Virologic failure and second-line antiretroviral therapy in children in South Africa - The IeDEA Southern Africa Collaboration

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Abstract

Background—With expanding pediatric antiretroviral therapy (ART) access, children will begin to experience treatment failure and require second-line therapy. We evaluated the probability and determinants of virologic failure and switching in children in South Africa.

Methods—Pooled analysis of routine individual data from children who initiated ART in 7 South African treatment programs with 6-monthly viral load and CD4 monitoring produced Kaplan-Meier estimates of probability of virologic failure (two consecutive unsuppressed viral loads with the second being >1,000 copies/ml, after ≥24 weeks of therapy) and switch to second-line. Cox proportional hazards models stratified by program were used to determine predictors of these outcomes.

Results—The 3-year probability of virologic failure among 5485 children was 19.3% (95%CI: 17.6–21.1). Use of nevirapine or ritonavir alone in the initial regimen (compared to efavirenz), and exposure to prevention of mother to child transmission regimens were independently associated with failure (adjusted hazard ratios (95%CI): 1.77(1.11–2.83), 2.39(1.57–3.64) and 1.40(1.02–

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1.92) respectively). Among 252 children with ≥1 year follow-up after failure, 38% were switched to second-line. Median (IQR) months between failure and switch was 5.7(2.9–11.0).

Conclusion—Triple ART based on nevirapine or ritonavir as a single protease inhibitor appears to be associated with a higher risk of virologic failure. A low proportion of virologically failing children were switched.

Keywords

antiretroviral therapy; virologic failure; children; second-line therapy; resource-limited setting

Introduction

With expanding access to antiretroviral therapy (ART) for HIV-infected children, increasing numbers are likely to experience treatment failure and require second-line regimens. Prior to 2010, WHO pediatric guidelines did not define virologic failure (VF) and viral load monitoring remains unavailable in most resource-limited settings.[1–2] In contrast, industrialized country guidelines stipulate strict viral load criteria for switching at thresholds as low as 2 consecutive measurements >400 copies/ml.[3–4]

Due to poor access to viral load monitoring in resource-limited settings, there is limited published data on VF in children.[1] Existing studies are limited by cohort size, exclusive use of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens and/or failure definitions based on a single elevated viral load measurement.[5–9] Poor access to and lack of experience with second-line therapy, as well as national policies that may restrict second-line use, have resulted in low numbers and proportions of children being switched even in larger cohorts.[5–6, 10–14] Predictors of which children are switched in resource-limited settings have therefore not been examined.

The International epidemiologic Databases to Evaluate AIDS (IeDEA) Southern Africa collaboration includes 7 South African pediatric ART programs with data on more than 6000 children who had initiated treatment before 2008.[15–16] Regular viral load monitoring (at least 6-monthly) is part of routine ART care in South Africa.[17] However, until 2010, national pediatric treatment guidelines did not provide clear direction on management of VF.[17] We aimed to examine the probability of VF and its associations, and, in children with VF, to determine the probability of switching to second-line and identify factors that predicted which children were switched.

Methods

Study design, setting and population

Data for this multicenter analysis were collected prospectively at sites. Each site has institutional ethical approval for contribution of data to IeDEA analyses, and transferred data anonymously to the IeDEA data center between May 2007 and February 2008. The analysis included treatment-naïve children (<16 years) initiating ART with ≥3 antiretroviral drugs between June 1999 and February 2008.

Treatment regimens

All treatment sites are part of the South African national treatment program that commenced in April 2004 with the following first-line regimen guidelines: stavudine (d4T), lamivudine (3TC) and either efavirenz (EFV) or, if <3 years/<10kg, a protease inhibitor (PI).[17] For most children this was lopinavir/ritonavir (LPV/r), however ritonavir alone (RTV) was recommended for children with tuberculosis or <6 months old.[17] The latter two

recommendations changed during 2007; LPV/r with additional RTV boosting was introduced for children with tuberculosis and LPV/r dosing recommendations became available for children <6 months old.[18–19] Some cohorts introduced these practices before 2007, and also used more varied regimens before commencement of the national program, including NNRTI-based regimens in children <3 years old, RTV alone as the "third drug" in children of all ages, and zidovudine (ZDV) instead of d4T. National guidelines were otherwise adhered to in all provinces and permitted restricted individual drug substitution for intolerance or non-availability of the recommended drug in suitable formulation.[17]

National guidelines second-line regimens were ZDV + didanosine (ddI) with either LPV/r (EFV-based first-line), or an NNRTI (PI-based first-line).[17] The NNRTI was (nevirapine) NVP for children <3 years old at switch, and EFV for older children.[17] Decisions to switch could be made by the program clinician without formal Department of Health approval. Second-line regimens were accessible at all sites.

