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SALVAGE THERAPY WITH LOPINAVIR-RITONAVIR (*Kaletra*®) IN HEAVILY PRETREATED CHILDREN

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 on behalf of the Spanish Pediatric Collaborative Group on HIV-infection in children.

Background

Triple combination therapy is the standard of antiretroviral treatment of most HIV-1 infected children and has led to a dramatic decrease in morbidity and mortality. Nevertheless, issues related to potency, compliance and tolerance pose serious drawbacks to achieve maximal suppression of viral replication. Nowadays, many HIV-1 infected children in developed countries have already been treated with several antiretroviral regimens including NRTI, NNRTI and PI. Lopinavir/ritonavir (*Kaletra*®) is a promising PI because of its durable efficacy and good tolerance. It has shown a potent antiviral effect in treatment-naïve as well as in experienced children. However the experience in heavily pretreated children, including the three families of antiretrovirals, is still scarce. Since the recent availability and approval of *Kaletra* in children in Spain, it is widely being used, mainly as salvage therapy. We report on our experience on the usage of *Kaletra* in children in 12 Spanish hospitals.

Objectives

To assess the safety of combination therapy including Kaletra in antiretroviral-experienced HIV-1 infected children.

- To determine the clinical, immunological and virological effectiveness of Kaletra-including regimens in this selected population
- To analyze possible baseline characteristics associated with virological failure

Patients and methods

The study population includes all HIV-1 infected children followed in 11 Spanish hospitals, in whom *Kaletra* has been given as salvage therapy after prior antiretroviral treatment and virological failure. Virological failure was defined as a baseline plasma HIV-1 RNA greater than 5000 copies/ml (3.7 log₁₀). Children treated with *Kaletra* with a lower baseline viral load were excluded from the analysis. Data were retrospectively reviewed until July 01, and prospectively thereafter according to a standardized protocol. Clinical assessment and laboratory determinations were done at baseline, one month, 3 months and every three months from the initiation of *Kaletra*. As of February 02, median follow-up from the initiation of the current treatment was 9.8 months (range 3-18 months). 52 children have been treated with *Kaletra* for more than 3 months. Forty-three children are evaluable at 6 months and 14 at one year after the initiation of Kaletra. All but 2 children acquired HIV-infection through vertical transmission. All children were of white race, and 58% were girls. 32 and 46% were on C and 3 categories. 86% and 57% have had prior therapy with PI and NNRTI, respectively. Adherence to treatment and tolerance was evaluated through parents and children interview.

The viral load was performed by Amplicor in most children. A level of HIV-1 RNA under 400 copies/ml was considered below the limit of detection. Children with plasma HIV-1 RNA below 400 copies/ml were considered to have 2.6 log₁₀. The dosage of lopinavir/ritonavir was 230mg/57.5 mg/m² b.i.d in children without concomitant NNRTI and 300 mg/75 mg/m² b.i.d. in those with NNRTI. The maximal dose was 400/100 mg and 533/133 mg b.i.d., respectively. 86% and 57% have had prior therapy with PI and NNRTI, respectively. All but 7 had been previously treated with PI for a median of 43 months (21-52), and 62% with NNRTI for a median of 22 months (7-61). Baseline genotypic resistance was available in 45 children. Median number of mutations associated with PI-resistance was 6 (1-11). 20 (38%) children had the K103N and 11 (21%) the Y181C mutation. Either one or both mutations were present in 61% of children.

