Single drug substitution from stavudine to abacavir or tenofovir for HIV-infected children and adolescents on combination ART: describing the impact on virological outcomes

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Abstract:

Background: In an era geared towards HIV treatment optimization, data regarding the impact of single drug substitutions on viral suppression in routine care settings is critical. This study compares viral suppression in children and adolescents who switched from stavudine to either abacavir or tenofovir, to those who remained on stavudine.

Methods: This retrospective cohort study examined routine clinical information from children and adolescents <19 years initiated on stavudine-containing ART prior to 2010, at a large public sector paediatric ART clinic in South Africa. In children who switched, observation time (T_0) was set at the time of switching from stavudine to either abacavir or tenofovir. In those who did not switch, T_0 was set at the first visit after 1 April 2010. Incidence of viral rebound (>400 copies/ml) and virological failure (VF, two consecutive VL>1000 copies/ml) were calculated, and Kaplan-Meier survival curves for first viral rebound as well as VF were plotted. Cox proportional hazard models were used to estimate the association between viral rebound and switching.

Results: The 723 children in the cohort contributed 14882.7 person-years (pys) of follow-up time. The median age at cohort entry was 9.3 years and 47.4% were male. Of these, 566(78%) had a switch from stavudine and 157(22%) did not. At 6 months, the incidence of viral rebound in children who switched was 6.2/100pys (95%CI: 3.7-10.6), compared to 14.4/100pys (95%CI: 8.1-26.8) in the non-switch group (*P* value =0.02). Those who switched were significantly less likely to experience rebound (adjusted hazards ratio: 0.39, 95%CI: 0.17-0.91) at 6 months after T_0 but this was not sustained at 12 months (adjusted hazards ratio: 0.89, 95%CI: 0.49-1.60). Although more children had VF in the switch group by database closure (OR 1.88, 95%CI: 1.02-3.48), there was no significant difference in incidence of virological failure (switch group: 0.61 (0.49-0.78); non-switch group: 0.42 (0.25-0.73); p-value=0.40). Similarly, no significant difference in incidence of VF was seen on survival analysis.

Conclusion: There was no significant difference in viral rebound or virological failure between groups. Switches to more palatable drugs with fewer side effects may improve adherence and viral suppression in the short term.

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Main text

Introduction

Despite substantial public health successes in prevention of mother-to-child transmission of HIV an estimated 320 000 children [260 000 - 400 000] are living with HIV in South Africa, the country with the largest HIV epidemic in the world [1, 2]. The UNAIDS 90-90-90 strategy is focussed on identification, initiation of antiretroviral therapy (ART) and retention of HIV-positive children and adolescents in care, with viral suppression [3]. Logically, durable viral suppression for children and adolescents must be treated as a priority in all HIV programmes, particularly in high burden settings such as South Africa. In an era with a growing focus on treatment optimization across all age groups, the potential virological effects of large scale drug substitutions as new, more effective drugs become available warrants consideration. Programmatically, such practices have been implemented without vigorous surveillance. A key example is the single substitution of stavudine to either tenofovir or abacavir in South Africa, implemented when stavudine was phased out globally [4, 5].

A number of clinical trials, many in adult patients, report no significant difference in sustained virological suppression when one single nucleoside reverse transcriptase inhibitor (NRTI) is substituted with another NRTI [6, 7]. There is, however, little data on the impact of large scale treatment switches on virological control within the routine clinical care context, particularly in children or adolescents. Data presented from a large non-trial adult Canadian cohort in 2014 suggests that drug switches in virally suppressed patients is associated with virological failure [8]. In children and adolescents, adherence in paediatric populations is often more challenging than in adults [9, 10] and changes to formulations, dosing, and changes in daily routine activities may have a greater impact on adherence and virological control [11, 12]. The virological efficacy of a newly substituted agent is also an important consideration. Reports of possible reduced viral efficacy when comparing stavudine to tenofovir in clinical trial settings [13] and to abacavir in large routine care programmes [14, 15] have raised concerns about the use of these agents in children.

While stavudine is no longer used routinely, data related to outcomes with a single substitution when it was phased out could contribute to an approach to large scale single drug switches.. Key

questions on how stable, virally suppressed children and adolescents weather adjustments to their regimens may be answered by studying this early treatment optimization intervention. These data will be relevant to clinical practice and ART programmes as novel treatment agents and formulations become available for children and adolescents. Our study investigated the effect of single NRTI substitutions on the incidence of viral rebound in children and adolescents attending a large paediatric public HIV clinic in Soweto, South Africa.

Methods

Study design and setting

We conducted a retrospective cohort study using routinely collected data at the Harriet Shezi Children's Clinic (HSCC), Chris Hani Baragwanath Academic Hospital in Soweto, South Africa. This is a large public ART clinic, which provides services to children and adolescents in the mostly-urban surrounding population.

Subjects

Children and adolescents <19 years who initiated ART at HSCC from 2004-2010 were included in the cohort if: they had initiated on a standard stavudine-containing ART regimen; they had at least two consecutive viral load measurements of <400copies/ml within the 12 months preceding study entry; and they had not undergone any regimen changes (other than a single NRTI substitution) before 1 April 2010. The cut-off of <400 copies/ml was used as this was previously the lowest limit of detection of available viral load assays, which later changed over time. Children were excluded if there was documented participation in clinical trials or documented HIV drug resistance prior to study entry. The selection process is represented in Figure 1.

Standard of care

As per country guidelines, anthropometry and clinical examination are done at every clinical visit and monitoring bloods are done at regular intervals: CD4 and viral load monitoring were done 6 monthly in virally suppressed patients from 2004-2010, and annually thereafter [4, 5, 16, 17].

Stavudine, an NRTI, was used in first line regimens in South Africa from 2004. Children on ART with stavudine-related side effects were switched to either abacavir or tenofovir (depending on age and clinical criteria) from 2008 when these agents first became available in the country – this clinical strategy was included for broad application across the ART programme in the 2010 South African national guidelines [17]. In 2013 the South African guidelines officially recommended that stavudine be replaced by abacavir for those <15 years and tenofovir for those ≥15years for all patients who were stable and virally suppressed on their ART regimen [4]. Large scale NRTI switches were subsequently implemented.