National guidelines advised single dose NVP (sdNVP) for mother and infant for prevention of mother to child transmission (PMTCT), with triple ART for pregnant women with WHO stage 4 disease or CD4 ≤200 cells/μl.[20–21] However, in the Western Cape province, PMTCT programs began before national roll-out, with a variety of regimens being used including sdNVP or ZDV from 34 weeks ± sdNVP. Similarly, after national implementation of the sdNVP regimen, the Western Cape province and McCord Hospital used more effective PMTCT regimens (Table 1).[22]

Key variables

Socio-demographic and clinical data at ART start included age, gender, clinical stage (stage 3 [2002 3-stage WHO classification] and stages 3/4 [2005 4-stage WHO classification] were combined)[23–24], exposure to PMTCT regimens and starting regimen. Weight, viral load, CD4 absolute count and percent were available at ART start and 6-monthly thereafter. Access to viral load and CD4 measurement was similar across sites. Viral load measurements were performed using Amplicor 1.5 (Roche Diagnostics) or NucliSens EasyQ assays (bioMerieux), which have good comparability.[25] Severe immune suppression was defined according to WHO guidelines.[2] "Baseline" measurements were those taken closest to ART initiation and within 6 months (CD4 and viral load) or 2 weeks (weight) prior, to 1 week after commencing ART. Sex-adjusted weight-for-age z-scores (WAZ) were calculated using WHO 2007 reference values for children ≤10 years of age.[26]

Outcomes

Virologic failure (VF) was defined as 2 consecutive (≤12 months apart) viral load measurements ≥400 copies/ml with the second being >1,000 copies/ml, and both taken after 24 weeks on ART, and not during a treatment interruption. Sensitivity analyses used different thresholds (400, 5,000 and 10,000 copies/ml) to define VF. Children were considered to have switched to second-line if any of the following occurred <1 year after a viral load measurement >400 copies/ml: (i) commencement of ≥2 new drugs including a class-switch from PI to NNRTI or vice versa, (ii) class-switch from NNRTI to PI or vice versa only, with reason documented as treatment failure or (iii) change of both NRTIs and change from RTV to LPV/r with reason documented as treatment failure. Immunologic failure was defined according to South African guidelines criteria for switching as either CD4% below baseline value after 24 weeks of therapy or CD4%<50% of peak value during preceding treatment.

Analysis

Continuous and categorical variables were summarized using medians and interquartile ranges (IQR) and proportions respectively. Kaplan-Meier probabilities of virologic and immunologic failure and switch were estimated. Predictors of failure and switch were determined using Cox-proportional hazards models stratified by site to account for between-site heterogeneity. Only children with ≥6 months of follow-up after failure were included in the switch model. The following variables were included *a priori* in multivariable models: age, gender and immune suppression at ART initiation (failure model); age, gender and treatment duration at time of failure (switch model). Thereafter multivariable models retained variables with adjusted p-values <0.1. In comparison to known lack of PMTCT exposure, missing PMTCT exposure information had no effect on failure, so these categories were combined. Separate failure models were generated including and excluding WAZ and stage, as missing data for these variables and exclusion of children >10 years old due to lack of WHO WAZ reference values substantially reduced the number of children that could be included in the model. The proportional hazards assumption was met for all models. Statistical analyses were performed using Stata version 10 (STATA Corporation, College Station, TX).

Results

Data from all South African IeDEA sites providing pediatric ART were included (Table 1). This comprised 6266 children of whom 781 (12%) were excluded for the following reasons: missing or inconsistent baseline data (n=85), non-naïve (n=39), mono/dual therapy (n=64) and starting regimen not recorded (n=593). The final dataset comprised 5485 children (49% female) with median (IQR) follow-up of 16 (6–29) months. During follow-up 344 (6%) children died, 411 (7%) were lost to follow-up and 885 (16%) were transferred out after median durations of 1.5, 5.8 and 12.9 months respectively. There were 13877 viral load and 12749 CD4 percent measurements during follow-up with median (IQR) intervals between measurements of 168 (104–190) and 168 (126–197) days respectively.