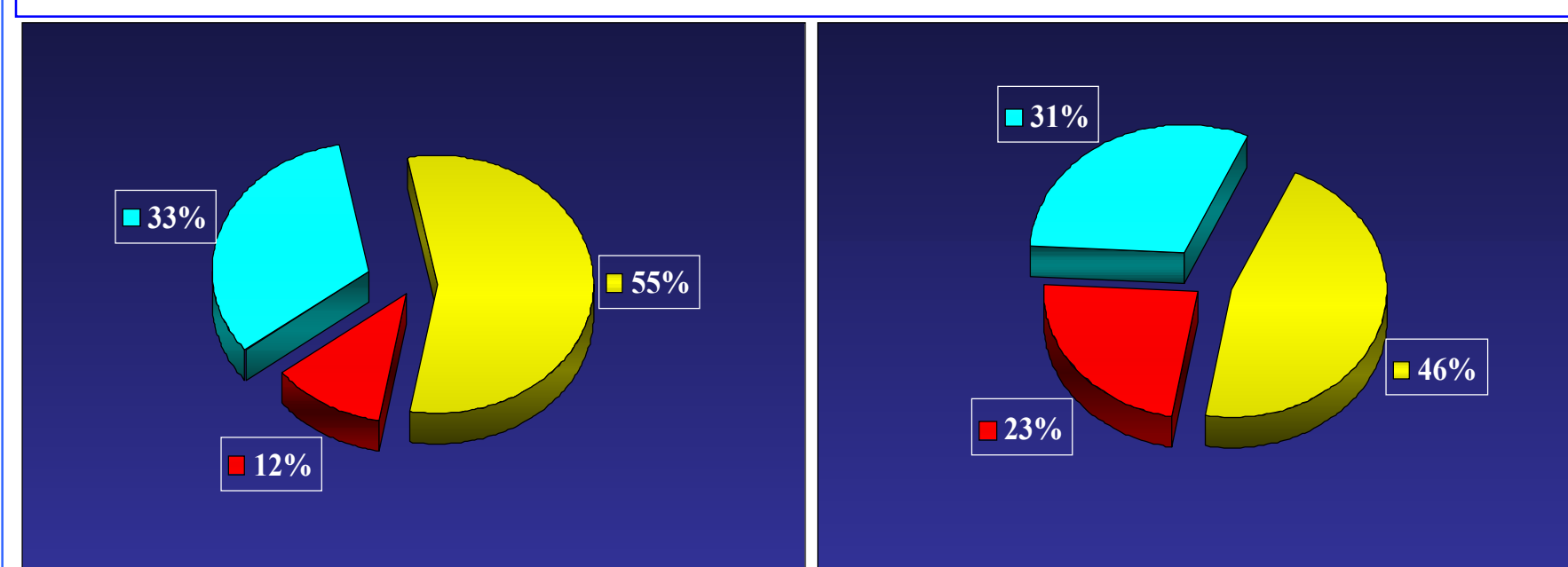
Comparative analysis was performed with regard to baseline number of PI-associated mutations (less or ≥ than 6). In addition, comparisons were made among NNRTI-naïve and NNRTI-experienced patients; and among children who had or had not another PI in the salvage regimen. Changes in continuous data were analyzed by paired-t test. Distributions of qualitative variables were compared with chi-square or Fisher's exact test. Comparative analysis between groups was done by Student's t or Mann-Whitney U test when appropriate.

Baseline characteristics of children

n	52	
Mean age ± SE* (years)	9.2 ± 0.56	
Median (range)	9.4 (1.4-17.1)	
Female	22 (42%)	
Mean absolute CD4 cells	665 ± 75	
Median (range)	532 (6-3244)	
Mean %CD4 cells	20.8 ± 1.46	
Median (range)	19 (0.5-49)	
Mean log ₁₀ plasma RNA	5.02 ± 0.08	
Median (range)	4.99 (3.92-6.08)	
	naive	experienced
NNRTI	20 (38 %)	32 (62%)
PI	7 (13%)	45 (87%)

CLINICAL AND IMMUNOLOGICAL CATEGORIES

Category A: 6 (11 %) Category 1: 12 (23 %)
 Category B: 17 (33 %) Category 2: 16 (31 %)
 Category C: 29 (56 %) Category 3: 24 (46%)



