Poster Number: 843

Virological and immunological responses in infants receiving a Lopinavir/Ritonavir (LPV/r) based regimen

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Abstract

- **Background:** There are few data on virological and immunological outcomes in infants starting early ART in sub-Saharan Africa.
- **Methods:** Infants aged 6-12 weeks with CD4% ≥25%(Part A, n=411) and CD4<25% (Part B, n=40) enrolled in the CHER trial commenced LPV/r, zidovudine, lamivudine either immediately or upon clinical/immunological progression. Virological response was defined as HIV RNA <400 copies/ml and immunological response as CD4% increase ≥10% from pre-ART level, at 24 and 40 (or 48 if missing at 40) weeks after ART initiation. The association between selected factors including age at initiation and response was assessed, ignoring randomized arm, using logistic regression.
- **Results:** By end April 2009, 386 children had started ART and had data for ≥1 outcome. Median age at initiation was 8.4 (IQR 7.1 to 11.2) weeks (79% treated by 12 weeks), weight-for-age z-score -0.8 (-1.6 to 0.0) and CD4% 32% (24 to 38%).

  HIV-1 RNA was <400 copies/ml in 71% of children at 24 weeks after initiation and 77% at 40/48 weeks. Eight percent rebounded to >400copies/ml at 40/48 weeks after suppression at 24 weeks. Virological response was not associated with age at initiation (OR at 24 weeks 1.04 per 4 weeks increase, 95% CI 0.95 to 1.14, p=0.39), CD4%, weight-for-age z-score, HIV-1 RNA or gender. However, only 5/15 (33%) children with active TB diagnosed before or within 1 month after initiation on concurrent TB therapy achieved HIV RNA <400 copies/ml at 24 weeks compared to 241/334 (72%) of the remaining children (OR 0.17, 0.06 to 0.55, p=0.003); the effect of baseline TB weakened slightly by 40/48 weeks (OR 0.32, 0.10 to 0.99, p=0.05). Median change in CD4% from pre-ART level was similar at 24 weeks (7%, IQR 1% to 13%) and 40/48 weeks (7%, -1% to 13%); corresponding proportions with CD4% increase ≥10% were 33% and 32%, respectively. CD4% increase ≥10% was more likely with lower CD4% at initiation, this being the only predictor of immunological response at both time-points.
- **Conclusions:** Virological response was satisfactory in this large cohort of infants initiating LPV/r-based ART, and similar to rates in infants from well-resourced settings. Younger age at initiation was not associated with improved response, but most started ART in the first few months of life. Although numbers are small, active TB diagnosed before or around the time of ART initiation was linked to short-term virological failure. Studies of resistance are ongoing.

Background

- Current guidelines recommend early treatment in HIV infected infants and where possible, infants exposed to perinatal NVP should receive LPV/r-based regimens for first-line antiretroviral treatment (ART)
- There is little data on virological outcomes in young African infants
- LPV/r is currently the only boosted Protease Inhibitor (PI) available in infancy
- It is important to characterise virological suppression in infants who initiate ART very early in life when HIV-1 RNA values are much higher and often before the child has any signs and symptoms of disease

Objectives

To evaluate early virological and immunological (CD4) response at 24 and 40 (or 48) weeks after initiating PI- based ART in infants

Definitions of outcomes

- Virological response was defined as HIV-1 RNA <400 copies per ml
- Immunological response was defined as an increase in CD4% of ≥10% from baseline level when starting ART

Methods I

- We analysed virological suppression and immunological response in infants from the Cher Cohort (Part A and B , n=451), irrespective of randomised Arm.
- Infants entered the trial at 6-12 weeks of age, receiving LPV/r, Zidovudine and Lamivudine either immediately or when developing clinical/immunological progression. Data were analysed from time of ART initiation.
- Specimens were stored for viral load and resistance testing while CD4 sampling (absolute count and percentage) was obtained in real time
- Viral load was performed on stored specimens 24 and 40 (or 48 if missing at 40) weeks post ART initiation using the Standard Roche Amplicor monitor assay version 1.5 RNA
- Included in the main analyses were children who started ART and had data available for ≥ 1 virological and immunological outcomes

Methods II

- The associations between baseline age, CD4%, CD4 count, HIV-1 RNA, weight-for-age z-score, TB‡ and gender with virological and immunological response were examined (Table 2)
- We also assessed whether the following factors were predictive of virological success at 40/48 weeks: CD4% value and change in CD4 percentage from baseline level at 24 and 40/48 weeks, and virological response at 24 weeks (Table 3)
- All analyses were done ignoring randomized Arm

Risk ratios were estimated using a modified Poisson regression approach for analysing binary outcome data*