Most children were severely ill at ART start (Table 2). The median (IQR) age of children commencing ART was 42 (15–82) months. The NRTI backbone was d4T/3TC for 89% of children. The most common "third" drugs were EFV(55%), LPV/r(33%), RTV alone(7%) and NVP(5%).

Virologic failure

The estimated probability of failure (second elevated value ≥1,000 copies/ml) by 36 months was 19.3% (95%CI: 17.6–21.1, Figure 1). Of the 523 children with VF, 311(59%) had never been virologically suppressed. Among these children whose viral load was never <400 copies/ml, 217 had both baseline and ≥1 subsequent viral load measurement performed between 6 and 15 months on ART, and 121 (55%) showed a virologic response to therapy (≥1 $\log_{10}$ reduction from baseline viral load during the first year on ART). Using different thresholds for the second unsuppressed viral load, the 36-month estimated probability of failure ranged from 14.6% (95%CI: 13.1–16.3) (cut-off=10,000 copies/ml) to 21.1% (95% CI: 19.3–23.0) (cut-off=400 copies/ml) (Figure 1). By one year and 3 years on ART, the estimated probabilities of a single viral load measurement >1,000 copies/ml were 16.9% (95%CI: 15.8–18.1) and 32.1% (95%CI: 30.2–34.1) respectively. By 3 years, 384 children had immunologic failure with an estimated cumulative probability of 12.6% (95% CI: 11.3–13.0). The probability of immunologic failure was lower than that for all definitions of VF, except in the early months as the immunologic failure definition did not require confirmation.

In the multivariable model of associations with VF, viral load >1 million copies/ml at ART initiation was the only disease characteristic that predicted failure (Table 3a). After adjustment for gender, age, baseline viral load and immune suppression, failure risk was increased with use of either NVP (adjusted hazard ratio (aHR): 1.77 (95%CI: 1.11–2.83) or RTV alone (aHR: 2.39; 95%CI: 1.57–3.64) compared to EFV in the initial regimen. Known PMTCT exposure was also associated with failure (aHR: 1.40; 95%CI: 1.02–1.92). Results were very similar using different thresholds to define VF. Results were also similar if additionally adjusted for WHO stage and WAZ, neither of which remained independently associated with failure. A further model was developed excluding children with virologic non-response, and results were similar except for an attenuated effect of PMTCT. Results of all additional analyses are shown in an online appendix (eTable 1).

Switching to second-line

The estimated probability of switching to second-line by 3 years after ART initiation for all children was 6.2% (95% CI: 5.2–7.5, Figure 1). Of the 153 children switched, 8 did not meet the VF criteria because there was only one unsuppressed viral load measurement (n=7) or consecutive measurements were both before 24 weeks on ART (n=1). Of 252 children with ≥1 year of follow-up after failure, 38% (95%CI: 32%–45%) were switched. The median (IQR) time to switch from failure was 5.7 (2.9–11.0) months and from first unsuppressed viral load was 9.5 (5.5–14.6) months. The median (IQR) interval between consecutive unsuppressed viral load measurements was 3.2 (2.5–5.4) months.

Most second-line regimens included ddI as one of the NRTIs (108/153; 71%). Other NRTIs included ZDV(66%), 3TC(25%); d4T(21%); abacavir(13%), and tenofovir(1%). The "third drug" in the regimen was LPV/r for 74% of children.

After adjustment for age at ART initiation, gender and treatment duration, children with more severe or progressive disease from the time of failure (higher viral load, CD4% <25 at switch, CD4% decline >1 percentage point per month between switch date and preceding visit) were more likely to be switched, while taking a PI-based initial regimen was negatively associated with switch (aHR 0.40; 95%CI: 0.17–0.91) (Table 3b). Failure to initially attain viral load <400 copies/ml after starting ART was not associated with switch in univariable or multivariable analysis. (aHR: 1.02; 95%CI: 0.52–1.99).

Discussion

Main findings

This study reports in detail on confirmed VF and switching in children on ART in a large African multicenter study where routine viral load monitoring was available. One in five children had met the analysis definition of confirmed VF by three years on ART. Baseline viral load >1million copies/ml, use of either NVP, or RTV as a sole PI, as well as PMTCT exposure independently predicted failure. Less than half of children with ≥1 year of follow-up after failure were switched, with a median interval between failure and switch of 5.7 months. Across all sites, current poor immunologic and virologic status together with being on an NNRTI-based regimen favored switch.

