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Mortality and Long-Term Virologic Outcomes in Children and Infants Treated with Lopinavir/Ritonavir

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Abstract

Background—There is scant data on young children receiving protease inhibitor (PI)-based therapy in real-life resource-limited settings and on the optimal timing of therapy among children who survive infancy. Our aim was to evaluate outcomes at the Hospital del Niño, Panama, where children have been routinely treated with lopinavir/ritonavir (LPV/r)-based therapy since 2002.

Methods—Retrospective cohort analysis of all HIV-infected children enrolled in care between January 1, 1991 and June 1, 2011. Kaplan-Meier method and Cox proportional hazards regression were used to evaluate death, virologic suppression, and virologic rebound.

Results—Of 399 children contributing 1,944 person-years of follow-up, 254 (63.7%) were treated with LPV/r and 94 (23.6%) were never treated with antiretrovirals (ARVs). Among infants, improved survival was associated with male gender (HR_{death} 0.54, 95% CI 0.32–0.92) and treatment with highly active antiretroviral therapy (HAART) (HR_{death} 0.32, 95% CI 0.12–0.83), while residence outside of Panama City was associated with poorer survival (HR_{death} 1.72, 95% CI 1.01–2.94). Among children who survived to 1 year of age without exposure to ARVs, LPV/r-based therapy improved survival (HR_{death} 0.07, 95% CI 0.01–0.33). Virologic suppression was achieved in 42.1%, 70.5%, and 85.1% by 12, 24 and 60 months of follow up among children treated with LPV/r. Virologic suppression was not associated with prior ARV exposure or age at initiation of therapy but was associated with residence outside of Panama City (HR_{suppression} 1.93, 95% CI 1.19–3.14). Patients with a baseline viral load > 100,000 copies/mL were less likely to achieve suppression (HR_{suppression} 0.37, 95% CI 0.21–0.66). No children who achieved virologic suppression after initiating LPV/r died.

Conclusions—LPV/r-based therapy improved survival not only in infants but also in children over 1 year of age. Age at initiation of LPV/r-based therapy or prior ARVs did not impact virologic outcomes.

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Keywords

Children; HIV-infection; mortality; virologic outcomes; Lopinavir/Ritonavir

Untreated HIV-infected children have a faster rate of progression than adults.[1] After the CHER Study demonstrated that early therapy in HIV-infected infants reduced mortality by 76%, [2] the WHO recommended HAART to all HIV-infected infants.[3] Based on the high risk of mortality among HIV-infected children under 2 years, the WHO also recommended treatment for children 12–24 months of age regardless of immunologic or clinical status, despite a lack of data from randomized clinical trials.[4–6] Lopinavir/ritonavir (LPV/r)-based therapy is the preferred first line option in children under 24 months exposed to maternal or infant NNRTIs because of high rates of NNRTI resistance. [7] However, there is concern that administration of LPV/r may not be feasible in many settings due to high cost, poor palatability, and inconvenient formulation.[5, 6]

We conducted a retrospective study of HIV-infected children receiving care at the Hospital del Niño in Panama City, where since 2002 HAART became available through the Ministry of Health to all children infected with HIV. The objective of this study was to evaluate survival and long-term virologic outcomes in young children who received LPV/r-based therapy. The results of this study have implications regarding the timing of ARV initiation in children over 12 months of age and for resource-limited pediatric HIV programs expanding access to LPV/r-based therapy.

METHODS

Clinical Setting

We evaluated clinical and laboratory data of HIV-infected children receiving care at the HIV Clinic in the Hospital del Niño, which cares for approximately 80% of the children with HIV infection in Panama. In 2002, HAART became available free of charge to all HIV-infected children through a national program sponsored by the Ministry of Health. The first line antiretroviral therapy regimen approved for children less than 3 years old was LPV/r with zidovudine and 3TC. Children under 3 years old received ARV therapy regardless of viral load, immunologic or clinical status. Patients enrolled in care prior to 2002 could have received zidovudine monotherapy (1993 to 1997) or dual therapy with zidovudine and 3TC (1997 to 2002) provided by the Ministry of Health. A small proportion received triple therapy through research studies. Co-trimoxazole prophylaxis was prescribed to all HIV-infected children based on clinical or immunologic criteria. In an effort to maximize retention, patients who have missed visits are identified by periodic database review and contacted by the hospital's department of social work for reestablishment of care.

