Analysis:

Patient baseline characteristics were summarized with simple descriptive statistics and stratified by year of ART initiation. Three separate models were run. For each model, person-time began at ART initiation and ended at the earliest of: (1) primary outcome of interest (i.e. single-drug substitution (model 1), treatment interruption (model 2), and second-line switch (model 3)); (2) loss to follow-up; (3) death; (4) transfer; (5) completion of 24 months of follow-up. Fine and Gray's competing risks regression method (17) was used to evaluate association of type of NRTI in first-line regimen on primary outcomes of interest: single-drug substitution, treatment interruption and second-line switch, accounting for attrition as a competing risk. Models were adjusted for age (categorized as 3-4.9, 5-9.9, 10-13.9 and 14-19.9 years of age) and gender, and CD4 count (categorized as <50, 51-100, 101-200, 201-350 and >350 cell/mm^3), hemoglobin levels (<10ug/dl vs. ≥10 ug/dL), WHO stage (18) and body mass index at ART initiation (19). Analyses were performed using the SAS 9.3 statistical software package (SAS Institute, INC., Cary NC).

Interaction:

The interaction between gender and NRTI and age and NRTI was assessed on the additive scale by calculating the risk due to interdependence (R(I))(20).

Ethical Review:

Approval for analysis of de-identified data was granted by the Institutional Review Board of Boston University and the Human Research Ethics Committee of the University of Witwatersrand.

CHAPTER THREE: RESULTS

In total, 2602 treatment-naïve, non-pregnant children between 3 and 19 years of age initiated a first-line ART regimen between April 2004 and December 2013 (Table 2). Demographic and clinical characteristics were similar across clinics. Patients were predominately female (55.7%) with median age of 10.4 years (interquartile range (IQR): 6.1-14.5), predominately on first-line regimen of stavudine/lamivudine/efavirenz (78.9%) with median time on treatment of 23.4 months (IQR: 12.6-24.0). At ART initiation, patients had a median CD4 count of 317 cells/mm^3 (IQR: 85-417). Over 24 months of follow-up, a total of 132 (5.1%; 95% CI: 4.3-6.0%) children died, 799 (30.7%; 95% CI: 29.0- 32.5%) were either lost to follow-up or died (attrition; 667 children (25.6%; 95% CI 24.0-27.3%) were lost-to-follow-up) and 885 (33.9%; 95% CI: 32.1-35.8%) transferred out, while the remaining 918 (35.3%; 95% CI: 33.5-37.1%) were alive and in care at the end of the first 24-months on ART. When stratified by year, we see an increased average age at ART initiation and proportion of female patients initiating ART, over time. There is a decrease in the median amount of time on ART over time. The proportion of patients with tuberculosis and WHO stage III/IV at ART initiation declined slightly over time, while the average CD4 count increased. The high proportion of death, attrition and transfers remained consistent over the years.

Primary outcomes

All clinics began phasing out stavudine in accordance with national guidelines in 2010 (Figure 1). Tenofovir was introduced after WHO recommended its use in first-line therapy in 2010; by 2013, <10% of HIV-infected children were initiated on stavudine.

While abacavir is included as a first-line NRTI in national guidelines for all patients <14 years of age, no patients between 3 and 14 were initiated on abacavir post-2010 for first-line therapy. Over the period of follow-up there were 398 (15.3%; 95% CI: 14.0-16.7%) single-drug substitutions; 187 (7.2%; 95% CI: 6.2-8.2%) treatment interruptions and 86 (3.3%; 95% CI: 2.7-4.0) switches to second-line therapy (Table 2). All outcomes were calculated individually in this case. Therefore, 25% of the overall 2602 patients experienced a single drug substitution, switch to second-line therapy, or a treatment interruption; 75% of patients did not experience a threat to regimen durability in the first 24 months on treatment.

