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Virologic Failure among Children Taking Lopinavir/Ritonavir-Containing First-Line Antiretroviral Therapy in South Africa

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Abstract

Objective—To report the outcomes, clinical management decisions and results of resistance testing among a group of children who developed virologic failure on first line lopinavir/ritonavir (LPV/r)-based therapy from a large cohort of ART-treated children in Soweto.

Design—Historical cohort study

Methods—Children with virologic failure were identified from a group of 1692 children <3 years who had initiated first-line LPV/r-containing therapy since 2000 up to end November 2011. Genotyping was conducted in some children and outcomes, management decisions and resistance results were described.

Results—152 children with virologic failure on first-line LPV/r-containing ART were included. Resistance testing was performed in 75/152 (49%) and apart from a younger age (11.1 vs 15.1 months, $p=0.04$), the children with vs those without resistance testing were similar for baseline characteristics (weight, CD4, VL and time to failure). Genotyping revealed that 8/75 (10.7%) had significant LPV/r-associated resistance mutations, including 2 with intermediate DRV resistance. Among 63/75 (84%) children remaining on LPV/r-based therapy, 32/63 (51%) achieved virologic suppression, 2 of these children with significant LPV mutations. 12/152 (8%) children were switched to NNRTI-based therapy in accordance with local guidelines at the time. Of these, 4/12

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(33%) resuppressed, and the rest did not achieve virologic suppression including the 2 with LPV mutations.

Conclusions—Virologic failure of LPV/r-containing first line regimens is associated with accumulation of LPV/r mutations in children. The implications are unclear and surveillance at selected sites is warranted for long-term virologic outcomes and development of resistance.

Keywords

HIV; children; lopinavir/ritonavir; virologic failure

INTRODUCTION

The World Health Organisation (WHO) recently released consolidated HIV treatment recommendations for adults and children(1). Recommendations for children <3 years of age advise that, where possible, the protease inhibitor (PI) lopinavir/ritonavir (LPV/r) should be used as part of first-line combination antiretroviral therapy (ART). This decision was based on results from the IMPAACT P1060 study where young children (<36 months) were randomized to either start LPV/r -or nevirapine (NVP)-containing regimens. Superior virologic outcomes of LPV/r-containing treatment were demonstrated, regardless of whether there was prior exposure to non-nucleoside reverse transcriptase inhibitors (NNRTI) as part of perinatal HIV transmission prevention (PMTCT).(2, 3) With even higher levels of NNRTI resistance mutations being recently described in children <2years of age in the era of improved PMTCT strategies, there is added concern about initiating treatment with NNRTI-based therapy.(4) In most resource limited settings (RLS) nevirapine is still the initial choice in combination ART for young children. In South Africa (SA), however, LPV/r-based therapy was recommended for first-line use in infants and children <3 years since 2004.(5) Virologic suppression rates with first line treatment are reportedly high among South African children. Data from the multicenter International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration showed a more than 80% viral suppression rate over a 3 year period among 6,078 children with 9,368 child-years follow up and that the probability of failure 3 years after ART start is 19.3%.(6, 7) Included were children <3 years taking a LPV/r-containing regimen. Among the 2,102 children attending the Harriet Shezi clinic in Soweto viral suppression rates of more than 90% were demonstrated over a similar period of time; although the <3-year old age group (who were prescribed LPV/r-based ART) achieved virologic suppression at a slower rate than older children.(8) Two small South African studies demonstrated that significant PI resistance did not occur in children failing LPV/r-containing regimens.(9, 10) However, a more recent report on resistance mutations found in adults and children over a 6 year period in South Africa, shows that among 490 LPV/r recipients, 42% of whom were children, 55 (11%) had 1 LPV-resistance mutations; including 45 (9.6%) with intermediate or high level LPV resistance. (11)

The medium- to long-term outcomes and drug resistance profiles in large cohorts of children, who develop virologic failure while on LPV/r treatment as part of first line therapy, have not been described. We report the outcomes, clinical management decisions and resistance genotyping results among a cohort of children who developed virologic

failure on first line LPV/r-based therapy from a large cohort of ART-treated children in Soweto.

MATERIALS AND METHODS

This is a retrospective cohort study of HIV infected children attending the Harriet Shezi Children's Clinic (HSCC) from April 2000 to November 2011, who developed virologic failure during an initial ART regimen with LPV/r. This was defined as failure to achieve virologic suppression (VL >400 copies/ml throughout follow-up) or virologic rebound determined by two consecutive VL measures >1000 copies/ml subsequent to virologic suppression <400 copies/ml whilst on LPV/r-based therapy.