Prevention of maternal-to-child transmission (PMCT) became available in 2002 with single dose zidovudine during labor and 6 weeks of infant prophylaxis with zidovudine monotherapy. Since 2005, all HIV-infected pregnant women were also offered protease inhibitor-based antiretroviral therapy. All HIV-exposed infants received free formula for nutrition through a government program since 2008.

Laboratory Studies

Until 2000, HIV diagnosis in HIV-exposed children was confirmed by repeat ELISA at 18 months of age. In 2000, viral load testing and CD4 count became widely available. Nucleic acid sequence-based amplification (NASBA) was used to confirm HIV diagnosis from 2000–2002, followed by qualitative RNA PCR (2002–2004) and subsequently proviral DNA PCR (2004–present). HIV RNA or proviral DNA testing was performed in all exposed

infants at 6 weeks of age. Infants who had a negative test at 6 weeks had a repeat test at 12 weeks to confirm that they were uninfected. All diagnostic testing was performed at Instituto Conmemorativo Gorgas de Estudios de Salud.

Patient Population and Definitions

A list of perinatally HIV-exposed children seen in the HIV Clinic at Hospital del Niño between January, 1991 and June, 2011 was obtained from a computerized registration clinic database. Patients were identified as HIV positive by medical record review of outpatient and inpatient visits and included patients who were diagnosed via routine maternal and infant screening as well as patients diagnosed later in childhood. Data were extracted from medical records, and entered into an Access database.

Endpoints, Data Analysis and Statistical Methods

Data was analyzed as a retrospective cohort, including all HIV-infected children seen at the clinic between January 1, 1991 and June 1, 2011. Patients were classified in “active care” if not dead or lost to follow up as of June 1, 2011. Tests of trends for continuous variables were conducted using Cuzick’s method.[8] All analyses were conducted using STATA (version 12).

Demographic and clinical characteristics were compared for three endpoints: death, virologic suppression (VL <400) while on LPV/r, and virologic rebound (two consecutive VL >400 or last available VL >400 following suppression) on LPV/r. Time-to-event analyses were conducted using the Kaplan-Meier method and, where applicable, Cox proportional hazards regression for multivariable regression.

To examine the effect of ARV selection on early mortality, patients enrolled at <1 year of age were aligned on a time metric of age, entering at enrollment and exiting at death or censoring (loss to follow-up, transfer to other clinic, end of study period, or 12 months of age). In Cox regression, ARV exposure was treated as a time-varying covariate; time-fixed covariates included sex, residence outside of Panama City, and PMCT. ARV regimens were classified as LPV/r-based HAART for any regimen containing LPV/r, mono/dual ART for any regimen containing 1 or 2 ARVs, or non-LPV/r-based HAART (including any NNRTI-based regimen, non-LPV/r PI-based regimens [boosted and non-boosted], and regimens with 3 NRTIs). For children with baseline CD4% available, a separate regression also including baseline CD4% was conducted as a sensitivity analysis.¹⁵ To analyze the effect ARV on mortality among children who survived the first year of life, the above analysis was repeated for all those alive at 12 months of age and the subset who were both ARV-naïve and alive at 12 months of age.

To investigate time to virologic suppression, all participants who started LPV/r and with 1 subsequent VL were aligned on a time metric of months since LPV/r initiation. Suppression was defined as first VL <400 copies/mL; participants were censored when switched to a non-LPV/r-based regimen, transferred to another clinic, lost to follow-up, or at time of last VL. We compared time to suppression among children who enrolled in infancy and started LPV/r at <1 or 1 year of age. Cox regression covariates included sex, residence outside of Panama City, PMCT, and exposure to previous ARV. Baseline VL was added as a categorical covariate for sensitivity analysis.