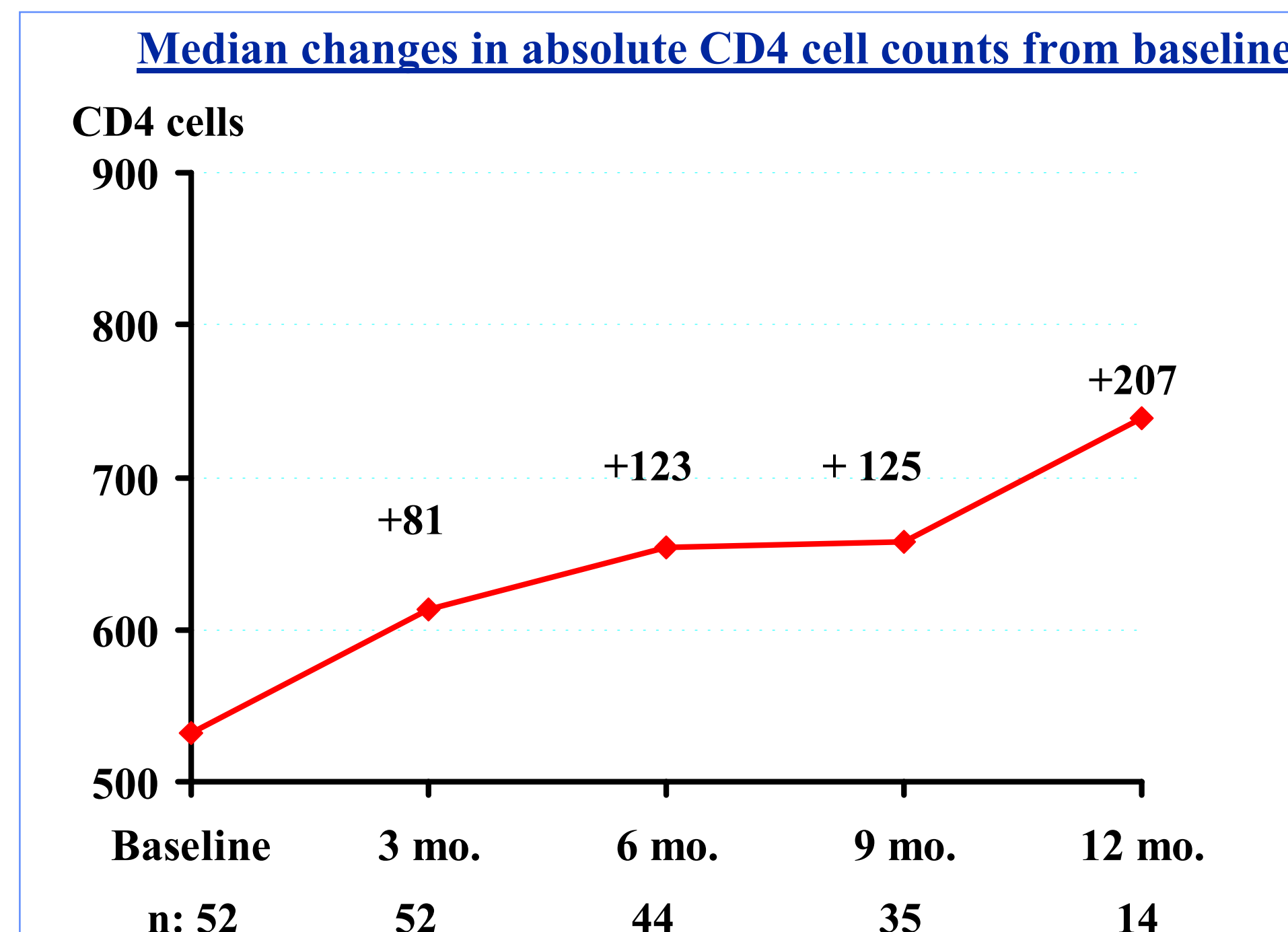
Prior antiretroviral treatment

	n	Median	Range
• AZT	49	35	0.8-108
• ddI	47	20	3.5-79
• 3TC	47	19	4-55
• d4T	49	30	1-55
• ddC	7	11	2-15
• Abacavir	17	7	0.3-19
• Nevirapine	21	17	0.2-41
• Efavirenz	31	14	1-61.5
• Ritonavir	35	13	2-55
• Saquinavir*	18	10.5	3-50.5
• Indinavir	27	21	1-35
• Nelfinavir	43	20	1-41
• Amprenavir	3	3	0.1-10