Study Setting

HSCC is a paediatric HIV clinic at Chris Hani Baragwanath Academic Hospital, a large public service, and academic hospital serving the population of Soweto in Johannesburg, South Africa. Most children access outpatient care at HSCC after referral from the paediatric wards. Antiretroviral therapy became freely available for all patients in South Africa from April 2004, although a few children attending HSCC started privately funded ART from 2000.

Standard of Care

South African guidelines at the time of the ART roll-out programme recommended that the first-line ART regimen consist of an NRTI backbone containing stavudine (D4T) and lamivudine (3TC) with LPV/r for children younger than 3 years or efavirenz (EFV) for those over 3 years or >10 kg in weight.(5) Prior to this, treatment regimens were based on what was available and affordable in SA for children. Abacavir (ABC) replaced D4T after a change in guidelines in 2010.(12) Standard treatment for pulmonary tuberculosis (TB) included rifampin, isoniazid, and pyrazinamide, with ethambutol for extrapulmonary TB cases. Children receiving LPV/r-based therapy, who were TB-co-infected received superboosted LPV/r (extra ritonavir); although sometimes the LPV/r dose was doubled.

Treatment-readiness and adherence counseling was conducted with patients by experienced lay counselors. However, there was no consistent system for recording adherence. Intensive counseling and home visits occurred where poor adherence to treatment or missed clinic visits were detected. Children were defined as defaulters if they had not returned to the clinic 6 months prior to database closure in November 2011. Regular clinical check-ups were scheduled 3-monthly. Monitoring blood tests (CD4, viral load (VL), full blood counts) were performed prior to ART initiation and 6-monthly thereafter or when clinically indicated, although from 2010 these were done annually after the first year on ART.M If a viral load was found to be elevated, this was re-tested at the subsequent clinical visit. Children who were ill or not thriving had more frequent clinic visits. For children failing first-line LPV/r-based ART, switching to NVP or EFV-based therapy was recommended. From 2010, individualized management was recommended for children failing LPV/r. (12)

Salvage therapy was difficult to access except on compassionate grounds. Where patients had significant drug resistance and/or where adherence was problematic, children sometimes

started a holding regimen with 3TC monotherapy whilst adherence issues were dealt with and salvage therapy was being sought.

Study Cohort

The TherapyEdge™ patient and clinic management database (ABL, SA) at HSCC was used to determine the children who had initiated a LPV/r-containing regimen and were treated for at least 6 months with at least 2 viral load measures post-ART initiation before the end of November 2011. Children experiencing virologic failure were retained on this dataset. Clinic doctors reviewed the charts for all children defined as treatment failures, seeking to confirm against the electronic database, dates such as birthdate, treatment initiation, resistance testing or switch to a second-line regimen. The chart review also included; checking the viral load data, whether resistance tests were done and whether the children had received TB treatment. The database was corrected and a final cohort was identified for analysis.

Laboratory tests

Laboratory tests were performed at the National Health Laboratory Services (NHLS). Plasma viral load was initially measured using the AMPLICOR HIV-1 MONITOR Test, v1.5 (Roche) with the lower and upper limit of detection at 400 RNA copies/mL and 750,000 RNA copies/mL respectively, and subsequently a NASBA-based viral load assay (Nuclisens EasyQ, Biomerieux) with lower and upper limits of detection at 25 and 3 million RNA copies/mL, respectively. The CD4 absolute cell counts and percent were measured using flow cytometry (Beckman Coulter). During the study period, guidance for resistance testing was lacking in SA, genotypic drug resistance tests were requested based on subjective assessment of treatment failure by the clinicians caring for the children. This was not necessarily in accordance with the definition of virologic failure used for the purposes of this analysis. Subsequently in 2012, the HIV Clinicians Society of South Africa published guidelines for genotyping in children with virologic failure defined as >1,000 copies/ml on 2 occasions 3-6 months apart.(13)

Specimens for drug resistance genotyping were performed at the NHLS, Tygerberg, SA. Genotyping was performed by two-step PCR and dideoxynucleotide terminator sequencing of PR and RT using a homebrew assay that amplifies HIV-1 nucleotide positions 2250 to 4229 (HXB2 numbering), spanning the complete PR gene and RT codons 1 to 262. This method was adapted from a method by Plantier et al(14) and validated for use in our setting. (15) Resistance results were matched to patients in the final cohort. The resistance data contained resistance associated mutations and resistance interpretation data which were generated using “Sierra”: The Stanford HIV Webservice (Version 1.0) available from: <http://hivdb.stanford.edu/DR/webservices/>.