Measurements

Retrospective, de-identified, demographic and clinical patient data were extracted from the HSCC electronic patient management database up to end of December 2015, to ensure data on virological outcomes and drug resistance testing could be analysed. A file review was also conducted to collect missing data, where possible. Data were imported into STATA 13.1 (StataCorp, College Station, TX) for management and statistical analysis.

The primary exposure was a single NRTI substitution from stavudine to either abacavir or tenofovir. Children who underwent a single NRTI substitution from 1 January 2008 to 31 March 2010 were designated to the "switch group". This time period was selected because it represents a period in which single NRTI substitutions were implemented for many (but not all) children and stavudine was still widely used, as per ART guidelines at the time [17]. Children who had not undergone a single drug substitution by 1 April 2011 were designated to the "non-switch group." Observation start (T_0), was set at the date of switch for children in the switch group and the first visit after 1 April 2010 for children in the non-switch group.

The primary outcome measure was the incidence of first viral rebound, defined as an increase in VL to 400 copies/ml at 6 and 12 months after T_0. Among patients experiencing viral rebound, we also assessed the proportion with virological failure (two successive VL measurements >1000 copies/ml at least three months apart), viral re-suppression (return of the subsequent VL measurement to <00 copies/ml) and persistent viraemia (sustained VL >400 copies/ml on the subsequent measurement, not meeting criteria for virological failure). Additionally, among children who had antiretroviral drug resistance testing, we describe the frequency of HIV drug resistance mutations and associated phenotypic drug resistance, based on the Stanford University HIV drug resistance database (HIVdb version 8.4) [18, 19].

Anthropometry measures included height-for-age z-scores (HAZ), weight-for-age z-scores (WAZ), and BMI-for-age z-scores (BMIZ): WAZ was used for children <5 years, and BMI-for-age z-scores used for children≥5 years, calculated as per the World Health Organization's child growth standards (<5 years) and growth references for school-going children (5-19 years) [20, 21]. These measures were chosen to align with commonly used measures in the ART programme. Normal WAZ, BMIZ and HAZ was classified between +2standard deviations (SD) to -2SD; underweight or stunted from -2SD to -3SD and severely underweight or severe stunting

<-3SD. Overweight children were classified with WAZ or BMIZ >+2SD. Immunosuppression categories were based on CD4 counts for children ≥5 years and CD4 percentages for children <5 years as follows: severe for CD4<15% or <200cells/mm^3; moderate for CD4 15-25% or 200-500cells/mm^3 and normal as CD4>25% of >500cells/mm^3.

Analysis

Patient characteristics at ART initiation and at T_0 were compared using descriptive statistics. The chi-squared test was used to compare categorical data and the Kruskall-Wallis test for continuous data. Outcomes after viral rebound (re-suppression, failure and persistent viraemia) were assigned at the subsequent viral load after rebound. Odds ratios were calculated to assess the direction of significant associations. Observation time (T_0) started on the date of switch for the switch group and from the first visit after 1 April 2010 for the non-switch group. Person-time at risk was calculated from T_0 to first viral rebound, last follow-up visit, death, transfer out, or database closure, whichever came first. The incidence of viral rebound was calculated using the number of children who experienced viral rebound divided by the person-years (pys) at risk. Kaplan-Meier survival curves with first viral rebound set as failure, comparing the switch and non-switch groups, were plotted up to 12 months after T_0. Additionally survival analysis and incidence of virological failure were performed, through to the time of database closure.

Crude and adjusted Cox proportional hazards models were used to assess associations with viral rebound at 6 and 12 months after T_0. Due to the complex co-factors which may contribute to viral rebound in the setting of drug switches in children, a causal diagram was created using a directed acyclic graph (DAG), based on literature review and expert opinion, to determine the set of covariates necessary to control for confounding [22]. DAGitty, a causal diagram graphical tool, was used to create the DAG and determine the minimal sufficient set of variables required for adjustment in the multivariate model (Figure 2) [23]. Adjusted Cox Proportional Hazards models included the primary exposure and the minimal sufficient set of confounders. Proportional hazard assumptions were checked by including time varying covariates in the models using interaction with log (time) and by using tests and graphs based on the Schoenfeld residuals.

Ethical considerations

Approval to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee as well as hospital management structures.

Results

Of the 3784 children who initiated a first line stavudine-containing regimen, 723 children met inclusion criteria for this study. Ineligible children were excluded on the basis of elevated viral loads, multiple drug switches prior to T_0 or inadequate follow-up time before T_0, as summarised in Figure 1. The median age at cohort entry was 9.3 years and 47.4% were male. Of those included, 566 (78.1%) had a single NRTI substitution (switch group): 540 (95.4%) were switched to abacavir and 26 (4.6%) were switched to tenofovir. The rest (157/723, 21.9%) did not have an NRTI substitution during the defined time period (non-switch group).

Children in the switch group were similar in age, sex, degree of immunosuppression, anthropometry and viral load at ART initiation compared to those in the non-switch group (Table 1). Proportionally more children initiated an NNRTI-based regimen in the switch group (76.6%) compared to the non-switch group (62.3%) (P<0.01). Children in the switch group were significantly more likely to be stunted (OR 1.53, 95%CI: 1.41-1.65) or severely stunted (OR 1.76, 95%CI: 1.61-1.92) at ART initiation. At T_0, older children (≥5years of age) were more likely to be switched from stavudine, with most in the 5-9 year age group (OR: 3.21, 95%CI: 2.93-3.51) at the time of switching. There were no significant differences between the two groups in anthropometry or degree of immunosuppression. By T_0, children in the switch group had a significantly longer median duration on ART (39.3 months, IQR: 29.0-50.6) than children in the non-switch group (31.3 months, IQR: 23.1-46.4) (P<0.01). Although there was a statistically significant difference in median log VL at T_0 between the switch group (1.4 log, IQR: 1.40-1.69) and the non-switch group (1.69 log, IQR: 1.40-1.69), both medians reflect a viral load <400copies/ml, the selected cut-off for VL suppression, with an overlapping IQR.