Time to virologic failure

Previous studies from Thailand and Uganda with all children on NNRTI-based regimens and failure defined using a single viral load measurement, reported similar proportions of children with VF at 12 months on ART as we report at 36 months using confirmed measurements.[5–6] Similarly, a recent cohort study found the frequency of consecutive viral load measurements >400 copies/ml among 116 children with follow-up ≥6 months to be

17%.[8] Nevertheless, the cumulative probability of a single elevated viral load measurement after one year on ART in our study (16%) is similar to the Thai and Ugandan studies. In contrast, prevalence of a single viral load measurement >400 copies/ml was 32% at a Tanzanian pediatric clinic, however 12% of those with VF were on second-line.[9] Notwithstanding, our study differs from these with use of PI-based first-line therapy, and possible differences in PMTCT exposure and adherence.

For those on NNRTI-based regimens, the confirmation of VF following adherence optimization, as reported in this study, is likely to identify patients who are truly failing with resistance to ≥1 drug in the regimen. For example, an adult study from South Africa showed that 86% of patients with confirmed viral load >1000 copies/ml had therapy-limiting NNRTI mutations.[27] Among children with VF in the Thai study, 89% and 97% had major NRTI and NNRTI resistance mutations respectively. We had no access to resistance testing for children failing therapy, and the prevalence of resistance among children on PI-based regimens with confirmed VF in our context remains unknown.

Comparisons with rich countries are difficult due to differences in age at ART commencement, previous mono- or dual-therapy, follow-up duration and first-line regimens. The UK Collaborative HIV Paediatric Study (CHIPS) reported 32% of 595 children having VF after a median follow-up of 3 years, while a Dutch cohort of 39 children on nelfinavir-based ART reported 74% virologic failure-free survival after 48 weeks.[28−29]

First-line regimen choice

The association between NVP-containing regimens and VF concurs with findings from previous pediatric and adult studies.[5−6, 30−31] It has been suggested that NVP may be under-dosed in children taking split adult fixed dose combination tablets, however, in South Africa, NVP is administered to children as a single drug in syrup/tablet form.[5−6] Children may harbor resistance from unrecorded exposure to sdNVP, and subsequent NVP-based ART would be expected to result in poor virologic outcomes.[32−33] Although the majority of sdNVP-exposed children in this cohort would have commenced PI-based regimens, it is likely that some initiated NNRTI-based regimens due to site variation in regimen use before national guidelines recommendations. This is supported by both the finding of an association between PMTCT exposure and subsequent failure, despite PMTCT under-ascertainment, as well as attenuation of this effect when those without virologic response to ART were excluded. This attenuation is expected as children with NVP resistance would most likely be virologic non-responders.

Despite our inability to adjust for potential confounding by concomitant tuberculosis and other confounding by indication, our findings suggest that RTV as the sole PI is indeed associated with failure. RTV is unpleasant tasting, associated with poor adherence, and results in a greater accumulation of major PI resistance mutations in comparison with LPV/r. [34, 35] However, as RTV use would have been more common in children with tuberculosis, we cannot exclude that worse outcomes may have been due to tuberculosis itself or the increased medication burden of ART combined with anti-tuberculous therapy.

Switching to second-line

This study reflects clinical practice in a setting with viral load monitoring but no supporting national or WHO guidelines regarding management of children with VF. This is reflected in the low proportion children switched after failure, and the delay between VF and switch. Heterogeneity in switching practice was also seen in the CHIPS study with nearly half of children with VF being switched before the date of first viral load >1000 copies/ml, but an equal proportion on first-line ≥6 months thereafter.[28] In our study, service factors may

contribute to the delay; clinical appointments are often 3- monthly with results only available for decision-making at subsequent appointments.

Nevertheless, less than half of children with confirmed VF for ≥1 year were switched, and those who were switched were on a failing regimen for a median of 10 months after the first elevated viral load measurement. In this study, factors other than VF were associated with being switched, including initial regimen, disease severity and progressive immunological decline.