n: Number of children with the drug. Length of time in months
 * Either hard gel or soft gel

Cumulative adverse effects occurring during the study period

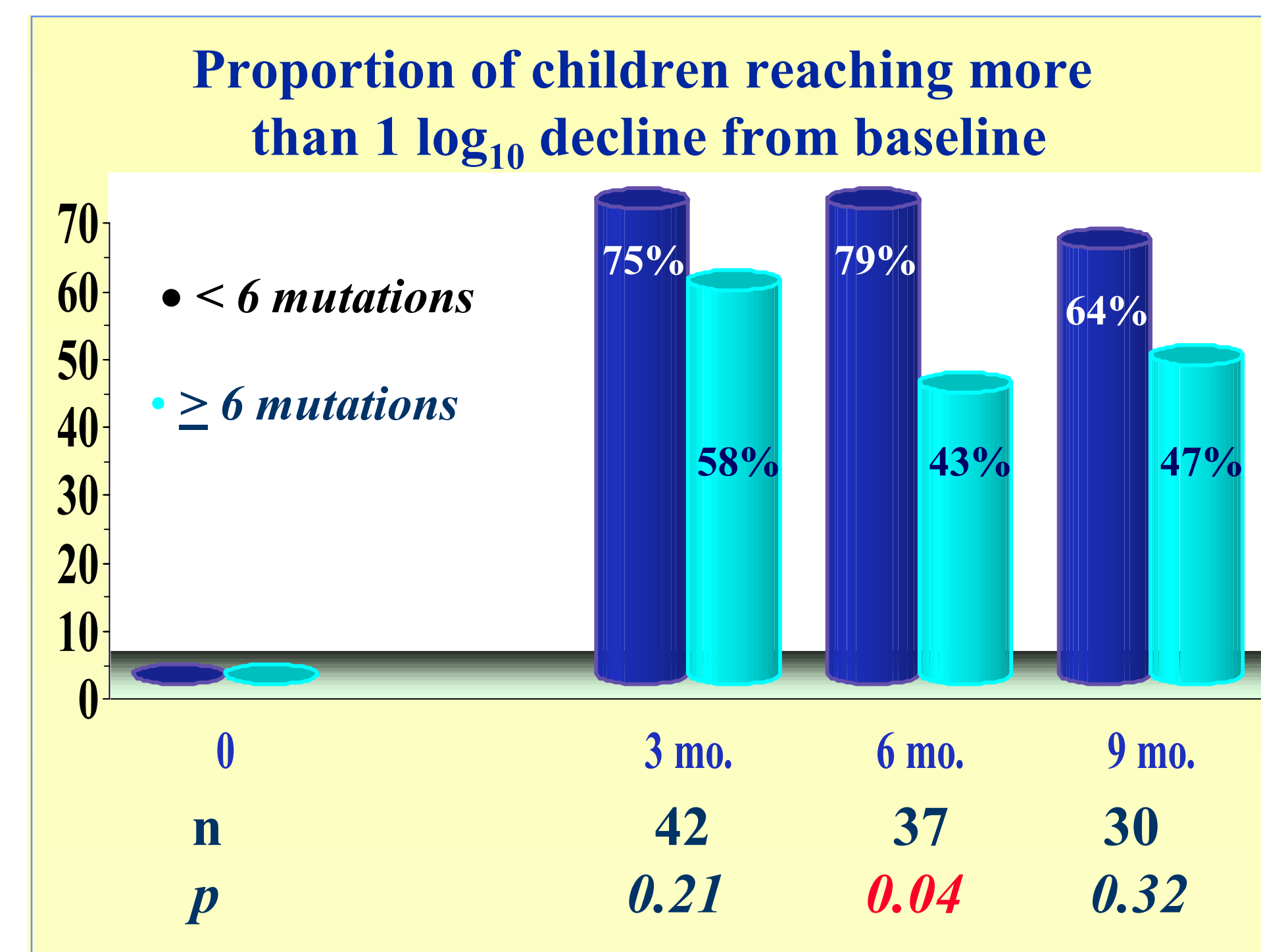
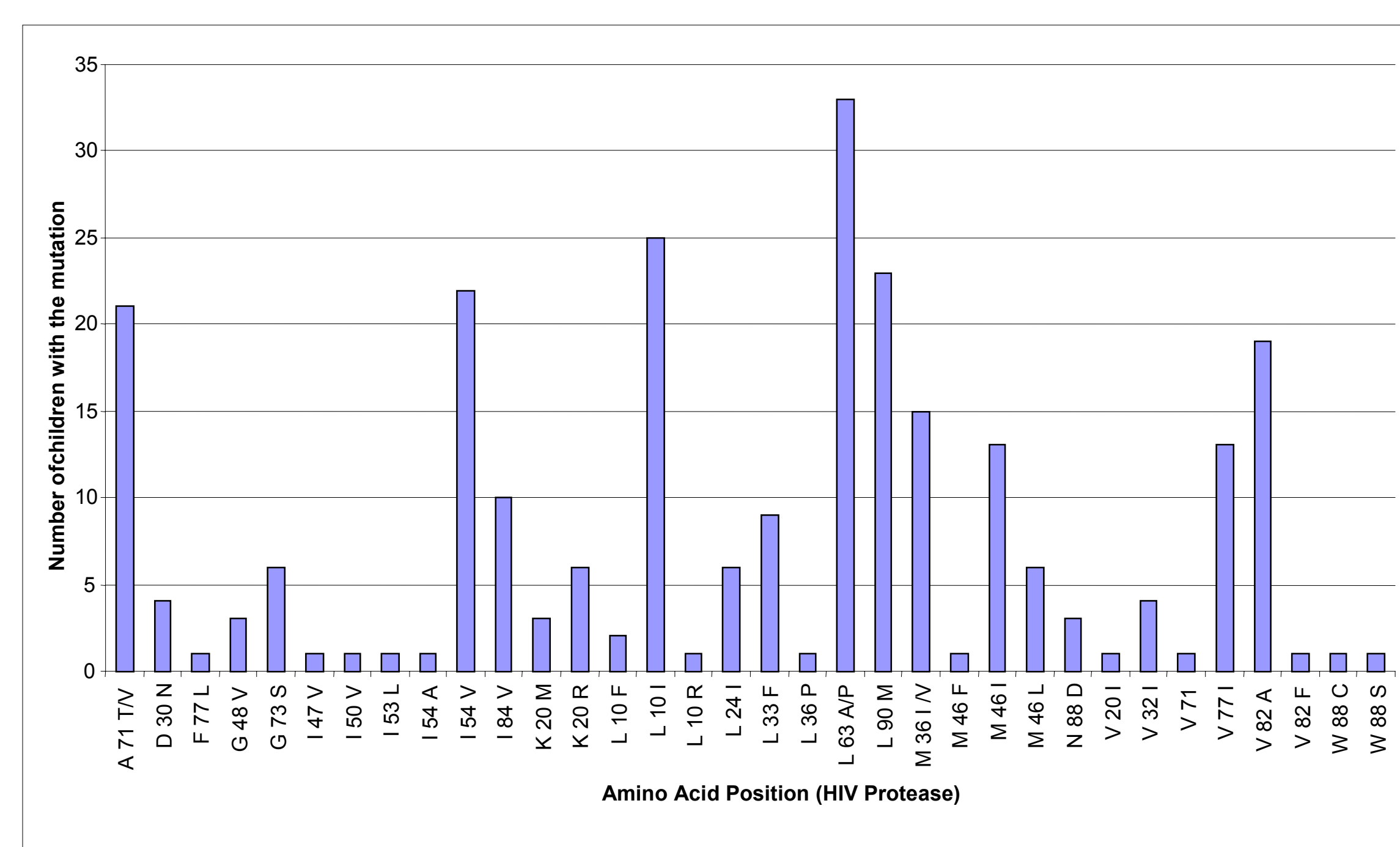
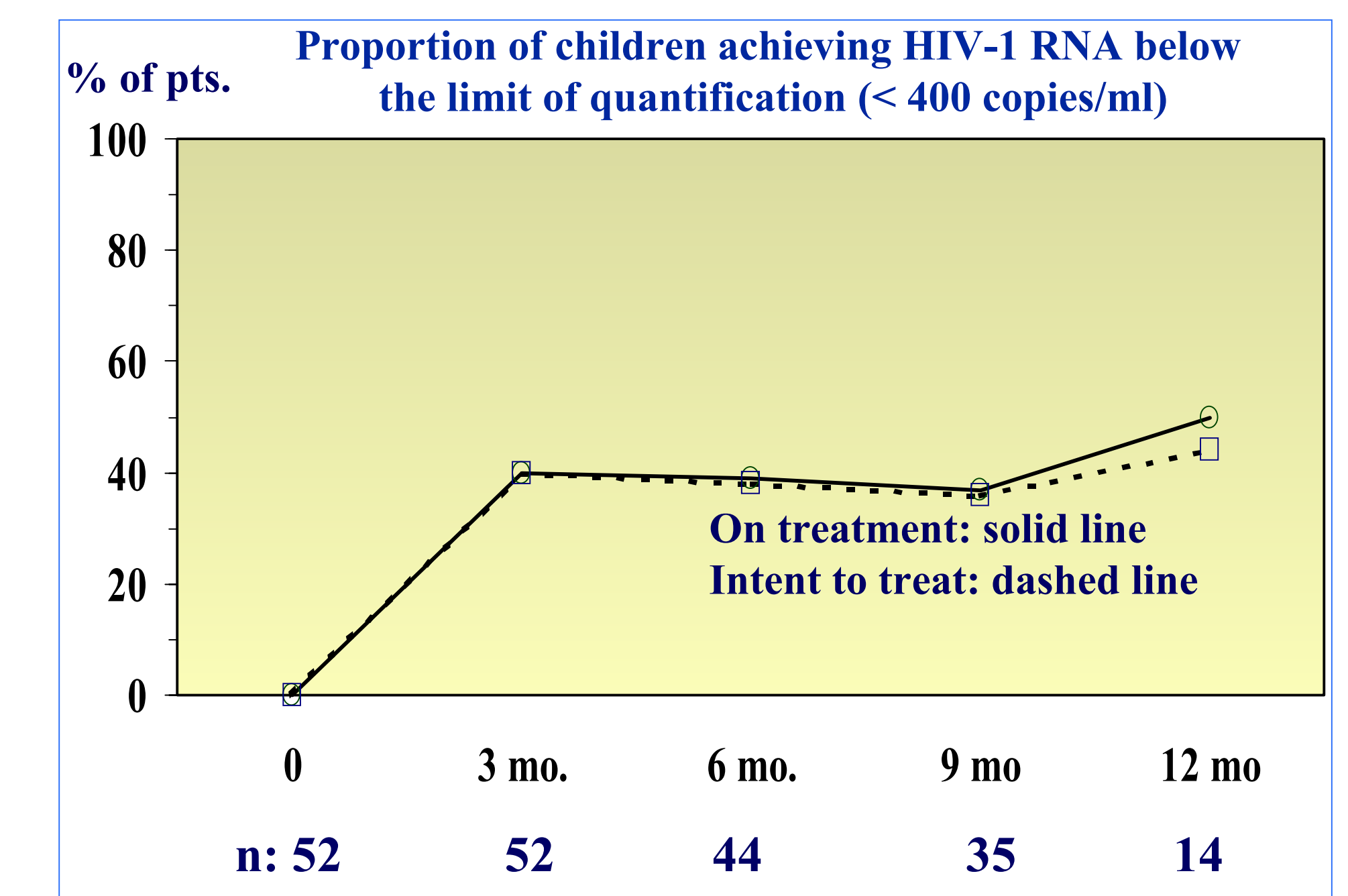
Adverse events	18 patients (35%)
Diarrhea	8 (15%)
Grade 2	7
Grade 3 (discontinue Kaletra)*	1
Rash (one also on EFV)	4 (8%)
Vomiting	3 (6%)
Abdominal pain (grade 1-2)	3 (6%)
Nausea	1 (2%)
Hypercholesterolemia at month 6 (>200 mg/dl)	18/38 (38%)
14 children (27%) had >200 mg/dl at baseline	
Median increase in cholesterolemia at 6 months was 18.5 mg/dl (0.48 mmol/l) (p:0.021)	
Hypertriglyceridemia at month 6 (>300 mg/dl)	5/37 (13.5 %)
3 children (6%) had >300 mg/dl at baseline	
Median increase in triglyceridemia at 6 months was 30 mg/dl (0.41 mmol/l) (p>0.11)	
* Withdrawal of Kaletra at 3 months	1
1 child switched 2 other antiretrovirals, maintaining Kaletra, at 12 months because of virological rebound to baseline	