Viral rebound at 6 and 12 months

A total of 562.3 person-years (pys) were observed by 12 months after T_0, with a median of 4 (IQR: 4-5) clinical visits in the non-switch group and 5 (IQR: 4-5) clinical visits in the switch group within 12 months (P=0.03). In the first six months after T_0, the incidence of viral rebound was 8.0 (95%CI: 5.4-11.8) overall, with an incidence of 6.2 /100pys (95%CI: 3.7-10.6) in the switch group and 14.4 /100pys (95%CI: 8.1-26.8) in the non-switch group (P=0.02). The probability of viral rebound was significantly greater (log rank=0.01) at six months after T_0 for the non-switch group 0.06 (95%CI: 0.04-0.12) than for the switch group 0.02 (95%CI: 0.01-

0.04). By 12 months risks of rebound were similar at 9.8/100pys (95%CI: 7.2-13.2) in the switch group and 12.1/100pys (95%CI: 7.4-19.7) in the non-switch group (*P*=0.52). The Kaplan-Meier estimates at 6 and 12 months (Figure 3) indicate a reduction in the difference in probability of rebound between the two groups over time.

Cox proportional unadjusted hazards confirmed that children in the switch group were significantly less likely to experience viral rebound within the first six months after switch (HR: 0.40, 95%CI: 0.18-0.89). By 12 months this effect persisted but was not statistically significant (HR: 0.83, 95%CI: 0.47-1.47). No other risk factors (prior elevated VL, age, sex, anthropometry, immunosuppression, regimen, ART start year or time on ART) were significantly associated with rebound in univariate analyses at 6 or at 12 months (Table 2 and Table 3).

The minimal sufficient set for inclusion in the multivariate model, based on the DAG, included time on ART and year of ART start (Figure 2). After adjusting for confounders, the difference remained significant at 6 months (aHR: 0.39, 95%CI: 0.17-0.91), but not at 12 months (aHR: 0.89, 95%CI: 0.49-1.60).

Virological failure and resistance accumulation

Virological outcomes were available for 614/723 (84.9%) of children at database closure. Those without reported outcomes were either transferred out or lost to follow up without 2 VL results recorded in the database. By database closure, 131 children experienced viral rebound, as detailed in Table 4. The overall median time of follow-up after T_0 was 19.5 months (IQR: 11.1-34.6) with no significant difference in follow-up between groups (*P*=0.61). Of those experiencing rebound 107/131(81.7%) were in the switch group of which 82 progressed to virological failure (76.6%); 10 re-suppressed (9.3%) and 15 developed persistent viraemia (14.1%). For the non-switch group, 13/24 (54.2%) progressed to virological failure, 7/24 (29.2%) re-suppressed and 4/24 (16.7%) developed persistent viraemia. A significantly higher proportion of children in the switch group had virological failure at database closure (OR 1.88, 95%CI: 1.02-3.48) and the majority (77.9%) of children experiencing VF were on NNRTI-based regimens (table 5). However, there was no significant difference in incidence of virological failure between switch and non-switch groups across the observation period, and in particular at database closure (switch group: 0.61 (0.49-0.78); non-switch group: 0.42 (0.25-0.73); *p*-

value=0.40). Similarly, survival analysis showed no significant difference between the groups (Figure 4).

During the observation period, 15 HIV drug resistance tests were performed among 14 children: one child had 2 tests. Most (12/15) samples had major drug resistance mutations: all were for children in the switch group, receiving an NNRTI-based regimen and had been switched from stavudine to abacavir. K103N/R mutations were present in 8/12 samples (66.7%) conferring high level NNRTI resistance, with 6/8 (75%) also having the M184V mutation conferring high level resistance to lamivudine. Three of these six children had the abacavir-associated L74V mutation in addition, and one had an additional thymidine analogue mutation, Y115F. One child developed the K65R mutation independent of the other mutations mentioned above: K65R is known to confer NRTI resistance to multiple NRTIs, and to be selected for by abacavir [24].

Discussion

To our knowledge, this is the first study in children reporting virological outcomes after large scale single drug substitutions in routine clinical care. Our study investigated the effect of a single NRTI substitution on the risk of viral rebound in children and adolescents on ART in a public sector setting. We found that in children who were previously virally suppressed, a single NRTI substitution did not result in increased risk of viral rebound within 12 months of switch and children who switched were at lower risk of rebound by 6 months post switch. This suggests that a single drug switch in children and adolescents in a routine clinical care environment is safe and does not compromise virological outcomes in the short term. This is an important finding as it suggests that with new drugs available, among virologically suppressed children where there is no concern regarding adherence and underlying resistance, single drug switches to new, safer and more tolerable options for children are possible. While evidence from clinical trials support the implementation of NRTI drug substitutions in adults who have never had VF [6], the evidence-base for the impact of drug substitutions on viral loads in children in real-world settings is limited. Our findings are in contrast with findings in the CANOC cohort in 2014, a large Canadian non-trial adult cohort which reported on an association between drug switches and later virological failure [8]. However, there are significant differences between this cohort and ours: within the Canadian cohort, 601/986 (61%) of patients underwent more than one switch over time, many across different drug classes. The authors proposed that individuals who had undergone substitutions might have had lower tolerability to ART, and this may have selected a cohort at higher risk of poor adherence. In our study, children and adolescents with multiple switches were excluded from the analysis. Additionally, many of these children were dependant on caregivers for administering medication.