To assess the durability of virologic suppression, time to virologic rebound was analyzed in all participants who achieved virologic suppression while on LPV/r and with 1 subsequent VL available. Participants were aligned on a time metric of months since virologic suppression, exiting at virologic rebound (first of two consecutive VL > 400 copies/mL, or last VL if > 400 copies/mL) or censoring (switch to non-LPV/r regimen, transfer, loss to

follow-up, or time of last VL). Cox regression covariates were identical to those used for suppression.

Human Subjects Review

This study was approved by the Hospital del Niño and Johns Hopkins Institutional Review Boards.

RESULTS

Baseline characteristics

Characteristics of the 399 children enrolled in care between 1993 and 2011 are shown in Table 1. Half (51.9%) of the children enrolled in care after HAART became widely available (2002), a third (33.1%) when dual therapy (AZT/3TC) was offered (1997–2001), and 15.0% when only AZT monotherapy was available (1993–1996). About half (53.1%) of children enrolled before 1 year of age. Over the study period, median time from enrollment to initiation of any ARV decreased (4.5 months < 1997 , 2.5 months $1997-2001$, 1.1 months 2002 , $P_{\text{trend}} < 0.001$). Among patients treated with LPV/r, 35.4% started therapy with a CD4 $> 25\%$ and 20.5% without a baseline CD4. Overall, 207/399 (51.9%) of all children and 86/148 (58.1%) of children without baseline CD4% available were diagnosed with an opportunistic infection (OI) or hospitalized within one year of entering the study.

Mortality among children who enrolled at < 1 year of age

To evaluate the effect of HAART on infant mortality, we limited our analysis to the 202 children who enrolled in care before one year of age and had at least one follow-up visit after enrollment. The median age of enrollment among infants was 14.4 weeks. Approximately half (102, 50.5%) never received ARV, 36 (17.8%) received mono- or dual-therapy, 58 (28.7%) HAART, and 6 (3.0%) mono or dual ARV followed by HAART. Because only 11 children received non-LPV/r-based therapy, we were unable to compare mortality between LPV/r containing regimens and other HAART. The infant mortality rate was 94.0 (71.6–123.4) deaths per 100 child-years among untreated children, compared to 25.7 (9.7–68.6) per 100 child-years among those receiving dual therapy, and 23.5 (10.6–52.3) per 100 child-years among those receiving HAART (Table 2). Among female infants, the mortality rate was 78.5 (56.9–108.3) deaths per 100 child years; for male infants, 50.8 (34.3–75.1) deaths per 100 child-years. Overall, 28 infants died within 2 weeks of enrollment (1 received HAART, none received mono or dual therapy, and 27 were untreated). Six infants who received HAART died- all within the first month of therapy (range 4 to 31 days).

In a Cox proportional hazards model including gender, residence outside Panama City, PMCT, and ARV exposure, HAART and male gender were associated with lower mortality, while residence outside Panama City was associated with higher mortality (Table 3). Adjustment by CD4 percentage removed the effects of gender, HAART, and residence but this analysis was limited by a large number of missing values (Table 3).

Mortality among children who survived to 1 year of age

Next, we explored the effect of HAART on the 272 HIV-infected children in our cohort who survived to 1 year of age (“survivors”) and had ≥ 1 follow-up visit. Approximately half (140/272, 51.5%) of these children enrolled in care after infancy (median age at enrollment = 1.62 years, IQR 0.31 to 2.59 years). Of these children, 86/272 (31.6%) had a baseline CD4% $> 25\%$ and 62/272 (22.8%) had no baseline CD4% available. Within one year of study entry, 135/272 (49.6%) were hospitalized or diagnosed with an OI, including 31/62 (50%) of those without a baseline CD4%. 47/272 (17.3%) had received LPV/r before 1 year

of age. From 12–72 months of age, most of these children (210/272, 77.2%) received HAART; of these, 141 (67.1%) received only LPV/r-based regimens, 29 (13.8%) only non-LPV/r-containing regimens, and 40 (19.0%) both LPV/r and non-LPV/r-containing HAART. Only 31 (11.4%) received only mono- or dual- therapy, and 31 (11.4%) no therapy. Overall, mortality rates were lowest among children receiving a LPV/r-based regimen (0.43 per 100 child years, 95% CI 0.11–1.72), followed by non-LPV/r-based HAART (1.85 per 100 child years, 95% CI 0.46–7.41) (Table 2). Mortality rates among untreated children (7.27 per 100 child years, 95% CI 4.13–12.81), and children receiving mono- or dual- therapy (13.70 per 100 child years, 95% CI 8.11–23.13) were higher than among those who received HAART (Table 2). In multivariate analysis adjusting for gender, residence outside Panama City, PMCT, and ARV exposure, treatment with a LPV/r-based regimen was associated with significantly higher survival (Table 3). We were unable to adjust for CD4 percentage due to missing values.