Impact of Kaletra-including regimen on baseline characteristics

	Baseline	3 months	6 months	9 months	12 months
n	52	52	44	35	14
Absolute CD4	532 (6-3244)	+ 81 * (-1174, 838)	+122* (-1109, 1091)	+125* (-1754, 1038)	+207* (-390, 1006)
CD4 (%)	19 (0.5-49)	+1 * (-12, 30)	+ 2,5 * (-10, 17)	+ 3 * (-14,20)	+ 4 * (-5, 26)
Viral load (log ₁₀)	4.99 (3.92, 6.08)	-1.70 * (+0.56, -3.4)	-1.42 * (1.41, -3.52)	-1.34 * (0.48,-3.4)	2.12* (0.18, -3.4)
Undetectable %	-	21/52 40%	17/44 39%	13/35 37%	7/14 50%

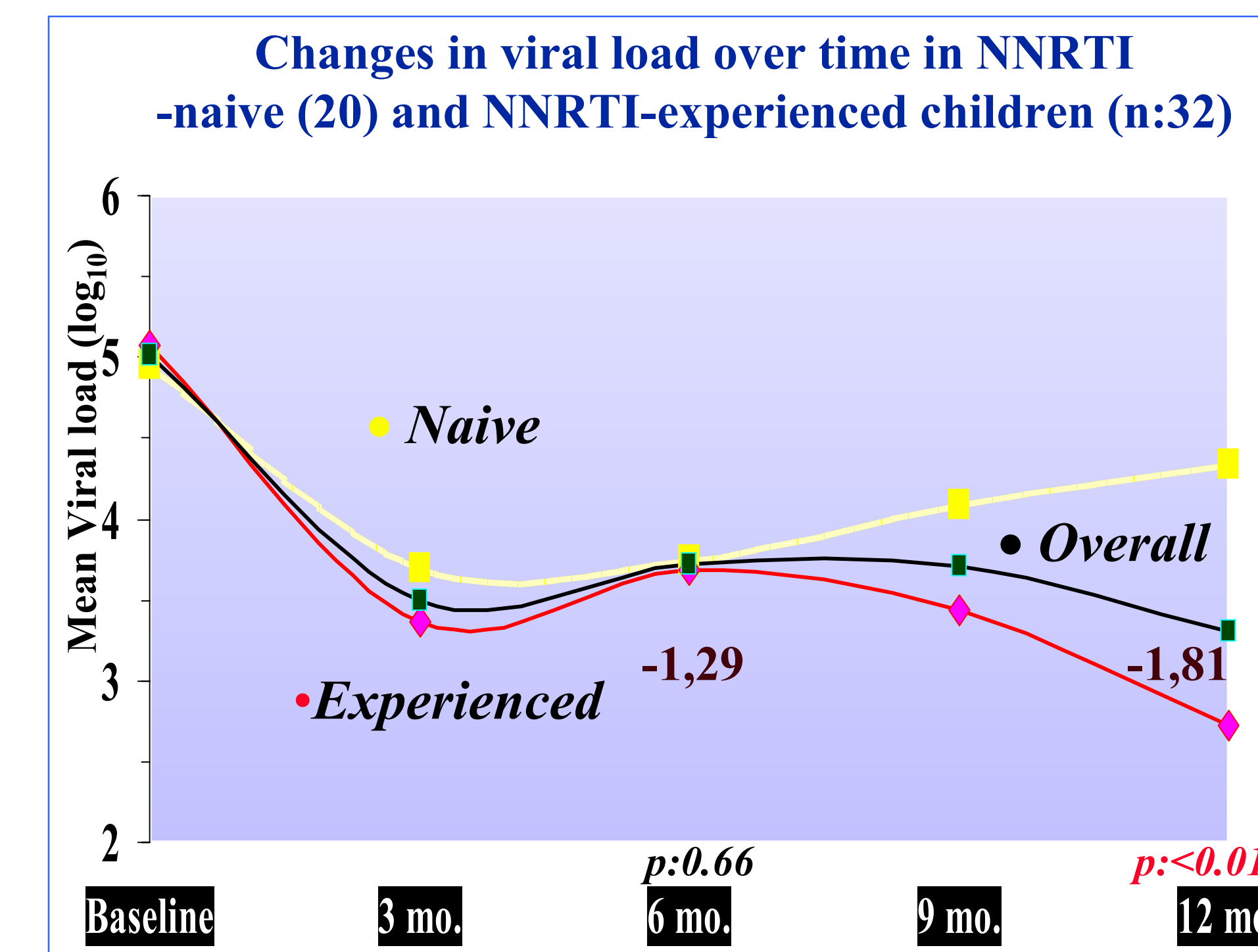
Values expressed as median (range) * p<0.05 at all timepoints compared with baseline



Univariate analysis of possible factors involved in virological response at 6 months

	n*	%>1 log ₁₀ decline	p	% BLQ**	p
Baseline Viral load <10 ⁵	20/13	65/56	0.31	44/35	0.38
Naive to NNRTI	18/27	56/63	0.4	35/44	0.36
Naive to PI	6/39	64/33	0.16	40/33	0.57
Tx with NNRTI	12/33	75/54	0.18	67/28	0.024
Tx with dual PI	5/45	62/40	0.39	42/25	0.42
No. of baseline PI mutations (<6)	14/23	79/43	0.04	39/35	0.55

*n: number of children with/without the factor. Tx: treatment
 ** BLQ: Below limit of quantification (< 400 copies/ml)



Conclusions

• Lopinavir/ritonavir has a good safety profile, and is well tolerated in the short term in HIV-1 infected children, enabling the adherence to treatment. In this study, a significant increase in plasma cholesterol, but not in triglycerides levels has been observed after treatment.

• Lopinavir/ritonavir in combination with other antiretroviral agents provide a marked clinical, immunologic and virologic improvement to most HIV-1 infected children with extensive prior antiretroviral treatment experience, including patients with previous exposure to NNRTI and PI.

• For this study population, the number of baseline genotypic mutations associated with PI has been predictive of the virological response at 6 months.