- Sensitivity analyses were done to include those missing HIV-1 RNA samples at the pre-defined time points due to death or loss to follow-up, who were assumed to have failed virologically

‡ Definition of baseline TB: A child was considered to have baseline TB if diagnosed with active TB before ART initiation but had not completed anti-tuberculosis treatment or if they were diagnosed within 1 month of ART initiation. Anti TB treatment included Rifampicin

**Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004; 159: 702-06*

Results

- Of 451 children enrolled between July 2005 and March 2008, 387 started ART by end of April 2009 and had data for ≥1 outcomes so were included in the main analyses (Figure 1 and Table 1)

Table 1:Baseline characteristics at ART initiation (N=387)

Median age at ART initiation: weeks (range)	8.4 (IQR 7.1 to 11.4)
Weight for age z score (range)	-0.8 (-1.6 to 0.0)
Male gender	166 (43%)
Median CD4 % (IQR range)	32% (24 to 38%)
HIV-1 RNA level >750,000 copies/ml	188 (59%)
Initiated on ART by age 12 weeks	305 (79%)
Number with active TB	15* (4%)

* 7 children were diagnosed with TB while treatment-naïve and were still on anti-tuberculosis treatment at ART initiation, while 8 were diagnosed within the first month of starting ART

VIROLOGIC RESPONSE:

- 71% (246/349, 95% CI 65-75%) achieved HIV-1 RNA was <400 copies/ml in at 24 weeks after ART initiation and 77% (245/320, 95% CI 72-81%) at 40/48 weeks
- When assuming those missing HIV-1 RNA samples due to death or loss to follow-up had failed virologically, the proportion with HIV-1 RNA <400 copies/ml was 65% and 68% at 24 and 40/48 weeks, respectively
- Only 5/15 (33%) with active TB and on concurrent TB therapy achieved HIV RNA <400 copies/ml at 24 weeks compared to 241/334 (72%) of the remaining children (RR 0.47, 95% CI 0.23–0.96; p-value=0.04) (Table 2)
- At both 24 and 40/48 weeks, virological response was not associated with gender, age, CD4%, weight-for-age z-score, HIV-1 RNA at initiation in multivariate analyses (Table 2)

IMMUNOLOGIC RESPONSE:

- A CD4% increase >10% from baseline level occurred in 33% (95% CI 28 to 38%) and 32% (95% CI 27 to 37%) at 24 and 40/48 weeks respectively
- Median change in CD4% from baseline level was similar at 24 weeks (7%, IQR 1 to 13%) and 40/48 weeks (7%, IQR -1 to 13%)

Figure 1: Flow diagram of children enrolled in CHER trial included in analyses

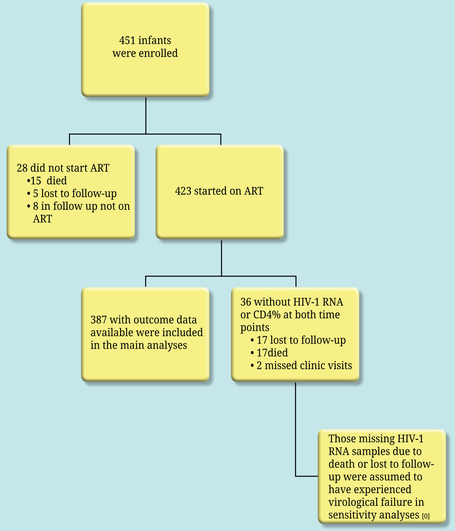

Figure 2: Percentage of children with VL <400 c/ml by age at initiation

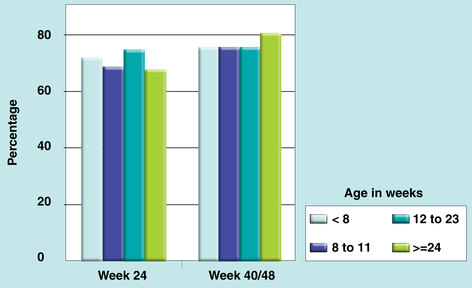

Figure 3: Percentage of children with VL <400 c/ml

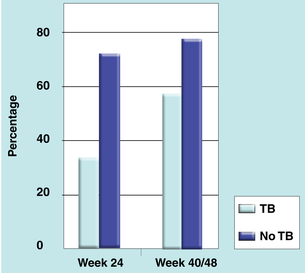

Table 2: Associations between selected baseline factors and virological and immunological response at 24 and 40/48 weeks