Significant lopinavir (LPV) associated resistance was defined as having at least intermediate level LPV resistance according to the Stanford HIV Drug Resistance Database i.e. the following mutations: L10F, L24I, V32I, L33F, M46IL, I47A, I50V, I54MLV, L76V, V82ATSFMC, I84V, L89V, L90M.

Ethical Issues

Approval to conduct a historical data probe was obtained from the Human Sciences Research Ethics Committee (HREC) of the University of the Witwatersrand, Johannesburg, SA.

Statistical methods

Data were analysed using R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Frequency tables were created and the Wilcoxon rank-sum test was used to analyse continuous variables, χ^2 test or Fisher's exact test was used to compare proportions, as appropriate.

RESULTS

During the study period 1692 children started LPV/r-based therapy, 1203 had sufficient follow up data to be included and 1028 achieved virologic success. After detailed chart review of 175 children who originally met criteria for a failed first-line regimen, 23 were further excluded due to; insufficient follow-up time or clinical information eg missing charts (11), starting treatment elsewhere (2), being on a clinical trial with regimens containing agents other than LPV/r or an NNRTI regimen(6), or age older than 36 months at ART start (4). Therefore 152/1203 (12.6%) children with evaluable follow-up VL data were deemed to have failed initial LPV/r-containing therapy and included in the analyses Among these 75/152 (49%) had blood sent for genotyping. The group with resistance testing was younger than those not tested (11.1 vs 15.1 months, $p=0.04$). Other than this, demographics at baseline were not significantly different between those who did or did not have resistance testing; all children demonstrated generally poor health with a low median CD4% (<15%), poor nutritional status, median WAZ <-3SD, and almost half (45%) on TB treatment. Time to virologic failure was similar amongst those who had compared to those without resistance testing, median 21.6 months (IQR 14.2, 30.5). Most children started a stavudine-containing NRTI backbone, consistent with treatment guidelines at the time (Table 1).(5)

Of the 152 children, 97 (64%) initially achieved virologic suppression and 55 (36%) never suppressed. When analyzing the baseline demographic characteristics of children according to initial suppression, the only significant difference we found was that more children who achieved initial suppression had started a stavudine-containing regimen 94/97 (96.9%) vs 39/55 (70.9%) $p<0.001$ (data not shown).

Among the 75 children with genotyping, intermediate or high-level resistance mutations to lopinavir (LPV) were detected in 8 (10.7%). Children with LPV resistance mutations were similar to those without LPV mutations in terms of prior HIV-TB co-treatment (50% (95% CI: 16%, 84%) vs 63% (95% CI: 50%, 74%) respectively), CD4 count (mean 1198 cells/mm³ (95% CI: 703, 1663) vs 1302 cells/mm³ (95% CI: 1122, 1486) respectively) or CD4 percent at last visit (mean 22% (95% CI: 15, 29) vs 29 (95% CI: 26, 31) respectively), and mean time to failure among those with vs without LPV resistance was 22 (95% CI: 17, 27) vs 24 (95% CI: 21, 28) months respectively. The proportion of children initiated on a stavudine-containing regimen in those with compared to without detectable PI resistance

was 6/8 (75%) vs 63/67 (94%). The most commonly detected resistance-associated mutation was M184V in both groups, 7/8 (88%) and 37/67 (55%) respectively. Thymidine analogue mutations (TAMS) were detected in 2/8 (25%) and 4/67 (6%), and NNRTI resistance mutations were found in 1/8 (13%) and 8/67 (12%) children with and without LPV resistance mutations respectively (Table 2).

Despite the high viral loads 63/75 (84%) children were kept on their LPV/r-containing regimen; this included 4/8 (50%) with LPV resistance and 59/67 (88%) without LPV resistance. Approximately half of all children who remained on LPV/r subsequently achieved viral suppression, with similar proportions of children with (2/4 (50%)) and (30/59 (51%) without LPV resistance mutations achieving suppression. A further 2/8(25%) with LPV resistance, switched to 3TC monotherapy as a holding regimen. (Table 3) Of all the children 12/152 (8%) switched to an EFV-containing regimen, 2/8 (25%) with, 8/67 (12%) without LPV resistance and 2/77 (3%) who had no resistance testing. Of the 12 who switched to EFV, 4 (33%), achieved virologic suppression after the switch, with neither of the 2 with LPV resistance achieving virologic suppression.