Reluctance to switch a young child failing therapy without thorough assessment of adherence is reasonable in the context of access only to unpleasant second-line regimens, with no third-line/salvage therapy. In this respect, reduced switching of children on PI-based regimens is consistent with knowledge that viral escape is more likely due to poor adherence than resistance.[34] Nevertheless, poor access to a wider range of second-line drugs, particularly for children failing first-line PI-based regimens following sdNVP exposure, may result in an understandable reluctance to switch children to a drug to which their virus may be resistant.

If the intention of treatment guidelines is to avoid prolonged viraemia, this study suggests the need for more intensive monitoring and adherence interventions soon after a single elevated viral load. The PENPACT1 trial recently reported similar outcomes overall for children switched at viral load measurements of 1,000 or 30,000 copies/ml, however highlighted the importance of adherence interventions after initial elevated viral load measures.[36–37] In addition, children on NNRTI-based therapy switched at 30,000 copies/ml accumulated more NRTI-resistance mutations compared to those switched at 1,000 copies/ml, suggesting that switching guidelines should be tailored according to regimen.[36–37] In large programs, viral load monitoring could additionally be used to manage patient load by stratifying risk. More clinical and adherence input could be given to unsuppressed patients while those with sustained virologic suppression could be managed less intensively.[7, 38]

Strengths and limitations

This is a large combined cohort of children across many sites providing different levels of care. In addition, viral load measurements were available for >75% of children in care at each 6-monthly duration, and it was possible to use as an outcome confirmed virologic failure rather than a single measure. The large number of infants and inclusion of a PI in first-line enabled us to examine the effect on virologic outcome of RTV as the sole PI, as well as LPV/r in comparison to NVP or EFV as components of first-line regimens. The size of the cohort resulted in a relatively large absolute number of failures and switches, permitting investigation of switching practice.

Despite the study size, and the general application of the public health approach to ART provision, the study cohorts, being relatively well-resourced and urban, may not be representative of all sites across the region or even South Africa.

Data was collected in the context of routine care in busy clinics. There is limited data on key possible predictors of VF such as tuberculosis co-infection, adherence and PMTCT, as well as on clinical events. Missing data on other variables limited the range of variables and number of children that could be included in multivariable models. Tuberculosis co-infection not only affects first-line regimen choice, but may impact on virologic outcomes directly or through drug-drug interactions or reduced adherence. We could not explore the extent to which our observed associations with failure were mediated through poor adherence, due to limited data. PMTCT exposure data was only recorded for 40% of children. Furthermore, exact PMTCT regimens were not recorded, so the effect of different

regimens could not be examined. The effect of severe clinical disease at ART initiation on VF may have been reduced by combining stage 3 and 4 disease. Due to lack of detailed clinical event data as well as confounding by indication (with sicker children being preferentially switched), we were unable to determine the clinical consequences of delayed switching.

Conclusion

This study demonstrates the probability of VF in children on ART in South Africa at 3 years to be nearly 20%. The time between failure and switch and low proportion of children switched to second-line in this and other studies supports use of clearer definitions of VF and clinical practice guidelines for managing children with unsuppressed viral load, tailored to starting regimen. In addition, access to second-line drugs for PMTCT exposed children failing PI-based ART is important for better pediatric HIV care in the countries where the majority of HIV-infected children reside.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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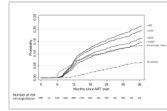
Figure 1.
Kaplan-Meier probability of virologic failure using different viral load values (measured in copies/ml) to define failure, as well as immunologic failure and switch.
Solid lines indicate virologic failure defined as two consecutive unsuppressed viral loads with the second viral load being above the threshold value indicated; dashed line indicates immunologic failure; dash-dot line indicates switch to second line.
Note: The numbers in parentheses in the risk table refer to virologic failure events defined as two consecutive viral load measurements >400 copies/ml with second viral load >1000 copies/ml and this is used as definition of failure in analyses.

Table 1

Characteristics of sites providing ART for children.