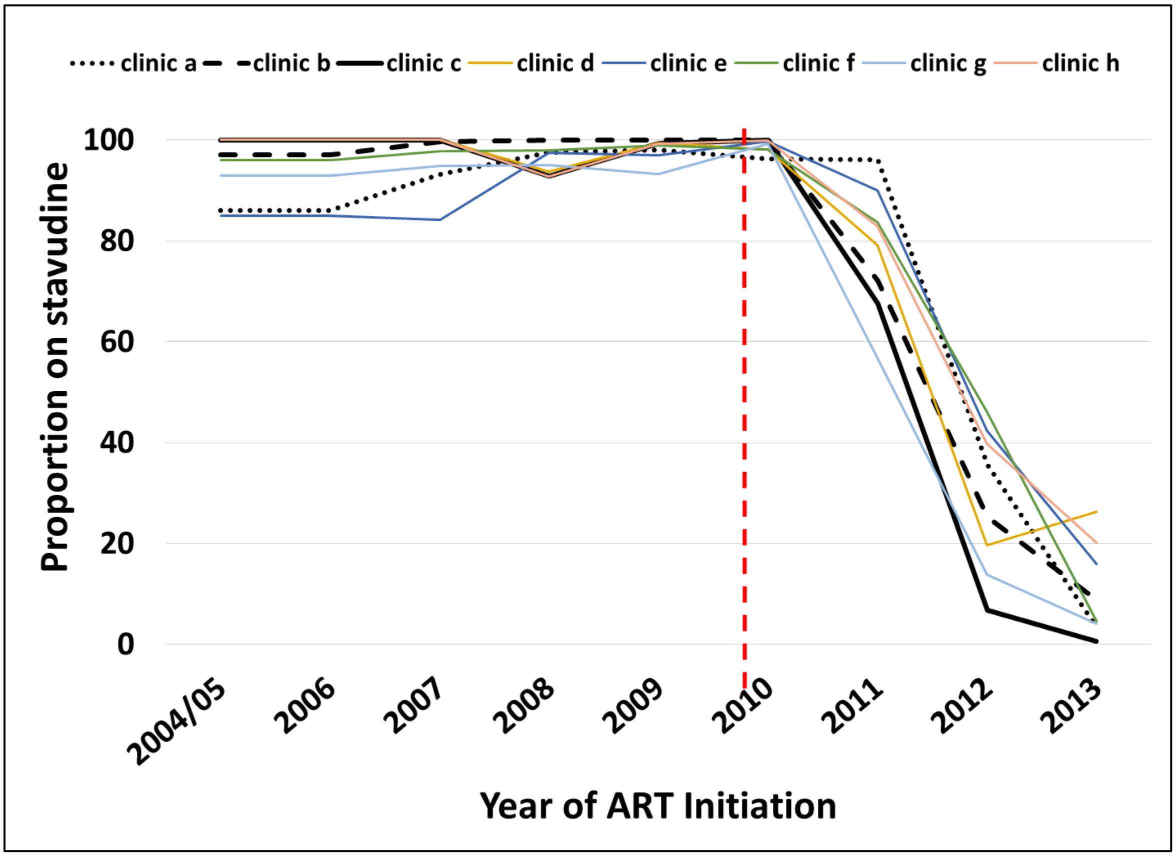
Characteristics		2004/05 (n=238) n (%)	2006 (n=305) n (%)	2007 (n=334) n (%)	2008 (n=509) n (%)	2009 (n=552) n (%)	2010 (n=371) n (%)	2011 (n=139) n (%)	2012 (n=110) n (%)	2013 (n=44) n (%)	Total (n=2602) n (%)
Clinic	Clinic A	35 (14.7	35 (11.5)	44 (13.2)	52 (10.2)	74 (13.4)	26 (7.0)	17 (12.2)	-	-	283 (10.9)
	Clinic B	39 (16.4)	68 (22.3)	71 (21.3)	91 (17.9)	81 (14.7)	62 (16.7)	10 (7.2)	14 (12.7)	4 (9.1)	440 (16.9)
	Clinic C	4 (1.7)	5 (1.6)	12 (3.6)	12 (2.4)	29 (5.3)	14 (3.8)	7 (5.0)	5 (4.6)	2 (4.6)	90 (3.5)
	Clinic D	7 (4.1)	4 (1.3)	15 (4.5)	30 (5.9)	40 (7.3)	43 (11.6)	15 (10.8)	15 (13.6)	4 (9.1)	173 (6.7)
	Clinic E	79 (33.2)	83 (27.2)	69 (20.7)	124 (24.4)	113 (20.5)	61 (16.4)	19 (13.7)	16 (14.6)	6 (13.6)	570 (21.9)
	Clinic F	26 (10.9)	57 (18.7)	91 (27.3)	152 (29.9)	154 (27.9)	107 (28.8)	19 (13.7)	9 (8.2)	6 (13.6)	621 (23.9)
	Clinic G	43 (18.1)	37 (12.1)	19 (5.7)	27 (5.3)	27 (4.9)	31 (8.4)	35 (25.2)	34 (30.9)	13 (29.6)	266 (10.2)
	Clinic H	5 (2.1)	16 (5.3)	13 (3.9)	21 (4.1)	34 (6.2)	27 (7.3)	17 (12.2)	17 (15.5)	9 (20.5)	159 (6.1)
NRTI	zidovudine	22 (9.2)	18 (5.9)	8 (2.4)	8 (1.6)	7 (1.3)	17 (4.6)	7 (5.0)	14 (12.7)	5 (11.4)	106 (4.1)
	tenofovir	-	-	-	-	-	64 (17.3)	99 (71.2)	85 (77.3)	30 (68.2)	278 (10.7)
	stavudine	216 (90.8)	287 (94.1)	326 (97.6)	501 (98.4)	545 (98.7)	290 (78.2)	33 (23.7)	11 (10.0)	9 (20.5)	2218 (85.2)
NNRTI	efavirenz	217 (91.2)	280 (91.8)	308 (92.2)	460 (90.4)	517 (93.7)	330 (89.0)	118 (84.9)	99 (90.0)	39 (88.6)	2368 (91.0)
	nevirapine	21 (8.8)	25 (8.2)	26 (7.8)	49 (9.6)	35 (6.3)	41 (11.1)	21 (15.1)	11 (10.0)	5 (11.4)	234 (9.0)
Age (years)	3-4.9	42 (17.7)	46 (15.1)	67 (17.1)	95 (18.7)	111 (20.1)	49 (13.2)	6 (4.3)	1 (0.9)	2 (4.6)	409 (15.7)
	5-9.9	125 (52.5)	150 (49.2)	140 (41.9)	219 (43.0)	237 (42.9)	137 (36.9)	8 (5.8)	5 (4.6)	2 (4.6)	1023 (39.3)
	10-13.9	38 (16.0)	48 (15.7)	72 (21.6)	104 (20.4)	102 (18.5)	63 (17.0)	24 (17.3)	11 (10.0)	6 (13.6)	468 (18.0)
	14-19.9	33 (13.9)	61 (20.0)	65 (19.5)	91 (17.9)	102 (18.5)	122 (32.9)	101 (72.7)	93 (84.6)	34 (77.3)	702 (27.0)