Table Supplemental Digital Content 1 details the clinical characteristics of the 8 children who developed LPV resistance. The age at ART initiation ranged from 2-36 months. Half were on TB co-treatment at start of or after commencing ART. Among the 6 children who experienced viral rebound, the time to the first detectable viral load ranged from 13.5-27.1 months (median 25 months). Most children were severely immunocompromised at baseline, but had improved immune status at their most recent visits. Of the 8 children with LPV resistance, 2 achieved virologic suppression, 2 defaulted care and 4 remained in care without achieving virologic suppression. Three children (cases 1, 5 and 8) had 5 LPV mutations: children 1 and 8 changed to 3TC monotherapy but defaulted care; patient 5 changed to EFV, remained in care but did not achieve virologic suppression. Cases 4 and 6 resuppressed whilst staying on LPV/r. Only patient 2 had NNRTI mutations. Seven patients had M184V mutations, with 5 having other NRTI mutations including TAMS. Cases 1 and 4 had intermediate level resistance to darunavir while 3 and 5 had low level DRV resistance, the rest were fully susceptible to DRV (data not shown).

DISCUSSION

We describe a large cohort of children with virologic failure after first line therapy with LPV/r as part of combination ART. Almost half had genotypic resistance testing, and in these 8/75(10.7%) had accumulated significant LPV mutations, including 2/8(25%) with intermediate DRV resistance. Among the 63/75 (84%) children who remained on LPV/r, 32/63 (51%) achieved virologic suppression. Included in these were 2 children with significant LPV mutations continuing on the LPV/r-based regimen. Only 12 children were switched to NNRTI based therapy in accordance with local guidelines at the time. Of these, 4/12 (33%) resuppressed, and the rest did not achieve virologic suppression including 2 with LPV mutations.(4)

In our study most children remained on LPV/r despite treatment failure. It is encouraging that around half achieved virologic suppression while continuing the same regimen. Weak

virologic responses may be attributed to decreased adherence or to the accumulation of PI resistance mutations. It is plausible that failure in many children was likely due to poor adherence of the unpalatable LPV/r syrup. Our data, however, clearly demonstrate that children failing an initial LPV/r regimen do accumulate significant LPV/r mutations albeit at a low level.

The clinical significance of the accumulation of LPV/r mutations in our cohort warrants further discussion since two of those with LPV resistance achieved virologic suppression while remaining on LPV/r. This is not surprising as prior to the availability of the second generation PI's darunavir/ritonavir (DRV/r) or tipranavir/ritonavir (TPV/r), LPV/r was often used in salvage therapy, and a high risk of failure was associated only with having at least 5 PI mutations.(16) Another study from South Africa also demonstrated a good virologic response in children on continued LPV/r therapy, despite the presence of LPV resistance, when compared to patients who switched to an NNRTI regimen.(17) The residual benefit could be due to the high inhibitory quotient of LPV/r (18) (requiring multiple mutations to prevent resistance) and the beneficial effect of continuous drug pressure on selecting less-fit viral variants.(19) However the response rate to LPV/r in patients with PI resistance is inferior to DRV/r or TPV/r.(20) None of the children in our cohort who had 5 or more LPV/r resistance mutations resuppressed, and 2 children had developed intermediate DRV resistance. Management decisions while awaiting salvage therapy were taken, such as using 3TC monotherapy, in the absence of good clinical evidence for doing so. The future clinical implications of maintaining failing regimens or switching to salvage therapy in the face of accumulation of these PI mutations requires further research, as does the role of resistance testing.

The number of children in our study who switched to EFV-based therapy was small, making interpretation of the results difficult. Nevertheless the relatively low rate of virologic success indicates a need to investigate this further. The rationale for WHO recommending a switch to NNRTI –based therapy in children >3 years who failed LPV/r-based therapy was based on data reported from the PENPACT 1 study, a randomised control study of older children who switched to an NNRTI-based regimen after failing a first-line PI-containing regimen, or who failed an NNRTI and switched to a PI-based regimen. Virologic responses were similar in both groups.(21) However, a report from Durban, South Africa, describes virologic outcomes of children failing first line therapy.(22) Eight children failed LPV/r-containing treatment and 6 months after regimen switch to NNRTI-based treatment, virologic suppression occurred in 2/8 (25%). NNRTIs have a lower genetic barrier than boosted PIs and require a regimen with full susceptibility to the 3 component drugs for durable suppression. Patients who failed a first-line PI regimen may have NRTI mutations or archived NNRTI mutations. This would explain the relatively low frequency of virologic suppression on an NNRTI second-line regimen in the Durban cohort and in our children.