For children who experienced rebound, a higher proportion developed virological failure in the switch group (76.6% vs 54.1%). However, the incidence of virological failure in the switch group was not significantly higher and there was no significant increase in VF seen on survival analysis. Thus the risk of progression to virological failure over time was not significantly different, and other factors should be considered as potential contributors. For one, the majority of children who progresses to VF were on NNRTI-based regimens, and a higher proportion of children were on NNRTIs (which have a lower genetic barrier to resistance) in the switch group. Abacavir has cross resistance with 3TC in the M184V mutation and requires fewer mutations to

acquire resistance than stavudine, in the face on an elevated VL. All children with drug resistance were on NNRTI-based regimens and the M184V and NNRTI-resistance mutations predominate. Additionally, children in the switch group were older and had longer ART exposure prior to entering the study, both of which may influence adherence through mechanisms such as treatment fatigue, adolescence and evolving social circumstances.

Certain drugs may be considered to be more robust than others, based on evidence of poorer virological outcomes, as was found in comparisons of abacavir- and stavudine-based regimens [14, 15]. Lack of experience with newer agents and uncertainty regarding outcomes may affect clinical decision-making regarding drug switches. Our findings indicate that virally suppressed children can be switched over to newer agents in cases where there are no concerns around adherence or drug resistance. The initial reduced risk of viral rebound might be explained by reductions in treatment side effects, which (even if not severe) do have an impact on treatment adherence [25]. There was a median of one additional clinical visit in the switch group. Although the clinical relevance of this is unclear, the potential contribution of additional adherence counselling and support must be considered, as this often accompanies any change in treatment regimen. By 12 months, a diminished effect of a single drug substitution could be expected as other important clinical factors may have greater effect on the viral load over time. These could include increasing age, disclosure-related issues, family dynamics and stress levels for both child and caregiver [12, 26, 27].

Limitations:

There are notable limitations in this study. These include the retrospective nature of this study, where routine clinical data was used. Missing data is therefore an important consideration and limiting factor. However, in this cohort, only 54/3784 children (1.4%) identified initially were excluded due to missing or inadequate information. For children included in the study, 109 children did not have virological outcomes at the time of database closure. These children were either transferred out or lost to follow-up before having 2 VL done and recorded on the database. Outcomes for these children may well be very different than the rest of the cohort. While adherence information was not available, inclusion criteria were strictly applied to select only children who had proven adherence with 2 documented suppressed viral loads within the 12 months prior to T_0. These selection criteria may, however, limit generalizability of these results.

Another limitation is the non-random allocation to the groups. Clinical information on possible contributors to treatment switch (e.g. presence of d4T-related side effects) was not available for analysis. This has been mitigated through the selection of children with demonstrated adherence and prolonged viral suppression, in an effort to control potential contributors to poor adherence.

The numbers of children with viral rebound were low, with only 58 children having viral rebound within 12 months of T_0. This is lower than would be expected within a routine cohort within this setting [28, 29], but is likely due to the strict selection criteria detailed above. However, this does pose some limitations in the interpretation of outcomes related to virological failure and the development of antiretroviral drug resistance due to small numbers.

Conclusions:

The study provides evidence of successful treatment optimization in a large paediatric cohort, with findings indicating that single NRTI substitutions in children and adolescents virally suppressed on ART, pose no threat to continued viral suppression in routine clinical care settings within the short term. Longer term outcomes are less clear, with multifactorial considerations for durable viral suppression clouding the picture, including regimen type, adherence, and the potential impact of changing psychosocial circumstances such as disclosure, adolescence and treatment fatigue.

These findings will be useful in informing programmes where drug substitutions are required when drugs are phased out and substituted with newly available drugs, resulting in improved regimens regarding pill burden, palatability, cost or safety. Although future treatment optimization interventions may be more complex, for example including substitutions of drugs from a different drug class, similar principles could be expected to apply. While available clinical trials provide robust data regarding single drug substitutions, findings from this study provide data more generalizable to routine healthcare settings

Competing interests

None of the authors have any competing interests or conflicts of interest to declare

Authors' contributions

All authors have read and approved the final manuscript for submission.

CF, LF and SS developed the concept. CF wrote the research protocol, supported by LF and SS. CF, SS and EK analysed the data and developed tables and figures. CF, SS, EK and LF wrote the manuscript. CF, SS and LF reviewed and edited the final manuscript.

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Tables

Table 1: Demographics and clinical characteristics of children in the switch and non-switch groups at ART initiation and at T_0

	Characteristics at ART initiation			Characteristics at T_0[†]		
	Non-switch group N=157	Switch group N=566	*P*-values[*]	Non-switch group N=157	Switch group N=566	*P*-values[*]
Sex			0.654			
Male	72 (45.9%)	271 (47.9%)		As at ART initiation	As at ART initiation	
Female	85 (54.1%)	295 (52.1%)				
Age			0.333			0.012
<5 years	84 (53.5%)	249 (44.0%)		48 (30.6%)	76 (13.4%)	
5-9 years	42 (26.8%)	240 (42.4%)		52 (33.1%)	272 (48.1%)	
10-14 years	28 (17.8%)	74 (13.1%)		44 (28.0%)	170 (30.0%)	
15-19 years	3 (1.9%)	3 (0.5%)		11 (7.0%)	46 (8.1%)	
>19 years	0	0		2 (1.3%)	2 (0.4%)	
Height-for-age z-scores			0.035			0.674
Normal	68 (46.0%)	191 (35.4%)		81 (57.0%)	326 (58.3%)	
Stunted	43 (29.1%)	186 (34.5%)		37 (26.1%)	151 (27.0%)	
Severe stunting	37 (25.0%)	162 (30.1%)		24 (16.9%)	82 (14.7%)	
Weight- and BMI-for-age z-scores [‡]			0.542			0.195
Normal	100 (68.0%)	395 (73.3%)		129 (91.5%)	516 (92.3%)	
Underweight	23 (15.7%)	62 (11.5%)		10 (7.1%)	23 (4.2%)	
Severe underweight	22 (15.0%)	81 (15.0%)		2 (1.4%)	10 (1.8%)	
Overweight	2 (1.3%)	1 (0.2%)		0	4 (0.7%)	
Immune suppression			0.179			0.643
Severe	41 (43.6%)	220 (53.1%)		1 (0.7%)	5 (1.0%)	
Moderate	39 (41.5%)	132 (31.9%)		13 (8.6%)	37 (7.0%)	
None	14 (14.9%)	62 (15.0%)		138 (90.8%)	483 (92.0%)	
Viral load			0.277			0.001
VL (log) median	5.04	5.08		1.69	1.40	
IQR	(4.34 – 5.52)	(4.37 – 5.65)		(1.40-1.69)	(1.40-1.69)	
ART Regimen			< 0.001			
NNRTI[§]	97 (61.8%)	433 (76.5%)		As at ART initiation	As at ART initiation	
PI [¶]	60 (38.2%)	133 (23.5%)				
Median time on ART			1.0			<0.001
Median	0	0		31.4	39.4	
IQR				(23.2-46.4)	(29.1-50.6)	