Characteristics		2004/05 (n=238) n (%)	2006 (n=305) n (%)	2007 (n=334) n (%)	2008 (n=509) n (%)	2009 (n=552) n (%)	2010 (n=371) n (%)	2011 (n=139) n (%)	2012 (n=110) n (%)	2013 (n=44) n (%)	Total (n=2602) n (%)
	median (IQR)	8.9 (5.6-10.7)	9.5 (5.8-11.5)	9.7 (6.0-12.6)	9.4 (5.6-12.1)	9.4 (5.5-12.5)	11.0 (6.6-16.4)	15.6 (13.6-18.9)	16.7 (15.5-19.3)	15.9 (14.3-18.9)	10.4 (6.1-14.5)
Gender	female	126 (52.9)	160 (52.5)	178 (53.3)	287 (56.4)	286 (51.8)	200 (53.9)	99 (71.2)	81 (73.6)	32 (72.7)	1448 (55.7)
	male	112 (47.1)	145 (47.5)	156 (46.7)	222 (43.6)	266 (48.2)	171 (46.1)	40 (28.8)	29 (26.4)	12 (27.3)	1153 (44.3)
CD4 count (cells/mm^3)	0-49	29 (12.2)	53 (17.4)	42 (12.6)	75 (14.7)	74 (13.4)	39 (10.5)	22 (15.8)	15 (13.6)	7 (15.9)	356 (13.7)
	50-99	22 (9.2)	13 (4.3)	33 (9.9)	41 (8.1)	40 (7.3)	35 (9.4)	12 (8.6)	6 (5.5)	2 (4.6)	204 (7.8)
	100-199	36 (15.1)	50 (16.4)	59 (17.7)	98 (19.3)	93 (16.9)	56 (15.1)	27 (19.4)	20 (18.2)	7 (15.9)	446 (17.1)
	200-349	44 (18.5)	40 (13.1)	35 (10.5)	79 (15.5)	81 (14.7)	71 (19.1)	33 (23.7)	31 (28.2)	12 (27.3)	426 (16.4)
	$\geq$350	45 (18.9)	73 (23.9)	90 (27.0)	146 (28.7)	196 (35.5)	112 (30.2)	21 (15.1)	15 (13.6)	10 (22.7)	708 (27.2)
	missing	62 (26.1)	76 (24.9)	75 (22.5)	70 (13.8)	68 (12.3)	58 (15.6)	24 (17.3)	23 (20.9)	6 (13.6)	356 (13.7)
	median (IQR)	275 (96-338)	260 (52-391)	307 (83-418)	365 (79-449)	357.2 (98-517)	297.1 (99-420)	255.6 (64-292)	253 (88-318)	329 (69-387)	317 (85-417)
WHO Stage	I/II	190 (79.8)	253 (83.0)	275 (82.3)	409 (80.4)	420 (76.1)	304 (81.9)	112 (80.6)	97 (88.2)	39 (88.6)	2099 (80.7)
	III/IV	48 (20.2)	52 (17.1)	59 (17.7)	100 (19.7)	132 (23.9)	67 (18.1)	27 (19.4)	13 (11.8)	5 (11.4)	503 (19.3)
Tuberculosis	n (%)	16 (6.7)	19 (6.2)	37 (11.1)	51 (10.0)	75 (14.0)	35 (9.4)	13 (9.4)	8 (7.3)	3 (6.8)	257 (9.9)
Hemoglobin (g/dL)	<10	75 (31.5)	110 (36.1)	109 (32.6)	199 (39.1)	239 (43.3)	162 (43.7)	62 (44.6)	58 (52.7)	26 (59.1)	1040 (40.0)
	$\geq$10	56 (23.5)	53 (17.4)	53 (18.9)	100 (19.7)	123 (22.3)	77 (70.8)	32 (23.0)	27 (24.6)	8 (18.2)	529 (20.3)

Characteristics		2004/05 (n=238) n (%)	2006 (n=305) n (%)	2007 (n=334) n (%)	2008 (n=509) n (%)	2009 (n=552) n (%)	2010 (n=371) n (%)	2011 (n=139) n (%)	2012 (n=110) n (%)	2013 (n=44) n (%)	Total (n=2602) n (%)
	missing	107 (45.0)	142 (46.6)	172 (51.5)	210 (41.3)	190 (34.4)	132 (35.6)	45 (32.4)	25 (22.7)	10 (22.7)	1033 (39.7)
	median (IQR)	10.3 (9.1-11.2)	10.5 (9.6-11.7)	10.6 (9.5-11.9)	11.6 (9.6-11.6)	10.6 (9.6-11.5)	10.6 (9.6-11.8)	10.9 (9.0-12.4)	11.2 (9.6-12.8)	11.1 (10.1-13.0)	10.8 (9.5-11.7)
Body Mass Index (kg/m^2)	median (IQR)	11.8 (8.2-15.0)	14.2 (10.3-16.9)	13.3 (9.5-16.3)	14.0 (11.5-16.8)	14.7 (11.5-16.8)	15.4 (12.2-17.2)	19.9 (15.8-21.1)	21.3 (17.7-23.5)	20.2 (16.2-22.7)	15.0 (11.0-17.6)
Time on ART (months)	median (IQR)	24.0 (22.5-24.0)	24.0 (16.9-24.0)	24.0 (17.4-24.0)	23.6 (14.7-24.0)	21.4 (11.3-24.0)	20.2 (8.7-24.0)	20.2 (7.3-24.0)	13.6 (7.0-24.0)	16.2 (6.8-24.0)	23.4 (12.6-24.0)
Vital status over 24-months of follow-up											
Alive	n (%)	85 (35.7)	104 (34.1)	116 (34.7)	173 (34.0)	185 (33.5)	136 (36.7)	48 (34.5)	47 (42.7)	24 (54.6)	918 (35.3)
Death	n (%)	15 (6.3)	17 (6.6)	20 (6.0)	28 (5.5)	26 (4.7)	16 (4.3)	3 (2.2)	5 (4.6)	2 (4.6)	132 (5.1)
Loss to follow-up	n (%)	71 (29.8)	75 (24.6)	80 (24.0)	108 (21.2)	146 (26.5)	97 (26.2)	47 (33.8)	31 (28.2)	12 (27.3)	667 (25.6)
Transfers	n (%)	63 (26.5)	105 (34.4)	117 (35.0)	197 (38.7)	195 (35.3)	122 (32.9)	41 (29.5)	27 (24.6)	6 (13.6)	873 (33.6)
Primary outcome over 24-months of follow-up											
Single-drug substitution	n (%)	3 (1.3)	22 (7.2)	39 (11.7)	81 (15.9)	125 (22.6)	95 (25.6)	17 (12.2)	10 (9.1)	6 (13.6)	398 (15.3)
Treatment interruption	n (%)	15 (6.3)	19 (6.2)	14 (4.2)	47 (9.2)	44 (8.0)	30 (8.1)	10 (7.2)	5 (4.6)	3 (6.8)	187 (7.2)
Second-line Switch	n (%)	11 (4.6)	11 (3.6)	10 (3.0)	15 (3.0)	16 (2.9)	13 (3.5)	6 (4.3)	1 (0.9)	3 (6.8)	86 (3.3)