The role of antiretroviral drug interactions with TB therapy requires further investigation. The high proportion of TB co-infection in our children is cause for concern. We have previously described a high prevalence of TB in children starting ART. In a prior report from our site, almost a third of children starting ART who were under 3 years of age were on TB treatment at ART start.(23) We have elsewhere compared the clinical outcomes of

children taking TB treatment with LPV/r-based ART to those in children who did not have TB.(24) No difference was demonstrated in virologic outcomes of children after one year, according to whether altered doses of LPV/r were used. Nevertheless, superboosting LPV/r has been found to result in therapeutic lopinavir levels (25) whilst doubling the dose of LPV/r has not.(26) There remains a scarcity of data on the outcomes of children particularly those under 3 years who require simultaneous TB and HIV medication. Continued surveillance for the development of excess treatment failure or resistance must occur, especially where drug interactions such as those between TB and ART medication are anticipated. There is urgency to investigate whether drug interactions may be reduced when newer classes of drugs are used in TB co-infected children.

Interestingly, in our group, significantly more children on stavudine-containing regimen achieved initial suppression than those on an abacavir-containing regimen. Similar data have recently been reported from another large paediatric HIV clinic in Johannesburg, where at 6 and 12 months on ART, viral suppression rate was poorer in ABC versus stavudine groups in those receiving both LPV/r- and EFV-containing regimens.(27) Why this occurs warrants active further prospective investigation.

Our study has several limitations. There were a large number of children who started LPV/r in whom we found insufficient follow-up data on the electronic data base system. These children may also have failed therapy, and we are therefore unable to make assumptions about the true proportion of children who failed in this cohort. Poor standardisation of measurements of adherence makes it difficult to determine the reason for virologic failure. The lack of data about which children had failed a PMTCT regimen also hampers our ability to interpret the NNRTI resistance mutations that were found in some children. These likely accumulated in the children subsequent to their use for PMTCT, which at the time, was the most common drug used for this purpose. The definition for virologic failure in this study was used for purposes of data analysis and was not a clinical definition at the time. It is possible that because of this some children who failed a PI-based regimen treatment might not have been included in the analysis. The variable intervals between repeat viral load testing and resistance testing make timing of virologic failure or development of resistance difficult to interpret and we may have underestimated time to failure because of this. Resistance testing was not consistently performed due to a lack of guidance. As a result some children had several tests and others were not tested at all. There is variability in the duration of follow-up after virologic failure because of the different times at which children entered the cohort. The lack of standardised management of children who had virologic failure on the LPV/r-containing regimen reflects the evidence vacuum within which the children were managed.

LPV/r-containing therapy appears to be the most potent regimen available for young children.(3) There are several challenges with using LPV/r, including poor palatability, refrigeration requirements prior to dispensing and the cost. In our study we demonstrate that significant LPV-associated resistance mutations as well as other PI including DRV mutations occur, albeit infrequently. It is encouraging to note though, that many children achieved virologic suppression whilst remaining on LPV/r after prior failure. Switching to a second-line NNRTI-based therapy may also result in subsequent virologic suppression

although perhaps less so than if LPV/r is continued. Prospective investigation of treatment outcomes and accumulation of resistance mutations is warranted at selected sites where WHO recommendations are implemented to determine the long term outcomes of using LPV/r as part of first line therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline demographic characteristics* of all 152 children who failed a LPV/r-containing first-line ART regimen, stratified by genotypic resistance testing

	All children (N=152)	Resistance test (N=75)	No resistance test (N=77)	p#
Age in months, median (IQR)	12.9 (6.7, 21.1)	11.1 (5.5, 19.9)	15.1 (7.8, 23.3)	0.04
Females, n (%)	71 (47%)	34 (45%)	37 (48%)	0.86
CD4 count (cell/ul), median (IQR)	546 (258, 1007)	594 (238, 1017)	523 (288, 935)	0.71
CD4%, median (IQR)	13.8 (9.0, 18.3)	13.2 (8.9, 17.1)	15.0 (9.1, 19.6)	0.23
Log ₁₀ viral load (copies/ml), median (IQR)	5.7 (4.9, 6.2)	5.7 (5.0, 6.1)	5.6 (4.9, 6.3)	0.44
Weight-for-age z-score, median (IQR)	-3.0 (-4.3, -1.5)	-3.2 (-4.6, -1.5)	-2.9 (-4.2, -1.4)	0.31
TB treatment, n (%)	67 (45%)	35 (47%)	32 (43%)	0.80
Time to virologic failure Median (IQR) months**	21.6 (14.2, 30.5)	21.6 (12.6, 30.5)	21.7 (15.2, 30.4)	0.6
Stavudine ART back-bone, n (%)	133 (88%)	69 (92%)	64 (83%)	0.16