[†]T_0: date of switch for the switch group; first visit after 1 April 2010 for the non-switch group.

*Chi-squared tests used to compare categorical data, Kruskall-Wallis test used for comparisons of continuous data.

[‡]Weight-for-age z-scores used for children under 5 years and BMI-for-age Z-scores used for children≥5 years based on standard deviations (SD) as per the WHO child and adolescent growth standards [20, 21]. Normal +2SD to -2SD; underweight -2SD to -3SD, severely underweight <-3SD, overweight >+2SD. No children had z-scores above +3SD. [§]NNRTI: non-nucleoside reverse transcriptase inhibitor. [¶]PI: protease inhibitor. Totals vary due to missing data.

Table 2: Unadjusted and adjusted hazard ratios of having viral load rebound at 6 months after T_0

Characteristics (T_0)	Unadjusted Hazard ratio (95% CI)	*P*-value	Adjusted Hazard ratio (95% CI)	*P*-value
Sex				
Female	1			
Male	0.92 (0.42-2.01)	0.83		
Age				
<5 years	1			
5-9 years	0.68 (0.25-1.81)	0.44		
10-14 years	0.45 (0.14-1.47)	0.18		
≥15	0.80 (0.16-3.98)	0.79		
Height for age				
Normal	1			
Stunted	0.98 (0.33-2.87)	0.97		
Weight for age (<5 years)				
Normal	1			
Underweight	0.60 (0.08-4.81)	0.63		
BMI for age (5-19 years)				
Normal	1			
Underweight	1.07 (0.14-8.29)	0.95		
Immune suppression				
None	1			
Immune suppressed	0.50 (0.07-3.68)	0.49		
ART start year				
2004-2005	1		1	
2006-2007	1.11 (0.43-2.86)	0.84	0.80 (0.27-2.35)	0.68
2008-2010	1.27 (0.48-3.40)	0.63	0.75 (0.20-2.85)	0.67
ART Regimen				
NNRTI	1			
PI	1.94 (0.46-8.27)	0.37		
Time on ART (months)				
<36	1		1	
≥36	0.74 (0.34-1.62)	0.45	0.72 (0.26-2.02)	0.53
Single NRTI switch				
No	1		1	
Yes	0.40 (0.18-0.89)	0.02	0.39 (0.17-0.91)	0.03
Ever had an elevated VL				
No	1			
Yes	1.10 (0.41-2.92)	0.86		

NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor.

Table 3: Unadjusted and adjusted hazard ratios of having viral load rebound at 12 months after T_0

Characteristics (T_0)	Unadjusted Hazard ratio (95% CI)	*P*-value	Adjusted Hazard ratio (95% CI)	*P*-value
Sex				
Female	1			
Male	1.22 (0.73-2.05)	0.44		
Age				
<5 years	1			
5-9 years	0.90 (0.41-1.96)	0.79		
10-14 years	1.30 (0.60-2.84)	0.51		
≥15	1.78 (0.66-4.78)	0.25		
Height for age				
Normal	1			
Stunted	0.73 (0.38-1.42)	0.36		
Weight for age (<5 years)				
Normal	1			
Underweight	0.54 (0.12-2.32)	0.41		
BMI for age (5-19 years)				
Normal	1			
Underweight	0.88 (0.21-3.69)	0.87		
Immune suppression				
None	1			
Immune suppressed	0.80 (0.43-8.02)	0.66		
ART start year				
2004-2005	1		1	
2006-2007	1.09 (0.58-2.02)	0.79	1.23 (0.63-2.39)	0.55
2008-2010	1.31 (0.69-2.47)	0.41	1.65 (0.74-3.71)	0.22
Time on ART (months)				
<36	1		1	
≥36	1.09 (0.65-1.83)	0.74	1.44 (0.75-2.75)	0.28
ART Regimen				
NNRTI	1			
PI	0.85 (0.21-3.48)	0.82		
Single NRTI switch				
No	1			
Yes	0.83 (0.47-1.47)	0.52	0.89 (0.49-1.60)	0.69
Ever had an elevated VL				
No	1			
Yes	0.98 (0.51-1.88)	0.94		

NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor.

Table 4: Virological and retention outcomes for the switch and non-switch groups

	Total N=723	**Non-switch group N=157**	**Switch group N=566**	***P*-values**
Median time on ART at DB closure	60.9 [IQR:45.2-79.2]	53.3 [IQR:41.9-70.1]	63.2 [IQR:47.9-82.8]	<0.01
Median follow up after T_0	19.5 months [IQR:11.1-34.6]	18.0 [IQR:13.4-25.4]	20.0 [IQR:9.3-37.0]	0.61
Outcomes at database closure				**<0.01**
Transferred out	613 (84.8%)	140 (89.2%)	473 (83.6%)	
Lost to follow-up	54 (7.5%)	15 (9.6%)	39 (6.9%)	
Death	1 (0.1%)	1 (0.6%)	0 (0%)	
Still in care	55 (7.6%)	1 (0.6%)	54 (9.5%)	
VL outcomes available at database closure	**614**	**152**	**462**	
Viral rebound	131	24	107	0.05
VL re-suppressed	17 (13.0%)	7 (29.2%)	10 (9.4%)	
Persistent viraemia[†]	19 (14.5%)	4 (16.7%)	15 (14.0%)	
Progressed to VF	95 (72.5%)	13 (54.1%)	82 (76.6%)	
VL outcomes available at 12 months	**599**	**151**	**448**	
Viral rebound	58	16	42	0.19
Re-suppressed	10 (17.2%)	4 (25.0%)	6 (14.3%)	
Persistent viraemia[†]	17 (29.3%)	6 (37.5%)	11 (26.2%)	
Progressed to VF	31 (53.5%)	6 (37.5%)	25 (59.5%)	