Table 2. Clinical and demographic characteristics at ART initiation and outcomes at 24-months of follow-up stratified by year initiated onto treatment at eight RTC Clinics, Johannesburg, South Africa (n=2602)

Figure 1. Trends in the use of stavudine in first-line ART for HIV-infected patients <20 years of age at initiation in South Africa



Single-drug substitution

Overall, the frequency of single-drug substitutions over 24 months on ART started to increase for the cohort of patients that started treatment in 2009, peaked in 2011 at 25%, and then declined to 10% in 2013 (Figure 2). When stratifying outcomes by age and year of treatment initiation, decreases in single-drug substitutions in patients <14 years of age begins two years after the 2010 change in the national guidelines (Figure 4a). Of note, while abacavir is included as a first-line NRTI in national guidelines for all patients <14 years of age, no patients between the ages of 3 and 14 were *initiated* on abacavir post-2010 for first-line therapy. All clinics followed national guidelines regarding antiretrovirals eligible for substitution in the NRTI drug class (stavudine, didanosine or zidovudine). These included tenofovir, stavudine, zidovudine or abacavir, depending on the NRTI included in the first-line regimen, with the occasional use of didanosine as an alternative (Figure 3). Of the 398 single-drug substitutions, abacavir was frequently used for stavudine substitution (14.3%; 95% CI: 12.9-15.8%), while tenofovir was the choice for zidovudine substitution (10.4%; 95% CI: 5.6-17.3%). Patients on tenofovir were predominately switched to zidovudine (4.3%; 95% CI: 2.4-7.2%). Models show that patients initiated on stavudine or zidovudine had a 4- and 5-fold, respectively, increase in the hazards of single-drug substitutions over the period of follow-up compared to tenofovir (Table 3). Consistent with known toxicity patterns, single-drug substitutions occurred earlier for patients on tenofovir (median 5.4 months after start of treatment IQR: 3.0-17.1), while substitutions of patients on zidovudine occurred at a median of 18.0 months (IQR: 7.1-21.7) and those on stavudine occurred at a median 20.2 months (IQR: 15.9-22.5) after start of treatment. When stratified by age, median time on ART prior to single-drug substitution is comparable for all age groups.

Figure 2. Trends in single-drug substitution, treatment interruption and second-line switching over 24-months on ART stratified by year of ART initiation HIV-infected patients <20 years of age in South Africa

