Lopinavir/Ritonavir Initiated at 7 days of Life Impairs Infant Growth

Poster #781

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INTRODUCTION

- Lopinavir/ritonavir (LPV/r) remains a key drug for therapy of pediatric HIV
- LPV/r proved efficacious as a postnatal prophylaxis in the ANRS 12274 trial among breastfed infants born from mothers not eligible for ART (at the time) with CD4 count > 350 cells/µL (1).
- LPV/r was not associated with more clinical or biological adverse events than lamivudine given in the control arm (1).
- However, a Cochrane review reported lower z-scores among HIV-infected children treated with LPV/r-based regimen compared with nevirapine-based regimen (2), but the role of HIV infection in this relationship makes the interpretation of this finding difficult.
- Among neonates, the FDA also warned against the risk of LPV/r when given to premature neonates (3).
- ***The objective of this study*** was to assess the effect of LPV/r on infant growth when given at 7 days of age until 1 year or end of breastfeeding, in comparison with lamivudine among HIV-exposed but uninfected infants.

METHODS

- The ANRS 12174 trial was implemented in 4 African countries (Burkina Faso, South Africa, Uganda and Zambia) and recruited 1273 HIV-uninfected breastfed children born from HIV-infected mothers with CD4 count>350 cells/µL and therefore not eligible for ART at the time (4). All mothers received the WHO PMTCT regimen during pregnancy, and neonates received nevirapine for their first 7 days of life.
- Children were randomized at 7 days for either lamivudine or LPV/r until the end of breastfeeding (max 50 weeks) as pre-exposure prophylaxis. Each month, weight and height were measured using standardized high-quality assessments.
- For these growth analyses, the 1266 children with available anthropometric data were censored when they stopped the study drugs.
- Z-scores were calculated and compared between arms using the linear mixed models, the Least Squares Means method at 6, 26 and 50 weeks and the spline regression models.

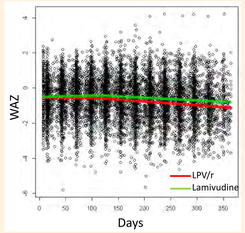
RESULTS

Baseline characteristics	Lopinavir-ritonavir (n=630)	Lamivudine (n=636)
Mothers		
Age (years)	27.1 (23.8-31.2)	27.0 (22.9-30.9)
Parity	2.8 (1.5)	2.7 (1.5)
Pre-delivery CD4 count (cells per µL)	528 (430-667)	531 (437-673)
Plasma HIV-1 RNA - Undetectable - Median (log10 copies per mL)	 274 (44%)** 3.4 (2.9-3.9)	 276 (45%)* 3.4 (3.0-3.9)
Any PMTCT regimen - During pregnancy - During labour	 607 (96%) 614 (98%)	 612 (96%) 626 (98%)
Highest education level completed - None - Primary - Secondary or tertiary	 80 (13%) 234 (37%) 316 (50%)	 85 (13%) 219 (34%) 332 (52%)
Infants		
Boys	321 (51%)	335 (53%)
Birthweight (g)	3000 (2740-3350)	3000 (2800-3325)

Data are mean (SD), median (IQR), or n (%). *19 Missing values **9 Missing values

Weight for Age Z-score (WAZ)

Comparison of WAZ between the two arms		Real Data: LPV/r n	LPV/r Mean (95%CI)	Lamivudine n	Lamivudine Mean (95%CI)	Difference of Means (95%CI)	P value	Least Squares Means: Difference of Means (95% CI)	P value
Data censored at the end of treatment	6 weeks	541	-0.54 (-0.63 ; -0.46)	547	-0.46 (-0.55 ; -0.37)	-0.08 (-0.20 ; 0.03)	0.16	-0.06 (-0.16; 0.04)	0.25
	26 weeks	474	-0.75 (-0.85 ; -0.65)	487	-0.55 (-0.65 ; -0.44)	-0.20 (-0.35 ;-0.05)	**<0.01**	-0.18 (-0.30; -0.05)	**<0.01**
	50 weeks	115	-1.09 (-1.32 ; -0.86)	128	-0.81 (-1.05 ; -0.57)	-0.28 (-0.61 ; 0.06)	0.10	-0.24 (-0.44; -0.05)	**0.02**



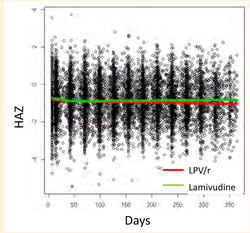
Spline regression model for WAZ

→ Overall, the Mixed Model showed a significant increase of the WAZ difference between arms over time (**p<0.01**)

→ The Spline Model confirmed this result, and showed that the WAZ difference between arms occurred early (**p=0.02**, Knot=118 days).