	HIV-1 RNA <400 copies/ml Risk ratio (95% CI)		Absolute CD4% increase>10% Risk ratio (95% CI)	
	At 24 weeks	**At 40/48 weeks**	**At 24 weeks**	**At 40/48 weeks**
Age (weeks) <8 8 -11 12-23 ≥24	1 0.98 (0.84–1.14) 1.20 (0.98–1.48) 1.00 (0.80–1.25) p=0.30	1 1.00 (0.87–1.15) 1.04 (0.85–1.28) 1.08 (0.91–1.29) p=0.79	1 0.89 (0.64–1.25) 0.58 (0.36–0.96) 0.90 (0.60–1.35) p=0.22	1 0.60 (0.32–1.13) 1.09 (0.40–2.95) 1.17 (0.51–2.70) p=0.25
Gender: female vs male	0.98 (0.86–1.12) p=0.77	0.99 (0.88–1.12) p=0.87	1.38 (1.04–1.83) **p=0.03**	1.15 (0.89–1.50) p=0.28
CD4% <25% 25-29% 30-34% ≥35%	1 0.98 (0.78–1.21) 1.03 (0.83–1.27) 1.04 (0.86–1.26) p=0.92	1 1.04 (0.88–1.23) 0.99 (0.83–1.17) 0.88 (0.74–1.04) p=0.20	1 0.66 (0.47–0.93) 0.41 (0.26–0.65) 0.26 (0.17–0.40) **p<0.001**	1 0.62 (0.45–0.85) 0.30 (0.18–0.49) 0.10 (0.06–0.19) **p<0.001**
HIV-1 RNA level (copies/mL) <300,000 300,000-749,999 ≥750,000	1.08 (0.91–1.29) 1.06 (0.88–1.27) 1 p=0.65	0.94 (0.80–1.11) 1.02 (0.86–1.21) 1 p=0.67	0.63 (0.38–1.05) 0.89 (0.60–1.33) 1 p=0.15	0.84 (0.54–1.31) 0.92 (0.57–1.48) 1 p=0.68
Active TB	0.47 (0.23–0.96) **p=0.04**	0.73 (0.46–1.15) p=0.17	0.87 (0.46–1.63) p=0.66	1.06 (0.63–1.78) p=0.82

Table 3: Virological response at 40/48 weeks - Predictive effect of virological and immunological factors after baseline

	Risk Ratio (95% confidence interval)	
HIV-1 RNA <400 copies/ml at 24 weeks	1.99 (1.53–2.58)	p<0.001
CD4% at 24 weeks, per 5%	0.99 (0.94–1.03)	p=0.56
CD4% at 40/48 weeks, per 5%	1.04 (1.00–1.08)	p=0.05
Change in CD4% from baseline at 24 weeks, per 5% increase	0.99 (0.94–1.03)*	p=0.56
Change in CD4% from baseline at 40/48 weeks, per 5% increase	1.06 (1.02–1.10)	p=0.005

* Change in CD4% from baseline at 24 weeks had a predictive effect if the change in CD4% at 40/48 weeks was not adjusted for (RR per 5% increase 1.05, 95% CI 1.01–1.08; p=0.009)

- Children with HIV-1 RNA ≤400 copies per ml at 24 weeks were twice as likely to suppress at 40/48 weeks compared to those who had failed virologically at 24 weeks (RR 1.99, 1.53–2.58; p-value<0.001)
- There was also an association between increase in CD4% at 40/48 weeks (from baseline level) and virological suppression at 40/48 weeks (RR per 5% increase in CD4% 1.06, 1.02–1.10; p=0.005)
- CD4% value at 40/48 weeks had only a weak predictive effect (RR per 5% 1.04, 1.00–1.08; p=0.05)

Conclusions

- Virological response was satisfactory in this large cohort of infants initiating lopinavir-based ART in South Africa, and similar to rates reported in infants from well-resourced settings
- Younger age at initiation was not associated with improved response but most started ART in the first few months of life
- TB diagnosed before or around the time of ART initiation was linked to short-term virological failure
- Virological suppression by 24 weeks and greater increase in CD4% from baseline level at 40/48 weeks were the only determinants of virological suppression at week 40/48
- As expected, CD4% increase ≥10% was more likely with lower CD4% at initiation, this being the only predictor of immunological response at both time-points
- We plan to relate suppression to adherence collected during the trial and to evaluate resistance patterns in children with detectable viral load

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- Support for this study was provided by the US National Institute of Allergy and Infectious Diseases (NIAID) through the CIPRA network, Grant U19 AI53217. The content of this publication does not necessarily reflect the views or policies of NIAID, nor does mention of trade names, commercial projects, or organizations imply endorsement by the US Government.
- Drug was provided by GlaxoSmithKline and the Departments of Health of the Gauteng and the Western Cape and, South Africa