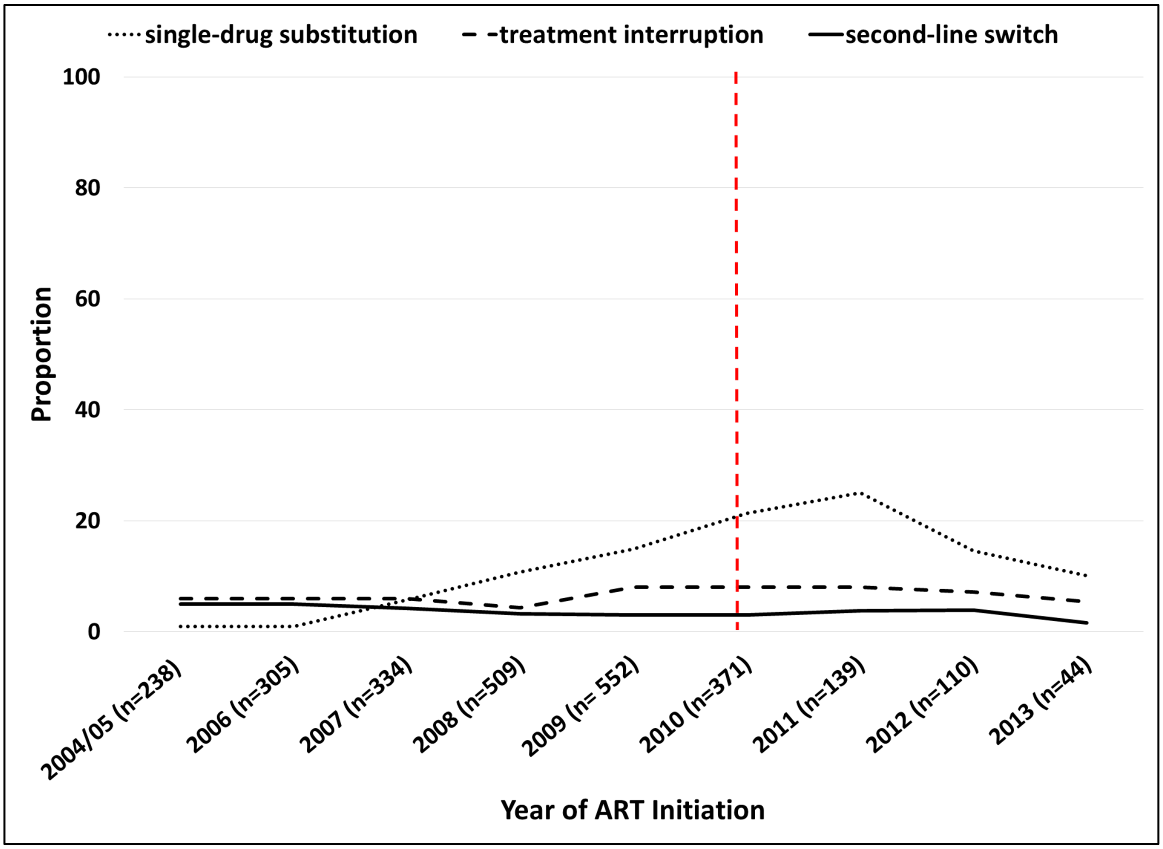
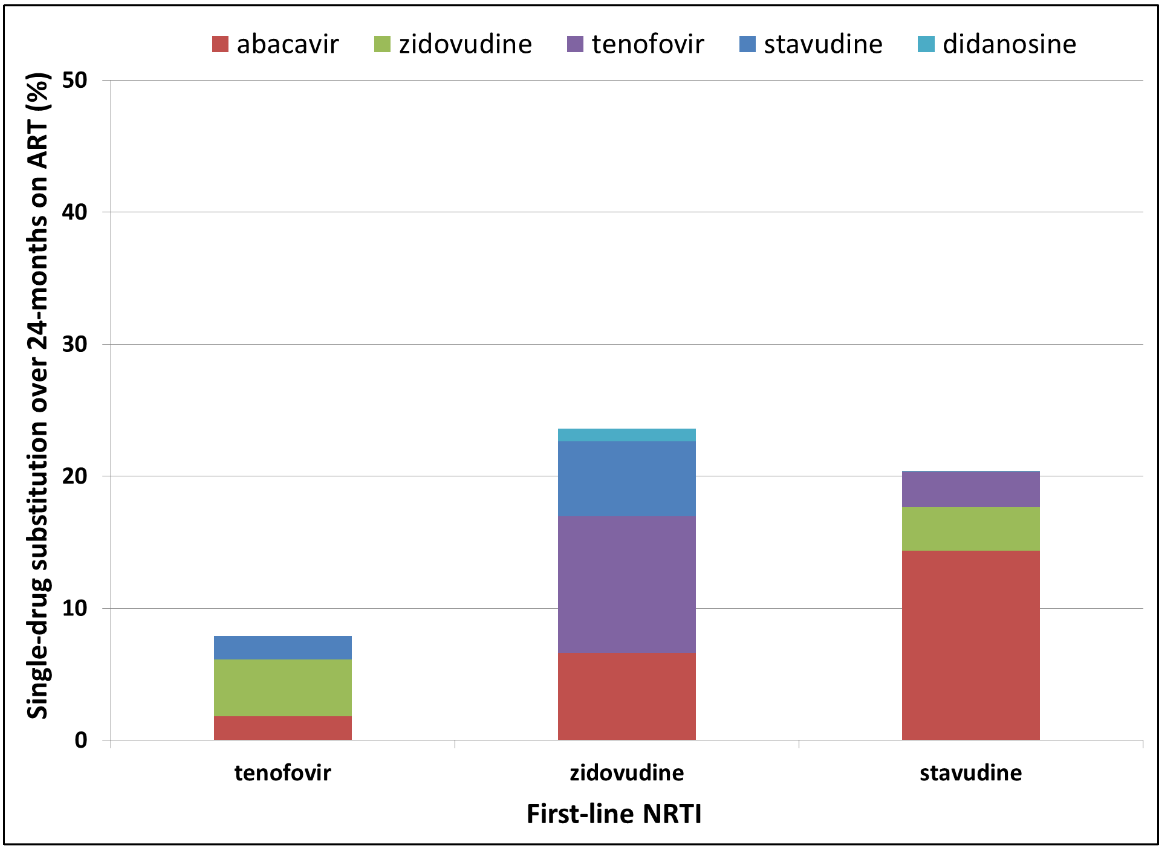


Figure 3. Proportion of patients with an NRTI single-drug substitution and the substituting NRTI in the first 24-months on treatment stratified by initial NRTI in first-line ART in HIV-infected children and adolescents in South Africa (N=398)



Treatment interruption

Treatment interruption over 24 months on ART peaked at 8% in 2009 and declined to 5% in 2013. Duration of treatment interruption was comparable between patients on tenofovir (4.1 months; IQR: 1.1-7.7) and zidovudine (4.9 months; IQR: 2.4-8.5), while patients on stavudine had a shorter median time of interruption (3.0 months; IQR: 1.0-8.4). When stratified by age, median time on ART prior to treatment interruption is comparable for the younger age groups at around 23 months (IQR: 12.6-24.0), while patients >14 had a shorter duration on ART prior to interruption (16.6 months; IQR: 9.6-23.9). Median time on ART prior to treatment interruption was comparable between tenofovir (4.1 months; 95% CI: 1.1-7.7) and zidovudine (4.9 months; IQR: 2.4-8.5), while patients on stavudine had a shorter duration (3.0 months; IQR: 1.0-8.4). Regression results showed patients initiated on stavudine had a 130% increase in the hazards of treatment interruption when compared to those on tenofovir, while those on zidovudine had a 60% decrease.