In the subset of 187/272 children who survived to 12 months of age without ARV exposure (“ART-naïve survivors”), treatment with LPV/r-based HAART was also associated with markedly improved survival (Table 2). Of these children, 53/187 (28.3%) had a baseline CD4% > 25%, while 45/187 (24.1%) had no baseline CD4% available; 79/187 (42.2%) were hospitalized or diagnosed with an OI within one year of study entry. No deaths occurred among any ARV-naïve children prescribed LPV/r-based HAART, precluding multivariable analysis in this subgroup.

In order to explore the possibility that censoring participants classified as “lost to follow-up” could underestimate mortality, mortality analyses were repeated using a composite outcome of loss-to-follow-up and death. In this secondary analysis, no significant changes were seen in patterns of infant mortality or mortality among those surviving to 1 year without ARV therapy.

Virologic suppression among patients receiving LPV/r

Among 209 children who received LPV/r and had viral load monitoring, 150 achieved virologic suppression. Forty-two percent of patients achieved virologic suppression one year after initiation of therapy, 70.5% by two years on therapy, and 78.4% by three years. Factors associated with virologic suppression were evaluated in a Cox proportional model including gender, place of residence, age at LPV/r initiation, PMCT, prior ARV, and baseline VL. Children living outside of Panama City more readily achieved virologic suppression (HR 1.93, 95% CI 1.19–3.14) (Table 4), while baseline VL >100,000 copies/ml was negatively associated with suppression (HR 0.37, 95% CI 0.21–0.66) (Table 4). Prior exposure to ARV or PMCT was not associated with virologic suppression in children receiving LPV/r. There was a non-statistically significant trend towards more rapid suppression among children who initiated LPV/r based therapy at an early age (Table 4.).

We also evaluated whether virologic suppression within 6 months of initiating therapy was associated with improved survival. No deaths occurred in patients who achieved virologic suppression, regardless of time to suppression, while 2 deaths (2.82/100 py, 95% CI 0.70–11.26) occurred among children who never suppressed their viral load.

Virologic rebound among patients who achieved virologic suppression on LPV/r

Among 135 patients who achieved virologic suppression and had subsequent viral load monitoring, 48 experienced virologic rebound. The proportion of patients with virologic rebound was 13.5% at one year, 22.2% at 2 years, and 39.1% at 3 years after virologic suppression.) Multivariate analysis adjusting for gender, place of residence, age at LPV/r initiation, PMCT, or prior ARV did not identify any factors associated with virologic

rebound (Table 5). Two thirds (32/48) of the children who experienced virologic rebound achieved virologic suppression subsequently. Results of HIV genotype testing performed in 18 children who experienced virologic failure while on LPV/r are available in the supplementary materials, Supplemental Digital Content 1, <http://links.lww.com/INF/B622>.

DISCUSSION

This cohort provided a unique opportunity to explore long-term outcomes in young children receiving LPV/r-based therapy. As expected, children who enrolled in care during infancy and received HAART before one year of age had markedly improved survival, but girls had higher mortality than boys. In addition, children who survived to one year without HAART also benefited from therapy, even though many had no baseline CD4 or had CD4 > 25%. Virologic suppression among children treated with LPV/r-based therapy was not affected by prior ARV exposure or age at therapy initiation. There were no deaths among children who suppressed on a LPV/r-based regimen, even if the time to achieve virologic suppression was prolonged. These results support early therapy for all HIV-infected young children, even in settings without capability to assess CD4 at baseline. The excellent outcomes in children who ultimately achieve virologic suppression with a LPV/r-based regimen suggests that clinicians should not discontinue LPV/r-based regimens prematurely due to concerns about resistance, but rather strengthen interventions to promote adherence in children with delayed virologic suppression or viral rebound.