Cohort name and location	Main level of care provided	Type of clinic and payment	Target population	Most likely PMTCT intervention*	First year of paediatric ART provision	Number of children on ART
Harriet Shezi, Chris Hani Baragwanath Hospital, Soweto	All levels	Public and research, Free ART	Children only	sdNVP to mother & infant	2001	1865
Rahima Moosa Mother and Child Hospital, Johannesburg	All levels	Public, Free ART	Children and pregnant women	sdNVP to mother & infant	1999	938
Red Cross Children's Hospital, Cape Town	Tertiary	Public and research; Free ART	Children only	ZDV from 34 weeks gestation + sdNVP to mother & infant	2001	828
Tygerberg Hospital, Cape Town	Tertiary	Public, Free ART	Adults and children, separate clinics	ZDV from 34 weeks gestation + sdNVP to mother & infant	2000	591
Khayelitsha Community Health Centre, Cape Town	Primary	Public, Free ART	Adults and children, separate clinics	ZDV from 34 weeks gestation + sdNVP to mother & infant	2001	650
Gugulethu Community Health Centre, Cape Town	Primary	Public and research, Free ART	Adults and children, separate clinics	ZDV from 34 weeks gestation + sdNVP to mother & infant	2001	209
McCord Hospital, Durban	Secondary	Government subsidized not for profit hospital, Small co-payment	Adults and children, combined clinics	sdNVP to mother & infant	2003	404
Total						**5485**

*This is the PMTCT intervention available through the public health system within the province in which each site is located. It is not necessarily the intervention that each individual child attending that facility received, as individual program PMTCT regimens varied and mothers may have accessed antenatal care in other provinces/programs.

Table 2

Characteristics of children at ART initiation, failure (2nd consecutive unsuppressed viral load>1000 copies/ml) and switch.

Characteristic	All children N=5485	Children with virologic failure N=523	Children with virologic failure switched to 2nd line N=145[*]
Female	2674 (49%)	235 (45%)	51 (35%)
Median (IQR) age (months)			
At ART start	42 (15 – 82)	37 (13 – 86)	60 (16 – 94)
At failure	NA	51 (26 – 103)	74 (29 – 108)
< 12 months of age at ART start	1158 (21%)	123 (23%)	26 (18%)
Severe immune suppression			
At ART start	3690/4577 (81%)	384/447 (86%)	119/128 (93%)
At failure	NA	184/493 (37%)	57/138 (41%)
Median CD4 percent			
At ART start; n	12 (7 – 17)	10 (5 – 15); 408	7 (3 – 12); 118
At failure; n	NA	20 (14 – 26); 464	18 (12 – 25); 127
WHO Stage 3 or 4 at ART start	2887/3832 (75%)	275/374 (74%)	88/116 (76%)
Viral load > 1 million copies/ml			
At ART start	777/3745 (21%)	110/388 (28%)	29/111 (26%)
At failure	NA	13/524 (2%)	4/145 (3%)
Median (IQR) log viral load			
At ART start; n	5.3 (4.7 – 5.9)	5.6 (5.0 – 6.1); 388	5.6 (5.0 – 6.1); 111
At failure; n	NA	4.2 (3.7 – 4.9); 524	4.4 (3.9 – 5.1); 145
Weight-for-age z-score <-2			
At ART start	1759/3646 (48%)	170/329 (52%)	46/89 (52%)
At failure	NA	73/385 (19%)	22/103 (21%)
Median (IQR) weight-for-age z-score	−1.93 (−3.36 to −0.96);	−2.08 (−3.43 to −1.07);	−2.14 (−3.31 to −0.96);
At ART start; n	3646	329	89
At failure; n	NA	−0.87 (−1.74 to −0.12); 385	−0.79 (−1.74 to −0.13); 103
PMTCT exposure			
Exposed	556 (10%)	67 (13%)	14 (10%)
Known unexposed	1644 (30%)	176 (34%)	61 (42%)
Exposure status unknown	3285 (60%)	280 (53%)	70 (48%)
First-line regimen			
Stavudine & lamivudine based	4857 (89%)	420 (80%)	103 (71%)
Nevirapine as third drug	254 (5%)	45 (9%)	20 (14%)
Efavirenz as third drug	3030 (55%)	251 (48%)	88 (61%)
LPV/r as third drug	1819 (33%)	140 (27%)	10 (7%)
Ritonavir alone	382 (7%)	88 (17%)	27 (19%)

[*] Note: 8 children were switched to second-line who did not meet criteria for virologic failure but had viral load >400 copies/ml preceding switch. These children are excluded from this column.

Table 3

Univariable and multivariable associations with (a) virologic failure in all children commenced on ART and (b) switch to second-line therapy in children with at least 6 months follow-up after a second consecutive unsuppressed viral load, with the second viral load being >1000 copies/ml (Cox proportional hazards models stratified by site).