Second-line switch

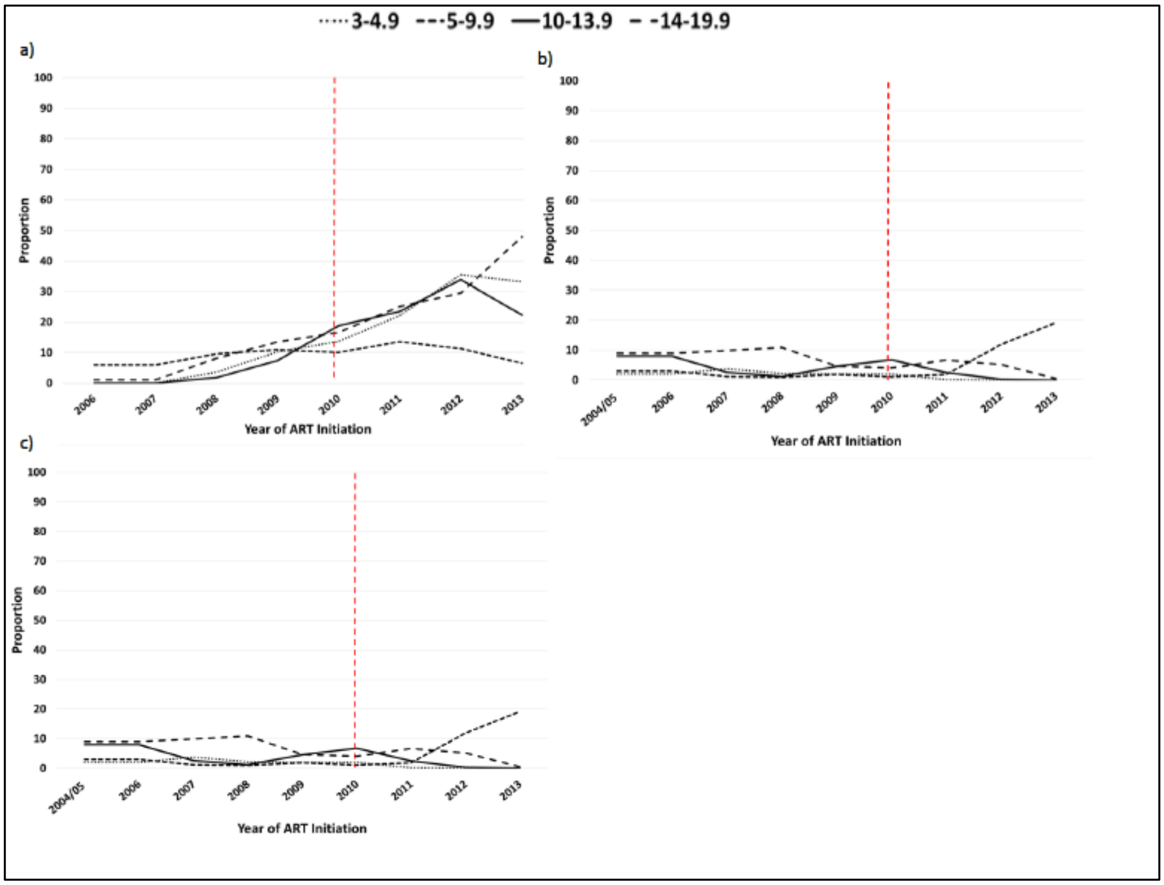
Second-line switches remained consistent at 3.3% (95% CI: 2.7-4.0%) over 24 months on ART over time. Time from ART initiation to second-line switch was comparable between all three NRTIs (tenofovir, stavudine, zidovudine) (20.5 months; IQR: 15.9-22.2). When stratified by age, there is comparable median time on ART prior to second-line switching in patients <14 years of age (21.0 months; IQR: 15.9-22.7), while patients ≥14 years old had a median of 18.5 months (IQR: 15.9-21.3). The majority

(62.8%; 95% CI: 52.2-72.5%) of patients experiencing a second-line switch initiated a second-line regimen comprised of zidovudine/lamivudine/lopinavir+ritonavir. Patients that were on stavudine or zidovudine compared to tenofovir had a 1.5 to 2-fold increase in the hazards of switching to second-line ART over the time period.

Hazard Ratios

Our results also suggest that children 14 to 20 years of age have an increased hazard of all three primary outcomes compared to patients 5 to 9.9 years of age (single-drug substitution – HR 1.6; 95%CI: 0.9-2.8; treatment interruption – HR 2.3; 95%CI: 1.4-3.8; and second-line switch – HR 3.7; 95%CI:1.2-11.2) (Figure 4, Table 3). Since we believed changes in the trends of substitutions, treatment interruptions, and second-line switching for sex and age (<10 vs. ≥10 years) could vary by NRTI used in first-line ART, we calculated the risk due to interdependence(R(I)). We showed a positive interdependence for gender and stavudine use in first-line ART for all three primary outcomes (single-drug substitution: 6.4%; treatment interruption: 10% and second-line switches: 5.6%). Therefore, 6.4% of single-drug substitutions in female patients on stavudine is related to the dual action of female gender and stavudine. The risk of single-drug substitution in doubly exposed patients (females exposed to stavudine) was 13.2% vs. the risk of 6.7%% in the doubly unexposed (males unexposed to stavudine). The risk of treatment interruption in the doubly exposed was 9.3% vs. the risk of -0.7% in the doubly unexposed, while the risk of second-line switching in the doubly exposed was 0.3% vs. the risk of -5.3% in the doubly unexposed. We did not see any signs of interaction when assessing the biological relationships between age and use of stavudine using the R(I).