Consistent with other studies, ARV markedly improved survival among infants. However, the high infant mortality in our cohort highlights the challenges of initiating timely HAART in real life clinical settings. Our cohort included severely immunocompromised infants, with a high proportion dying within 2 weeks of enrollment in care. Even though all infants in the CHER study had a CD4 >25% at enrollment, 61% in the deferred therapy group received HAART within 6 months of randomization based on clinical or immunologic deterioration. [2] Similar mortality rates among treated infants in our cohort (23.5/100 py) and infants randomized to deferred treatment in the CHER study (21.2/100 py) suggest that the Panamanian infants received the equivalent of deferred therapy, even if the policy at the clinic was to treat all infants with HAART.

Worse outcomes in infant girls compared to boys, even among those treated with ARV, is concerning but consistent with other studies.[9–11] In our study, the effect of gender on mortality was only observed in children under 12 months and disappeared after controlling for CD4 count. This suggests that higher mortality in infant girls may have been associated with later presentation to care. We were unable to evaluate whether other social factors, such as gender-based differences in parental attention, adherence to ARV therapy and health care follow up, explained the lower survival in infant girls. However, special attention should be paid identify structural factors that could negatively affect outcomes in HIV-infected girls.

The young age of enrollment in our study allowed us to evaluate outcomes in children who survive to one year of age without HAART. In our setting, CD4 count testing was not always available, but most ARV-naïve children who survived infancy after 2002 received LPV/r-based therapy even if they had a high CD4 percentage or no CD4 evaluation at baseline. Survival among children who received LPV/r-based therapy after infancy was significantly higher than among untreated children > 1 year of age, with mortality rates comparable to those in developed countries.[12] Our finding that LPV/r-based therapy reduced mortality in children who survived infancy has important implications for other resource-limited settings where CD4 count monitoring capabilities may be limited. Although we could not analyze the effect of baseline CD4 on HAART outcomes due to missing data, a

high proportion of children initiated therapy with a high CD4, suggesting that early therapy in young children may be beneficial regardless of immunologic status.

In our cohort, virologic suppression was achieved in 85% of children treated with a LPV/r-based regimen by 60 weeks of follow-up, but the rate of suppression was slower than reported in other studies, possibly because of a younger age at initiation of therapy.[13–16] Randomized pharmacokinetic studies have demonstrated lower LPV/r levels among infants < 6 weeks of age compared to older children[17, 18] and the poor taste of liquid LPV/r formulations is thought to impact compliance with therapy in young children. However, clinical trials have not demonstrated differences in long term virologic outcomes by age group in children treated with LPV/r.[16, 19] We found that infants who initiated therapy at < 12 months of age had equal rates of virologic suppression as older children. Consistent with the high genetic barrier to resistance for boosted PIs, the probability of virologic suppression was not associated with prior treatment experience. Similar to other studies in children failing LPV/r-based therapy, the prevalence of protease inhibitor mutations was low despite repeated episodes of virologic failure, suggesting that many failures are due to non-adherence.[20] In contrast, approximately one fourth of children acquired NNRTI resistance after only one interruption of NNRTI-based therapy.[21] The lack of association between time to virologic suppression and mortality in our cohort emphasizes the importance of persevering with therapy, and utilizing viral load monitoring to target patients in need of adherence interventions.

We were surprised that children living outside of Panama City (> 10 km away from the clinic) appear to more readily achieve virologic suppression compared to children living in close proximity to the clinic. A recent Ugandan study also found better adherence among rural than urban HIV-infected children, leading the authors to hypothesize that a higher level of parental interaction and lower peer pressure among rural children may contribute to better adherence [22]. In our study, parents who invested significant time and resources to travel from outside Panama City, in order to maintain their child on LPV/r-based HAART and regular virologic monitoring, likely represent a subgroup of rural parents especially committed to healthcare. Improved suppression among rural patients may result from a combination of environmental factors and parental self-selection, but is unlikely to represent the overall experience of rural patients – especially those who never access the clinic due to lack of resources or other barriers.