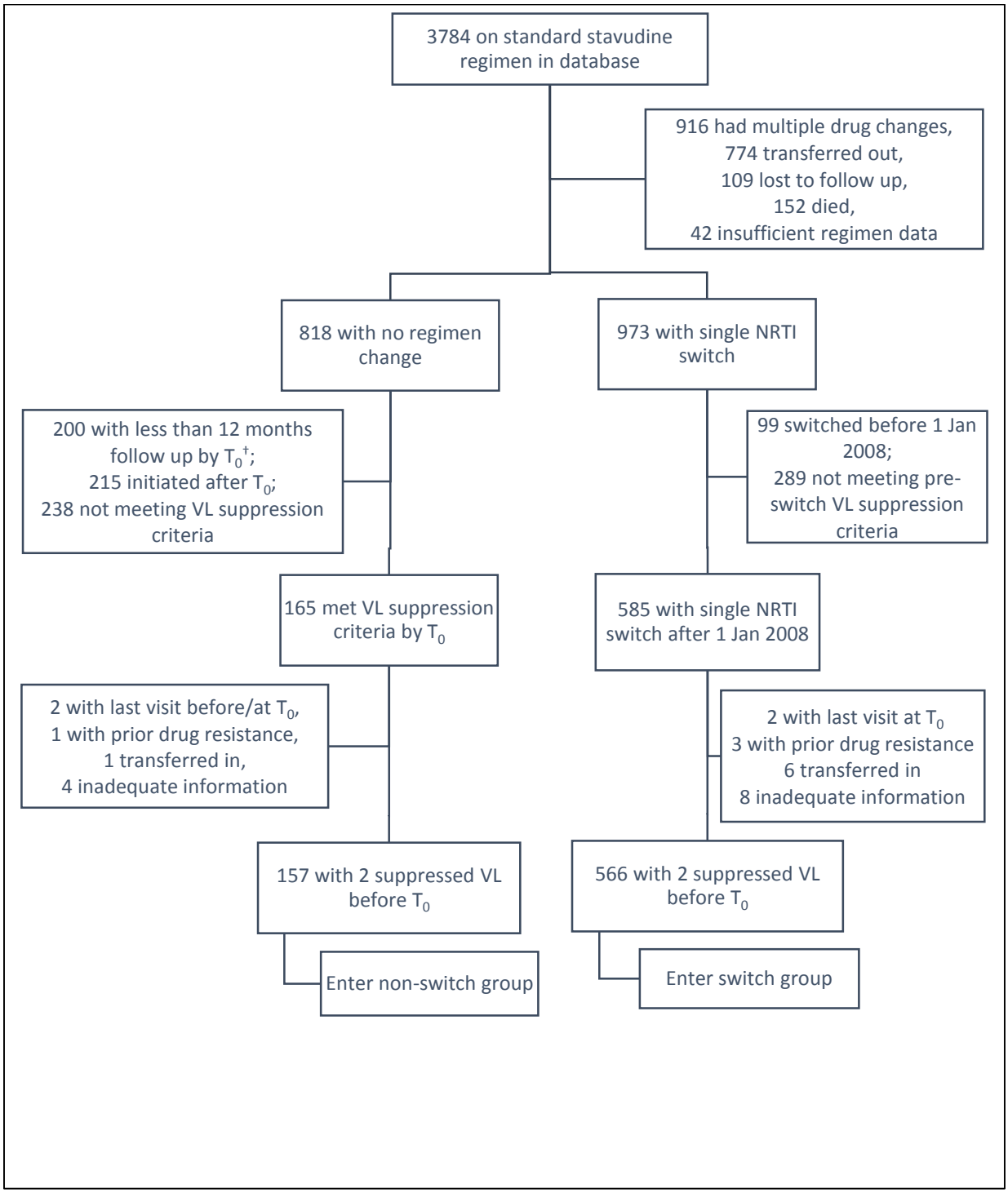
[†]2 of these patients eventually progressed to VF by database closure – one in the switch group and one in the non-switch group

Table 5: Differences in virological failure and drug resistance for switch and non-switch groups

	Total N=723	**Non-switch group N=157**	**Switch group N=566**	***P*-values**
Virological failure by database closure	95 (72.5%)	13 (54.1%)	82 (76.6%)	<0.01
NNRTI base	74 (77.9%)	5 (38.5%)	69 (84.1%)	
PI base	21 (22.1%)	8 (61.5%)	13 (15.9%)	
HIV drug resistance testing by database closure	**15**	**1**	**14**	0.03
No major mutations	2	1	1	
Major mutations	13	0	13	
NNRTI base	12	0	12	
PI base	1	0	1	

Figures

Figure 1: Selection processes for children included in both switch and non-switch study groups.



†T_0: date of switch for the switch group; first visit after 1 April 2010 for the non-switch group.