Figure 4. Trends in single-drug substitution (a), treatment interruption (b) and second-line switching (c) over 24-months on ART stratified by year and age at ART initiation in HIV-infected patients <20 years of age in South Africa



	Single-drug substitution		Treatment interruption		Second-line switch	
Variable	**Events (%)**	**Adjusted HR* (95% CI)**	**Events (%)**	**Adjusted HR* (95% CI)**	**Events (%)**	**Adjusted HR* (95% CI)**
NRTI						
tenofovir	8 (2.9)	Reference	18 (6.5)	Reference	13 (4.7)	Reference
zidovudine	15 (14.2)	5.3 (1.6-17.3)	4 (3.8)	0.4 (0.1-1.3)	5 (4.7)	2.0 (0.3-11.5)
stavudine	375 (16.9)	4.2 (1.6-11.0)	165 (7.4)	2.3 (1.1-4.7)	68 (3.1)	1.4 (0.5-4.4)
Age (years)						
3-4.9	68 (16.6)	1.0 (0.7-1.7)	26 (6.4)	1.1 (0.6-2.2)	8 (2.0)	1.2 (0.3-3.8)
5-9.9	180 (17.6)	Reference	62 (6.1)	Reference	19 (1.9)	Reference
10-13.9	82 (17.5)	1.5 (1.0-2.3)	29 (6.2)	0.8 (0.4-1.5)	19 (4.1)	2.0 (0.8-5.0)
14-19.9	68 (9.7)	1.4 (0.8-2.4)	70 (10.0)	2.0 (1.1-3.7)	40 (5.7)	3.3 (1.1-10.0)
Sex						
Male	177 (15.4)	Reference	86 (7.5)	Reference	33 (2.9)	Reference
Female	221 (15.3)	1.1 (0.8-1.4)	101 (7.0)	1.0 (0.6-1.4)	53 (3.7)	1.2 (0.6-2.3)
CD4 count (cells/mm^3)						
$\geq$350	53 (14.9)	Reference	25 (7.0)	Reference	20 (2.8)	Reference
200-349	62 (13.7)	1.1 (0.7-1.7)	20 (9.8)	1.2 (0.7-2.3)	9 (2.1)	0.9 (0.3-2.5)
100-199	56 (12.6)	0.8 (0.5-1.3)	42 (9.4)	1.3 (0.7-2.4)	14 (3.1)	1.1 (0.4-3.0)
50-99	28 (14.6)	0.9 (0.5-1.6)	31 (7.3)	1.4 (0.7-2.8)	9 (4.4)	0.9 (0.3-3.1)
0-49	53 (21.2)	0.9 (0.5-1.4)	43 (6.1)	1.2 (0.6-2.3)	18 (5.1)	1.6 (0.6-4.3)

*The model is clustered by site and adjusted for non-nucleoside reverse transcriptase inhibitor, body mass index, hemoglobin and World Health Organization stage.

Table 3. Model adjusted for predictors of single-drug substitution, treatment interruption and second-line switch for children and adolescents in the first 24-months on ART in Johannesburg, South Africa (n=2602)

CHAPTER FOUR: DISCUSSION

Published reports on treatment outcomes in pediatric patients with HIV are limited. This analysis provides data regarding first-line regimen durability of children initiated on ART in South Africa during ART programmatic changes to include both tenofovir and abacavir as NRTIs in first-line pediatric regimens. These data show there is overall compliance to the post-2010 guidelines, with a majority of children initiated on an appropriate ART regimen according to age, though no children <14 were initiated on an abacavir-containing regimen as first-line therapy. The single-drug substitution peak seen roughly 2 years post-2010 is likely a result of clinicians switching treatment-experienced pediatric patients from stavudine to either abacavir or tenofovir, as age-appropriate. That the peak of these guideline-congruent single-drug substitutions in patients younger <14 years of age begins two years after the national guidelines changes (Figure 4a) may be due to clinics prioritizing tenofovir in first-line regimens for adults before focusing on tenofovir for children.

The decline in both single-drug substitutions and treatment interruptions after 2010 may be a result of fewer side-effects and toxicities in those children initiated on tenofovir as per 2010 guidelines, but this does not fully account for the decrease in treatment interruptions seen since 2006 (pre-dating the guideline change). The proportion of switches to second-line regimens has not changed over time. While it is reassuring that with increased use of abacavir (in this population, after a single-drug substitution) and tenofovir, there has not been an increase in switches to second-line therapy, switches to second-line have not decreased. The introduction of first-line regimens including abacavir or tenofovir with a better tolerated side-effect profile, and therefore potentially increased adherence, might be expected to be associated with *decreased* switches to second-line. Given that adherence challenges in pediatric populations are multifactorial and due at least in part to family structure and caregiver ability and knowledge, improved side effect profiles are only one component of adherence to ART for children. However, it is important to note that overall in this cohort, regardless of initiating NRTI, 75% of patients did not experience either a single drug substitution, treatment interruption, or switch to second-line therapy.