There are several limitations to our study. This was a retrospective study and there was missing information, particularly regarding baseline viral loads and CD4 counts. We were careful to analyze separate cohorts by age at enrollment to avoid survival bias, but our untreated controls included children who enrolled in care before HAART became available. While clinical practice in other respects (such as use of TMP/SMX prophylaxis or vaccination regimens) did not change substantially before and after 2002, it is possible that unmeasured variables affected mortality rates during different time periods. Although LPV/r-based therapy appeared to be slightly superior to non-LPV/r-based HAART among children older than 12 months, there were few children who received non-LPV/r-based therapy and our study was not designed to compare different HAART regimens.

The findings from this operational study in a pediatric clinic can inform other resource-limited settings enrolling young children in care and using LPV/r as first line therapy. The benefits of LPV/r-based therapy were clear in all age groups, regardless of immunologic status, especially among children who achieved virologic suppression. The high infant mortality despite HAART points to the challenges of delivering early therapy in clinical settings and highlights the importance of improving early detection and linkage to care for HIV-exposed infants. Interventions should pay special attention to girls, who appear to have

a higher risk of death. Excellent outcomes among children who achieved virologic suppression on LPV/r, regardless of age or prior treatment exposure, emphasize the importance of viral load monitoring to identify children in need of interventions to improve adherence to therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics (n=399)

	Total n=399		Never received ARVs n=94		Ever on LPVr n=254	
	No.	%	No.	%	No.	%
Sex (Female)	207	(51.9%)	51	(54.3%)	132	(52.0%)
Status						
Active	182	(45.6%)	0	(0.0%)	180	(70.9%)
Dead	129	(32.3%)	79	(84.0%)	18	(7.1%)
Lost to follow-up	29	(7.3%)	10	(10.6%)	13	(5.1%)
Transferred to other clinic	51	(12.8%)	4	(4.3%)	36	(14.2%)
Transferred to adults	8	(2.0%)	1	(1.1%)	7	(2.8%)
Mode of transmission						
Perinatal	371	(93.0%)	83	(88.3%)	242	(95.3%)
Sexual	10	(2.5%)	4	(4.3%)	5	(2.0%)
Transfusion	7	(1.8%)	2	(2.1%)	3	(1.2%)
Unknown	11	(2.8%)	5	(5.3%)	4	(1.6%)
PMCT						
Yes	23	(5.8%)	6	(6.4%)	16	(6.3%)
No	349	(87.5%)	83	(88.3%)	216	(85.0%)
Unknown	27	(6.8%)	5	(5.3%)	22	(8.7%)
Race						
White	5	(1.3%)	0	(0.0%)	5	(2.0%)
Mestizo	124	(31.1%)	2	(2.1%)	116	(45.7%)
Black	44	(11.0%)	5	(5.3%)	36	(14.2%)
Indigenous	40	(10.0%)	7	(7.4%)	27	(10.6%)
Other	3	(0.8%)	0	(0.0%)	3	(1.2%)
Unknown	183	(45.9%)	80	(85.1%)	67	(26.4%)
Distance (binary)						

	Total n= 399		Never received ARVs n=94		Ever on LPVr n=254	
	No.	%	No.	%	No.	%
Panamá City	149	(37.8%)	38	(41.8%)	93	(36.9%)
Outside of Panamá City	245	(62.2%)	53	(58.2%)	159	(63.1%)
Cohort (date of enrollment)						
Before 1997	60	(15.0%)	27	(28.7%)	18	(7.1%)
1997 – 2001	132	(33.1%)	34	(36.2%)	71	(28.0%)
2002 and after	207	(51.9%)	33	(35.1%)	165	(65.0%)
Age category at study entry (years)						
< 1	212	(53.1%)	75	(79.8%)	114	(44.9%)
1 to < 2	46	(11.5%)	5	(5.3%)	34	(13.4%)
2 to < 5	81	(20.3%)	3	(3.2%)	65	(25.6%)
5+	60	(15.0%)	11	(11.7%)	41	(16.1%)
Hospitalizations and Illnesses						
Ever hospitalized	227	(56.9%)	55	(58.5%)	137	(53.9%)
Ever hospitalized for severe malnutrition	44	(11.0%)	10	(10.6%)	23	(9.1%)
Ever had pneumonia	146	(36.6%)	30	(31.9%)	91	(35.8%)
Ever had TB	27	(6.8%)	3	(3.2%)	20	(7.9%)
Ever had an OI	71	(17.8%)	18	(19.1%)	48	(18.9%)
Baseline CD4% - First CD4% in study, categorical						
< 15%	72	(18.0%)	5	(5.3%)	49	(19.3%)
15% to < 25%	78	(19.5%)	4	(4.3%)	63	(24.8%)
25% or greater	101	(25.3%)	5	(5.3%)	90	(35.4%)
None available	148	(37.1%)	80	(85.1%)	52	(20.5%)
ARV History						
Never on any ARV	94	(23.6%)	94	(100.0%)	-	-
Ever on monotherapy	49	(12.3%)	-	-	25	(9.8%)
Ever on dual therapy	76	(19.0%)	-	-	55	(21.7%)
Ever on triple therapy	275	(68.9%)	-	-	253	(99.6%)