(a)

Failure definition	2 consecutive unsuppressed viral loads with the second being >1000 copies/ml			
Characteristic at ART initiation	Unadjusted HR (95% CI) n=5485	p-value	Adjusted HR (95% CI) n=3605	p-value
Age				
≥ 2 years	1	<0.001[*]	1	0.934[*]
1 – 2 years	1.37 (1.07 – 1.75)		1.02 (0.71 – 1.48)	
< 1 year	1.83 (1.47 – 2.28)		1.07 (0.74 – 1.56)	
Female gender	0.88 (0.74 – 1.05)	0.16	0.92 (0.75 – 1.13)	0.442
Viral load > 1 million copies/ml	2.05 (1.63 – 2.58)	<0.001	1.67 (1.28 – 2.16)	<0.001
Severe immunosupression	1.48 (1.13 – 1.95)	0.004	1.25 (0.94 – 1.68)	0.131
WHO stage 3 or 4 (vs 1 or 2)[§]	1.35 (1.06 – 1.73)	0.016		
Weight-for-age z-score <-3 [§]	1.34 (1.06 – 1.69)	0.014		
Third drug in regimen				
Efavirenz	1		1	
Nevirapine	1.96 (1.37 – 2.80)	<0.001	1.77 (1.11 – 2.83)	0.016
Lopinavir/ritonavir	1.36 (1.10 – 1.67)	0.004	1.07 (0.76 – 1.51)	0.701
Ritonavir alone	3.06 (2.31 – 4.04)	<0.001	2.39 (1.57 – 3.64)	<0.001
PMTCT exposure				
Unexposed /unknown	1		1	
Exposed	1.64 (1.25 – 2.14)	<0.001	1.40 (1.02 – 1.92)	0.039
Year of ART initiation[†]				
> 2005	1			
≤ 2005	0.83 (0.66 – 1.04)	0.1		

(b)

Characteristic	Unadjusted HR (95% CI) n=367	p-value	Adjusted HR (95%CI) n=229	p-value
Age in years at ART initiation (per 1 year increase in age)	1.11 (1.05 – 1.16)	<0.001	1.03 (0.87 – 1.23)	0.698
Female gender	0.64 (0.44 – 0.92)	0.017	0.72 (0.42 – 1.25)	0.244
Years on treatment at time of failure (per 1 year duration on treatment)	1.38 (1.04 – 1.84)	0.025	1.37 (0.82 – 2.29)	0.229
Log$_{10}$ viral load at failure (per 1 log increase)	1.43 (1.15 – 1.78)	0.002	1.55 (1.11 – 2.16)	0.01
Current[§] immunological failure [*]	1.08 (0.67 – 1.75)	0.75		
Current[§] CD4 % <25	2.45 (1.56 – 3.84)	<0.001	1.94 (1.07 – 3.52)	0.029
Current CD4% decline >1unit /month[†]	4.37 (2.14 – 8.92)	<0.001	6.44 (2.15 – 19.25)	0.001
Current[§] weight-for-age z-score (per 1 unit increase in z-score)	0.94 (0.78 – 1.13)	0.521	1.14 (0.90 – 1.43)	0.281

(b)

Characteristic	Unadjusted HR (95% CI) n=367	p-value	Adjusted HR (95%CI) n=229	p-value
Current weight-for-age z-score decline > 0.1 units/month[†]	1.62 (0.64 – 4.11)	0.313	2.10 (0.58 – 7.58)	0.257
Viral load decline < 1 $\log_{10}$ since ART start[*]	0.88 (0.55 – 1.41)	0.596		
PI-containing regimen	0.39 (0.25 – 0.60)	<0.001	0.40 (0.17 – 0.91)	0.03
Year of ART initiation[*]				
> 2005	1			
≤ 2005	1.10 (0.52 – 2.32)	0.803		

[*] p-values derived from Wald's test

[§] Not included in multivariable model as missing information would have limited overall number of children that could be included

[†] Not included in multivariable model as p>0.1 after adjustment for other variables in the model

[*] Not included in multivariable model

[§] Measurement taken at time of switch

[†] Difference between measurements taken at time of switch and preceding visit

Note: Reasons for children having less than 6 months follow-up after failure (n=156), were death (n=5; 3%), loss to follow-up (n=15; 10%), transfer out (n=13; 8%) and failure occurring less than 6 months before database closure (n=123; 79%).