Figure 2: Causal diagram for potential pathways to virological failure

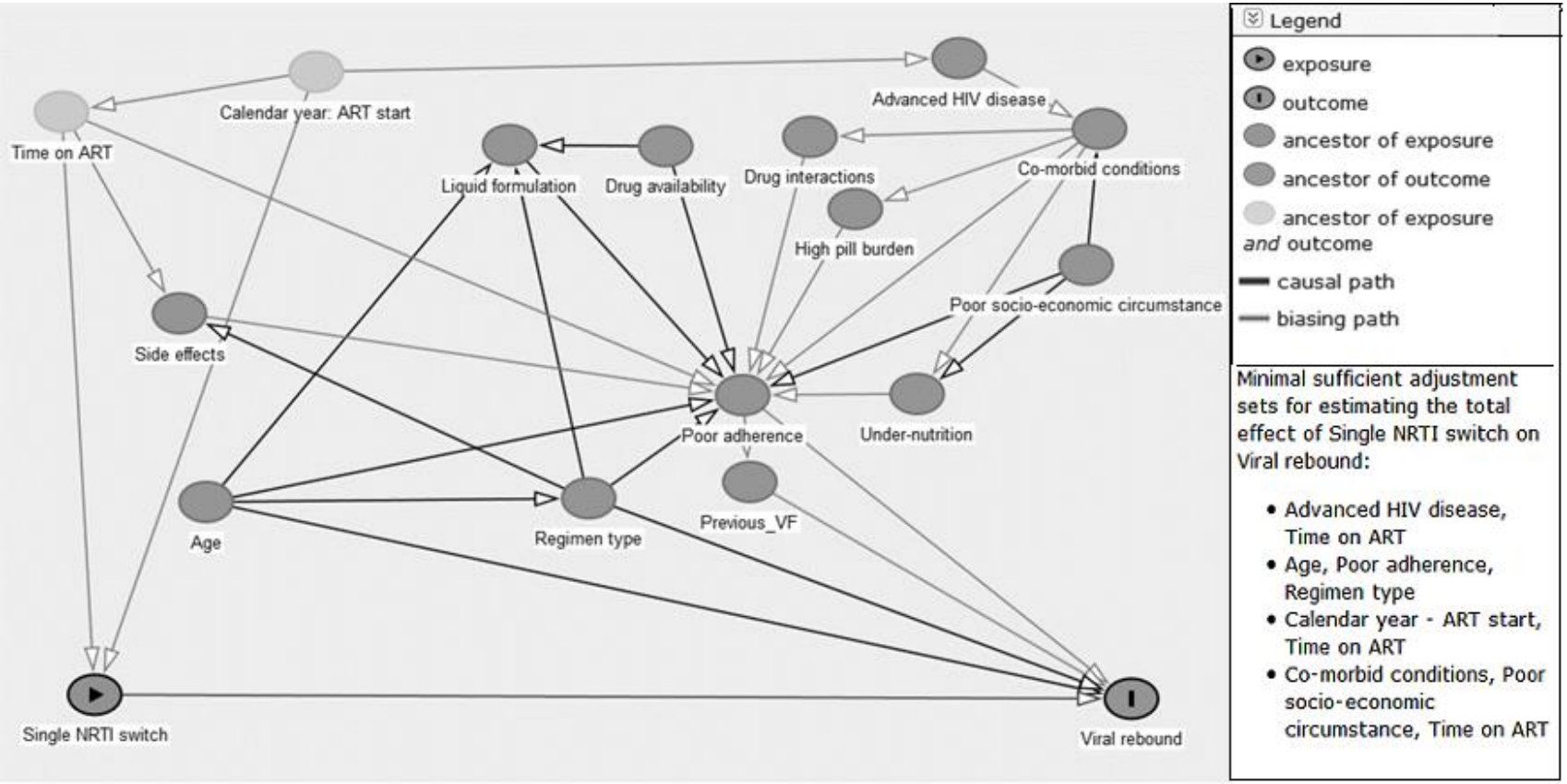
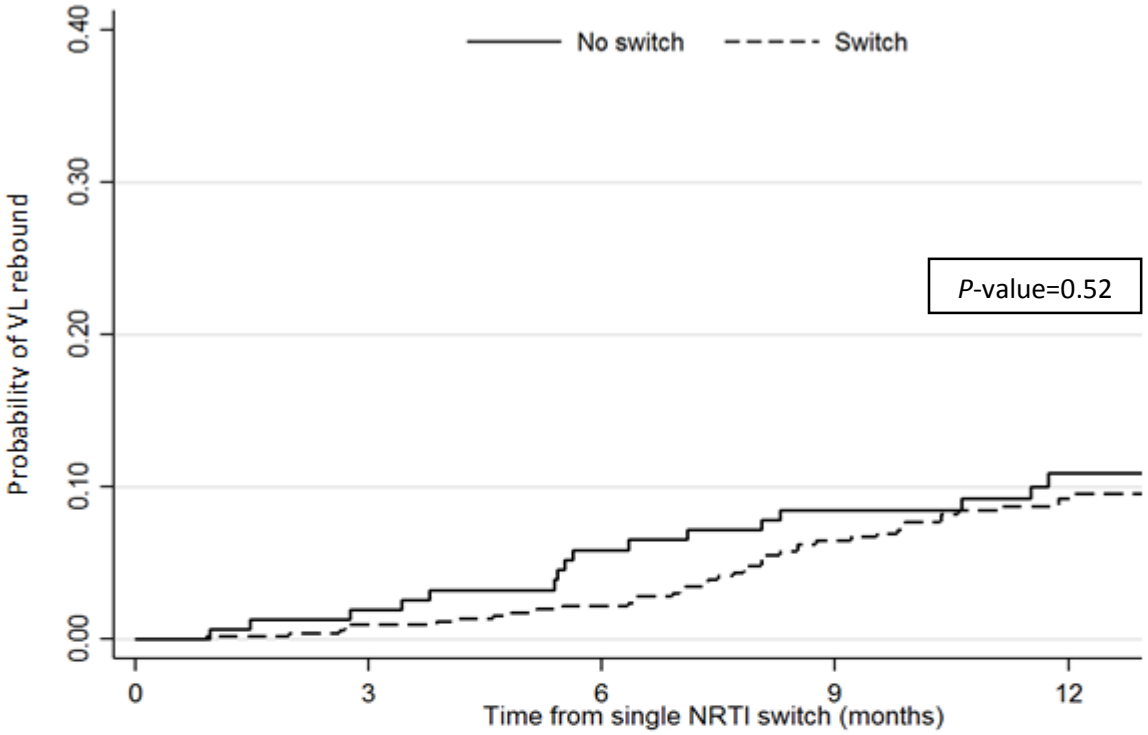