	Total n= 399		Never received ARVs n=94		Ever on LPVr n=254	
	No.	%	No.	%	No.	%
Ever on NNRTI	44	(11.0%)	-	-	41	(16.1%)
Ever on LPVr for 6+ months	224	(56.1%)	-	-	224	(88.2%)
Mono- or dual-therapy prior to LPVr initiation	64	(25.2%)	-	-	64	(25.2%)
Time to HAART, by cohort (median in months, SD)						
Before 1997	43.5	29.0	-	-	54.6	30.0
1997-2001	15.2	23.4	-	-	16.8	24.3
2002 and after	1.4	8.8	-	-	1.4	7.7
Age category at first HAART (years)*						
< 1	65	(16.3%)	-	-	62	(24.5%)
1 to < 2	45	(11.3%)	-	-	43	(17.0%)
2 to < 5	91	(22.8%)	-	-	83	(32.8%)
5+	74	(18.5%)	-	-	65	(25.7%)
Never started HAART	124	(31.1%)	-	-	1	(0.4%)
Ever virologically suppressed (<400) while on LPVr**						
	150	(71.8%)	-	-	-	-
Ever experienced VL rebound during study***						
	48	(35.6%)	-	-	-	-
Total	399	(100.0%)	94	(100.0%)	254	(100.0%)

* Denominator = ever received HAART (n=275)

** Denominator= on LPVr-based HAART and virologic follow up (n= 209)

*** Denominator= Achieved virologic suppression on LPVr and had viral load follow up (n=135)

ARV= Antiretroviral Therapy, LPVr/= Lopinavir/ritonavir, PMCT= Prevention of mother-to-child-transmission, NNRTI= non-nucleoside reverse transcriptase inhibitor, HAART= Highly active antiretroviral therapy

Table 2

Unadjusted Mortality Rates

	Mortality from 0–12 months of age			Mortality from 12–72 months of age					
	Deaths	Mortality rate (per 100 p-y)	[95% CI] (per 100 p-y)	All alive at 12 months		Alive and ARV-naïve at 12 months			
				Deaths	Mortality rate (per 100 p-y)	[95% CI] (per 100 p-y)	Deaths	Mortality rate (per 100 p-y)	[95% CI] (per 100 p-y)
By ARV regimen									
No ARV	52	94.0	[71.6, 123.4]	12	7.3	[4.1, 12.8]	12	7.3	[4.2, 12.9]
Mono/dual	4	25.7	[9.7, 68.6]	14	13.7	[8.1, 23.1]	6	8.6	[3.8, 19.1]
HAART (any)	6	23.5	[10.6, 52.3]						
HAART (LPV/r)				2	0.4	[0.1, 1.7]	0	0.0	-
HAART (non-LPV/r)				2	1.9	[0.5, 7.4]	2	3.2	[0.8, 12.9]
Overall	62	64.3	[50.2, 82.5]	30	3.6	[2.5, 5.1]	20	3.6	[2.3, 5.6]

ARV= Antiretroviral Therapy, LPV/r= Lopinavir/ritonavir, HAART= Highly active antiretroviral therapy