NA = Not available

* Baseline for growth: measurements determined at ART start date, baseline for CD4 and viral load: most recent measurements prior to ART start date up to 6 months prior to treatment commencement

** Time to first of confirmed viral load 1000 copies/ml (97 achieved virologic suppression, 57 with and 40 without resistance testing)

Wilcoxon rank sum test was used for all continuous variables and the χ^2 test was used for categorical variables

Table 2

Clinical characteristics and presence of significant non-protease inhibitor resistance mutations in children with resistance testing, stratified by the presence of lopinavir (LPV) resistance[#] mutations

	Total (N=75)	LPV Resistance (N=8)	No LPV Resistance (N=67)
Tuberculosis treatment ever given together with antiretroviral therapy n (%)	46 (61%; 95% CI: 49%, 72%)	4 (50%; 95% CI: 16%, 84%)	42 (63%; 95% CI: 50%, 74%)
CD4 count (cells/mm ³) at last visit, mean	1291(95% CI: 1128, 1469)	1198 (95% CI: 703, 1663)	1302 (95% CI: 1122, 1486)
CD4 percent at last visit, mean	28 (95% CI: 25, 30)	22 (95% CI: 15, 29)	29 (95% CI: 26, 31)
Time to virologic failure, mean months [*]	24 (95% CI: 21, 28)	22 (95% CI: 17, 27)	24 (95% CI: 21, 28)
Stavudine ART back-bone, n (%)	69 (92%; 95% CI: 83%, 97%)	6 (75%; 95% CI: 35%, 97%)	63 (94%; 95% CI: 85%, 98%)
M184V, n (%)	44 (59%; 95% CI: 47%, 70%)	7 (88%; 95% CI: 47%, 100%)	37 (55%; 95% CI: 43%, 67%)
TAMS, n (%)	6 (8%; 95% CI: 3%, 17%)	2 (25%; 95% CI: 3%, 65%)	4 (6%; 95% CI: 2%, 15%)
NNRTI resistance mutations, n (%)	9 (12%; 95% CI: 6%, 22%)	1 (13%; 95% CI: 0%, 53%)	8 (12%; 95% CI: 5%, 22%)

95% confidence intervals (CIs) were obtained using the exact binomial method for categorical variables and the bootstrap method for continuous variables.

[#] LPV resistance: L10F, L24I, V32I, L33F, M46IL, I47A, I50V, I54MLV, L76V, V82ATSFMC, I84V, L89V, L90M

^{*} Time to first of confirmed viral load 1000 copies/ml (57/75 suppressed, 6/8 with and 51/67 without LPV resistance)

Table 3

Clinical management decisions among children with resistance testing, by the presence of lopinavir (LPV) resistance[#] mutations

	Total (N=75)	LPV resistance (N=8)	No LPV Resistance (N=67)
Number remaining on protease inhibitor regimen (%)	63 (84%; 95% CI: 74%, 91%)	4 (50%; 95% CI: 16%, 84%)	59 (88%; 95% CI: 78%, 95%)
Number (%) resuppressed while continuing on lopinavir/ritonavir	32/63 (51 %; 95% CI: 38%, 64%)	2/4 (50%; 95% CI: 7%, 93%)	30/59 (51%; 95% CI: 37%, 64%)
Number (%) switched to efavirenz	10 (13%; 95% CI: 7%, 23%)	2 (25%; 95% CI: 3%, 65%)	8 (12%; 95% CI: 5%, 22%)
Number (%) switched to lamivudine monotherapy	2 (3%; 95% CI: 0%, 9%)	2 (25%; 95% CI: 3%, 65%)	0 (0%; 95% CI: 0%, 5%)

95% confidence intervals (CIs) were obtained using the exact binomial method.

[#] LPV resistance: L10F, L24I, L24I, V32I, L33F, M46I, I47A, I50V, I54MLV, L76V, V82ATSFMC, I84V, L89V, L90M