Height for Age Z-score (HAZ)

Comparison of HAZ between the two arms		Real Data: LPV/r n	LPV/r Mean (95%CI)	Lamivudine n	Lamivudine Mean (95%CI)	Difference of Means (95%CI)	P value	Least Squares Means: Difference of Means (95% CI)	P value
Data censored at the end of treatment	6 weeks	535	-0.92 (-1.01; -0.83)	544	-0.87 (-0.96; -0.78)	-0.05 (-0.18 ; 0.07)	0.41	-0.05 (-0.16 ; 0.05)	0.34
	26 weeks	473	-0.90 (-0.99; -0.82)	487	-0.83 (-0.93; -0.74)	-0.08 (-0.21 ; 0.05)	0.24	-0.04 (-0.15 ; 0.07)	0.46
	50 weeks	117	-1.13 (-1.34; -0.92)	130	-0.87 (-1.07; -0.67)	-0.26 (-0.55 ; 0.03)	0.08	-0.11 (-0.28 ; 0.04)	0.16



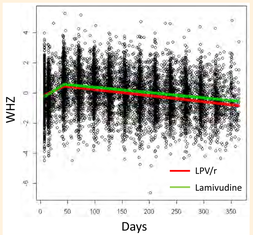
Spline regression model for HAZ

→ Overall, the Mixed Model did not show a significant increase of the HAZ difference between arms over time (**p=0.20**)

→ The Spline Model did not show a HAZ difference between arms over time either (Knot=42 days, **p=0.12**).

Weight for Height Z-score (WHZ)

Comparison of WHZ between the two arms		Real data: LPV/r n	LPV/r Mean (95%CI)	Lamivudine n	Lamivudine Mean (95%CI)	Difference of Means (95% CI)	P value	Least Squares Means: Difference of Means (95% CI)	P value
Data censored at the end of treatment	6 weeks	531	0.46 (0.35 ; 0.56)	541	0.53 (0.43 ; 0.63)	-0.05 (-0.18 ; 0.07)	0.34	-0.02 (-0.12; 0.09)	0.72
	26 weeks	471	-0.17 (-0.28 ; -0.06)	485	0.03 (-0.08 ; 0.14)	-0.20 (-0.36 ; -0.04)	**0.01**	-0.22 (-0.34; -0.09)	**<0.01**
	50 weeks	115	-0.70 (-0.94 ; -0.46)	128	-0.52 (-0.77 ; -0.27)	-0.19 (-0.53 ; 0.16)	0.29	-0.25 (-0.46; -0.03)	**0.02**

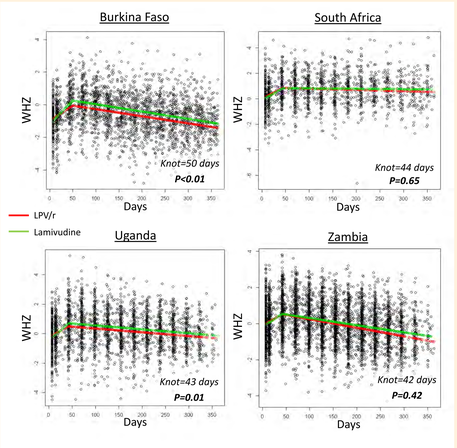


Spline regression model for WHZ

→ Overall, the Mixed Model showed a significant increase of the WHZ difference between arms over time (**p<0.01**)

→ The Spline Model showed that the WHZ difference between arms occurred very early (Knot=44 days), and slightly increased thereafter (**p<0.01**).

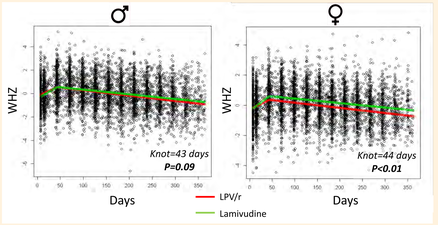
Analyses per country : Weight for Height Z-score



→ The Spline Model showed that the WHZ difference between arms occurred early and is significant in Burkina Faso and Uganda (**p<0.01** and **p=0.01** respectively).

Analyses per gender : Weight for Height Z-score

Comparison of WHZ at W50		Real data: LPV/r n	LPV/r Mean (95%CI)	Lamivudine n	Lamivudine Mean (95%CI)	Difference of Means (95%CI)	P value	Least Squares Means: Difference of Means (95%CI)	P value
Data censored at the end of treatment	Boys	65	-0.76 (-1.14 ; -0.39)	73	-0.84 (-1.14 ; -0.55)	0.08 (-0.39 ; 0.55)	0.74	-0.22 (-0.53; 0.09)	0.17
	Girls	50	-0.62 (-0.89 ; -0.36)	55	-0.09 (-0.49 ; 0.32)	-0.54 (-1.01 ; -0.06)	**0.03**	-0.28 (-0.57; 0.01)	0.05



- The results were similar for WAZ analysis by gender (data not shown).

- 1266 children for 14537 follow-up visits with anthropometric measurement, i.e. 82% of expected visits.
- Overall median of drug duration was 41.6 weeks (IQR 30.0-47.6): 41.3 weeks (IQR 28.9-47.3) in LPV/r group and 42.1 weeks (IQR 32.9-48.1) in Lamivudine group.

CONCLUSION

- When compared to lamivudine, prophylactic LPV/r given at 7 days of age for 1 year to HIV-exposed infants alters their weight-related z-scores while on drugs. This alteration occurs mainly in the first few weeks.
- The impact of LPV/r was clearly larger among girls.
- Surprisingly, the impact of LPV/r on growth was greater in Burkina Faso and Uganda than in South Africa and Zambia.
- Because the trial was randomized and enrolled HIV-uninfected children, the difference in z-score between arms can be attributed to LPV/r.
- In order to investigate whether the effect persist after drug withdrawal, infant growth at an older age among these children (5 years) will be assessed.

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