Table 3

Hazard of mortality

	Hazard of mortality (0–12 months) during infancy				Hazard of mortality (12–72 months) for children who survived to 12 months of age			
	Without baseline CD4%		With baseline CD4%					
	HR*	95% CI	p-value	HR**	95% CI	p-value	HR***	95% CI
Male sex	0.54	[0.32,0.92]	0.023	0.30	[0.08,1.12]	0.073	0.85	[0.41,1.75]
Residence outside of Panama City	1.72	[1.01,2.94]	0.046	2.75	[0.73,10.39]	0.136	0.84	[0.41,1.74]
PMCT	0.75	[0.34,1.69]	0.491	0.30	[0.03,2.76]	0.290	2.45	[0.30,20.12]
ARV Exposure								
ART-naïve	REF	REF	REF	REF	REF	REF	REF	REF
Mono/Dual	0.44	[0.16,1.26]	0.127	1.56	[0.30,8.23]	0.600	1.82	[0.83,3.96]
HAART (any)	0.32	[0.12,0.83]	0.019	1.28	[0.24,6.94]	0.776		
HAART (LPVr-based)							0.07	[0.01,0.33]
HAART (non-LPVr)							0.30	[0.06,1.40]
Baseline CD4% < 15%				6.62	[1.74,25.21]	0.006		

* n = 191 children enrolled from 0–12 months of age (excludes 11 children with missing data for 1 variable in the regression model)

** n = 104 children enrolled from 0–12 months of age with baseline CD4% available

*** n = 252 children who survived to 12 months of age (excludes 20 children with missing data for 1 variable in the regression model)
ARV= Antiretroviral Therapy, LPV/r= Lopinavir/ritonavir, HAART= Highly active antiretroviral therapy

Factors associated with virologic suppression among children treated with LPV/r for more than 6 months

Table 4

	HR *	95% CI	p-value	HR **	95% CI	p-value
Male sex	0.92	[0.66,1.28]	0.610	0.96	[0.63,1.47]	0.851
Residence outside of Panama City	1.43	[1.00,2.03]	0.048	1.93	[1.19,3.14]	0.008
Initiation of LPVr > 1 year	0.79	[0.53,1.18]	0.250	0.62	[0.34,1.13]	0.116
PMCT	1.00	[0.77,1.31]	0.989	1.18	[0.80,1.73]	0.402
Therapy prior to LPVr:						
Mono/dual	0.85	[0.57,1.28]	0.442	0.65	[0.38,1.12]	0.120
HAART	1.15	[0.75,1.75]	0.519	0.94	[0.55,1.58]	0.805
Baseline viral load prior to LPVr						
< 5,000				REF	REF	REF
5,000 to < 10,000				1.24	[0.35,4.32]	0.738
10,000 to < 100,000				0.68	[0.38,1.24]	0.210
> 100,000				0.37	[0.21,0.66]	0.001

HR= hazard ratio for *suppression*; HR > 1 indicates faster suppression., LPV/r= Lopinavir/ritonavir, PMCT= Prevention of mother-to-child-transmission, HAART= Highly active antiretroviral therapy

* n= 207 children who initiated LPV/r-based HAART and had virologic follow-up (at least one subsequent viral load). Excludes two children with unknown place of residence.

** n= 129 children who initiated LPV/r-based HAART, had virologic follow-up, and had a baseline viral load obtained prior to initiation of LPV/r

Table 5

Factors associated with virologic rebound among children who achieved virologic suppression on a LPV/r-based regimen

	HR	95% CI	p-value
Male sex	1.09	[0.61,1.96]	0.773
Residence outside of Panama City	0.63	[0.33,1.19]	0.154
Initiation of LPV/r > 1 year	1.46	[0.62,3.46]	0.390
PMCT	0.53	[0.24,1.18]	0.118
Therapy prior to LPV/r:			
Mono/dual	1.06	[0.55,2.03]	0.869
HAART	1.79	[0.93,3.44]	0.084

HR= Hazard ratio for rebound. HR > 1 indicates faster rebound., LPV/r= Lopinavir/ritonavir, PMCT= Prevention of mother-to-child-transmission, HAART= Highly active antiretroviral therapy