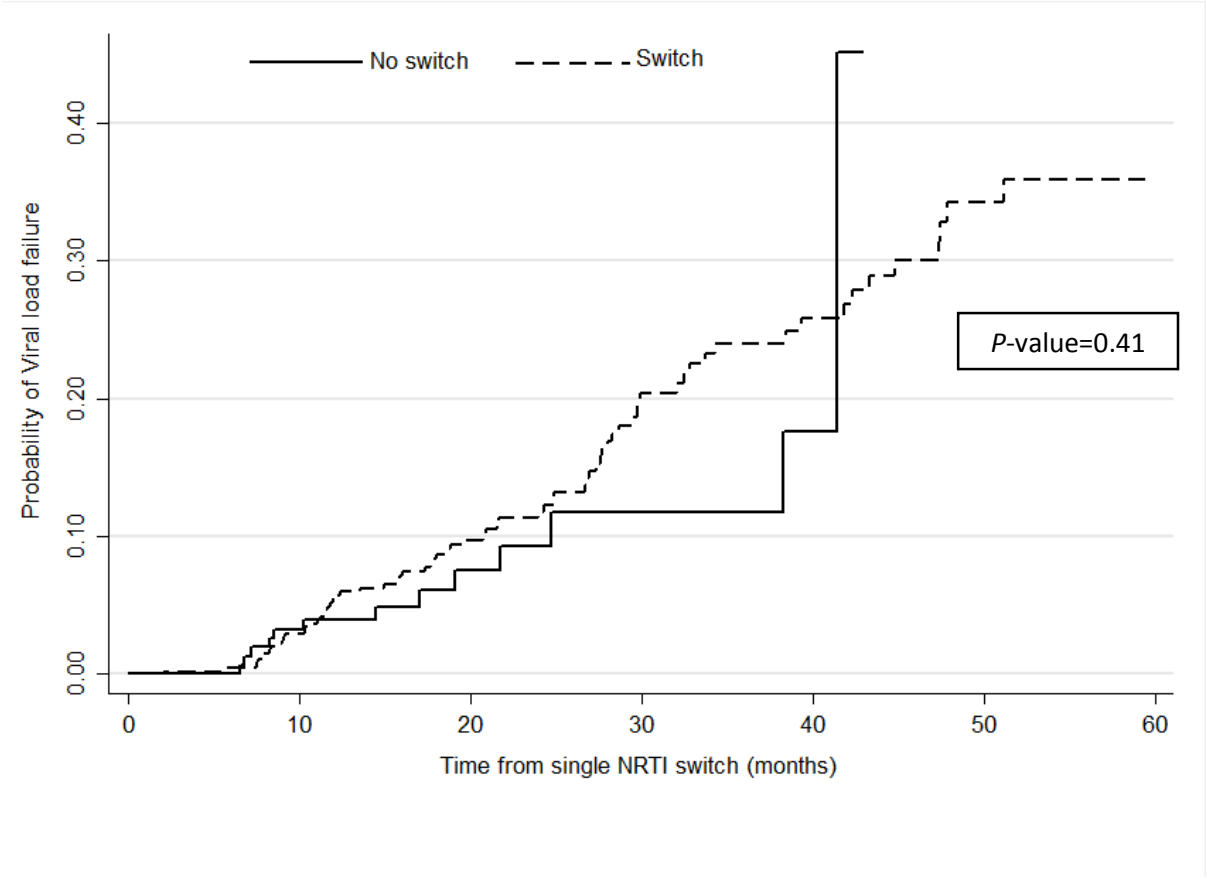
Figure 3: Comparison of time to viral rebound (VL≥400 copies/ml) between switch and non-switch groups of children, up to 12 months from T_0



Number at risk				
Non-switch (N=157)	153	143	135	99
Switch (N=566)	510	461	394	312
Cumulative person -years	157.5	312.5	451.9	562.3
Viral rebound incidence rates (per 100 person years)				
Switch	4.9 (2.2-10.8)	6.2 (3.7-10.6)	10.1 (7.2-14.0)	9.8 (7.2-13.2)
Non-switch	14.6 (6.1-35.2)	14.4 (8.1-26.8)	12.4 (7.2-21.3)	12.1 (7.4-19.7)
Overall	7.0 (3.9-12.6)	8.0 (5.4-11.8)	10.6 (8.0-14.1)	10.3 (7.2-13.3)
Log rank/ p-value	0.040	0.020	0.596	0.521

For this Kaplan-Meier graph, VL rebound ≥400 copies/ml was set as failure.

Figure 4: Comparison of time to viral failure (two consecutive VL>1000 copies/ml) between switch and non-switch groups of children, from T_0 up to time of database closure.



Number at risk						
No switch (157)	142	59	23	7	0	0
Switch (566)	402	249	129	81	41	0
Cumulative person years	5564.44	10050.29	12521.25	13793.62	14493.09	14882.73

Virological failure Incidence rates (per 100 person years)						
Switch	0.31 (0.18-0.53)	0.48 (0.35-0.67)	0.59 (0.64-0.77)	0.60 (0.47-77)	0.63 (0.50-79)	0.61 (0.49-0.78)
Non-Switch	0.38 (16-0.92)	0.37 (0.19-0.71)	0.38 (0.21-0.10)	0.39 (0.22-0.69)	0.43 (0.25-0.73)	0.42 (0.25-0.73)
Overall	0.32 90.20-0.52)	0.45 (0.34-0.61)	0.55 (0.44-0.69)	0.56 (0.45-0.69)	0.59 (0.4-0.72)	0.58 (0.47-0.71)
Logrank/ p-value	0.7673	0.4600	0.2918	0.2492	0.3991	0.4047