This is the first study in pediatric patients to examine single-drug substitutions, treatment interruptions, and switches to second-line therapy, though previous adult studies reported increased hazards of single-drug substitutions when comparing stavudine to tenofovir (9-15). We similarly found increased hazards of single-drug substitution when comparing both stavudine and zidovudine to tenofovir, adjusting for choice of NNRTI, BMI, WHO clinical staging and hemoglobin at time of initiation. Stavudine was also associated with increased hazards for treatment interruption compared to tenofovir. The oldest pediatric patients had increased hazards of all outcomes (though single-drug substitution was not significant), and female patients had a trend toward increased hazards for all outcomes. This is consistent with previous research in adults, which demonstrated increase risk of single drug substitution for females and higher risk of toxicity/side effects for women on stavudine (13,14,15,16,22,23). Differences in risk of toxicity between genders, and therefore increased risk of single drug substitution, may be related to better adherence in women than men (24, 25). There is a paucity of literature on adherence patterns in adolescents, with most studies dependent on self-reported ART adherence in adolescent populations (26, 27, 28), and therefore it is difficult to fully explain why female adolescent patients in this study had increased risk compared to male adolescents. The unique developmental changes in adolescence characterized by increased-risk taking behavior and decreased impulse control (29), at a time when adolescent patients may still need adherence support from family/caregivers, can adversely impact adolescent ART adherence. There is no available data on differences in adherence for male and female adolescents.

There are several limitations to this analysis. Reasons for single-drug substitutions, switches to second-line, and treatment interruptions are unknown in this dataset, and limit inferences regarding associations. Treatment interruptions for this analysis were defined using prescription data for all patients. If the time between stopping an ART regimen and resuming an ART regimen was >1 week, then the patient was defined as having a treatment interruption event. As the prescription data is hand-entered by a clinician or data entry clerk, it is possible that human error results in incorrect regimen dates. However, we don’t anticipate the rate of this outcome misclassification to be differential by initiating NRTI, and therefore, any bias in our estimates of risk of treatment interruption would be towards the null. Another limitation is lack of knowledge of children’s exposure to PMTCT, and the degree to which different PMTCT regimens may have influenced regimen durability, particularly for younger children. Importantly, the overall numbers of children under 3 years old in this cohort were limited (data not shown) and were excluded given the complexity of first-line therapy regimens for very young children recently exposed to PMTCT regimens. Additionally, there was a high rate of loss to follow-up and attrition in this cohort, similar to other pediatric studies.

Though there are significant limitations, a clear strength is the large numbers of HIV-infected children included in the analysis, and the fact that these children received care at large ART clinics without specialist pediatric care. This increases the generalizability of these results, as this represents “real world” conditions for many HIV-infected children in resource-limited settings. In this population of children receiving care in public clinics, over time, the median age of patients initiating ART increased, from 8.9 years old in 2004 to 15.9 years old in 2011. It is unknown if HIV diagnosis in these children was delayed from presumed perinatal transmission, or alternatively in older adolescents, represents infection post-natally. We are limited by the lack of knowledge regarding mode of transmission for all children included in this study. It does seem likely that older ages at initiation may be secondary to problems with linkages to care and ART initiation. In addition to older ages at time of ART initiation, we demonstrated that median time on ART decreased over time. Given that the proportion of death, attrition and transfers remained consistent over the years, it is unclear why this trend was noted over time.

Overall, this study shows that regimen durability in the first two years after ART initiation appears to have improved after introduction of tenofovir, with decline of both single-drug substitution and treatment interruptions, though no changes in switches to second-line therapy. The decrease in single-drug substitution was delayed in younger patients compared to older adolescents, and is hypothesized to reflect a delay in initiation of tenofovir for younger patients with prioritization of tenofovir for adult (and older adolescent) patients. Stavudine and zidovudine, when compared to tenofovir, were associated with increased hazards of all outcomes. While better side-effect profiles with tenofovir-containing regiments for pediatric patients might be assumed to result in increased adherence and therefore less need for switch to second-line, it is well-known that adherence for children and adolescents is multifactorial and dependent largely on caregivers' participation, which may be one factor for the overall decreased median time on ART over time in this cohort. Therefore, while the use of appropriate and efficacious first-line ART since 2010 has been demonstrated to have good uptake in South Africa for pediatric patients with decreasing trends of threats to regimen durability, further work on improving the adherence of all pediatric patients, especially adolescent patients, is crucial.

APPENDIX

Variable	Single-drug substitution		Treatment interruption		Second-line switch	
	Crude HR (95% CI)	**Adjusted HR* (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
Age						
3-4.9|stavudine	1.6 (0.6-4.4)	1.5 (0.4-4.9)	2.5 (0.3-18.3)	2.6 (0.4-19.2)	0.6 (0.1-4.7)	0.4 (0.1-4.9)
5-9.9|stavudine	Reference	Reference	Reference	Reference	Reference	Reference
10-13.9|stavudine	1.8 (0.7-4.9)	2.1 (0.6-6.7)	2.5 (0.3-18.5)	2.4 (0.3-17.5)	1.6 (0.2-11.9)	1.0 (0.1-7.7)
14-19.9|stavudine	1.6 (0.6-4.4)	1.7 (0.5-5.9)	5.6 (0.8-40.6)*	5.1 (0.7-37.1)*	2.9 (0.4-21.6)	1.7 (0.2-14.5)
Gender						
male|stavudine	Reference	Reference	Reference	Reference	Reference	Reference
female|stavudine	1.9 (1.0-3.4)	1.8 (0.9-3.8)*	1.0 (0.5-1.9)	2.0 (0.8-5.1)*	0.4 (0.2-0.9)*	0.9 (0.3-2.2)

*Interaction was assessed at $p<0.20$

[€]The model is clustered by site and adjusted for CD4 count, age, non-nucleoside reverse transcriptase inhibitor, body mass index, hemoglobin and World Health Organization stage at ART initiation.

Table 4. Adjusted models assessing the interaction between age at ART initiation and use of stavudine in first-line ART for children and adolescents in the first 24-months on ART in Johannesburg, South Africa (n=2602)

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