Long-term metabolic implications of initiating lopinavir/ritonavir-based regimens for infants and children: a follow-up study of IMPAACT P1060

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BACKGROUND

- The IMPAACT P1060 trial provided strong evidence for the superiority of lopinavir/ritonavir (LPV/r)-based regimens as initial therapy for young children, over nevirapine (NVP)-based regimens, with regards to risk of treatment failure (*i.e.*, death, going off the LPV/r or NVP component of randomized treatment, or virologic failure by 24 weeks of follow-up).
- WHO guidelines now recommend LPV/r-based regimens as first line antiretroviral therapy for children <3 years of age.
- WHO identified the "long term metabolic implications of using LPV/r-based regimens for infants and young children" as a key research gap.

OBJECTIVES

- **To compare total cholesterol and triglycerides over 7 years of follow-up in P1060 by randomized treatment group (LPV/r vs. NVP).**
- **To compare markers of metabolic syndrome, inflammation, microbial translocation, and immune activation by randomized treatment group (LPV/r vs. NVP).**

METHODS

STUDY POPULATION

P1060 enrolled 452 HIV-infected children at 2-36 months of age from six African countries and India and randomized them to initiate treatment with zidovudine, lamivudine, and either LPV/r or NVP. One participant who did not start their allocated treatment, and two participants who had missing baseline covariate information (1 missing CD4% and 1 missing triglycerides) were excluded from this analysis, because it is necessary to have all baseline covariate information to appropriately adjust for differential censoring over the 7 years of follow-up in this study. The final study population therefore included 449 children of whom 222 were randomized to LPV/r and 227 were randomized to NVP.

A subset of the P1060 population was randomly selected by arm to have biomarkers measured. Levels of adiponectin and leptin (markers of metabolic syndrome), C-reactive protein and IL-6 (markers of inflammation), LPS (marker of microbial translocation), and sCD14 (marker of immune activation) were measured in 117 participants (26% of total) at a median (Q1, Q3) of 45 (36, 48) weeks of follow-up.

DEFINITIONS AND STATISTICAL METHODS

Total cholesterol (non-fasting) was evaluated as a continuous and categorical outcome. Borderline cholesterol was defined as 170-199 mg/dL and high cholesterol as ≥200 mg/dL. Triglycerides (non-fasting) were categorized, with high triglycerides defined as >150 mg/dL. Biomarkers were $\log_{10}$-transformed and evaluated as continuous outcomes.

Participants were followed to the minimum of the year they switched off of randomized treatment due to a non-protocol reason, the year of their first missing expected cholesterol or triglyceride measure, or through the year of their last clinic visit or patient contact in P1060. Multivariable logistic regression models including age at baseline, sex, country of enrollment, breastfeeding status, baseline WHO stage, and baseline and time-updated measures of CD4%, HIV RNA, WHO height for age z-score, WHO weight for age z-score , cholesterol, and triglycerides were used to estimate inverse-probability weights for each type of censoring.

Weighted multivariable linear regression models and modified Poisson regression models, as appropriate, were used to estimate the effect of LPV/r vs. NVP on the outcomes of interest.

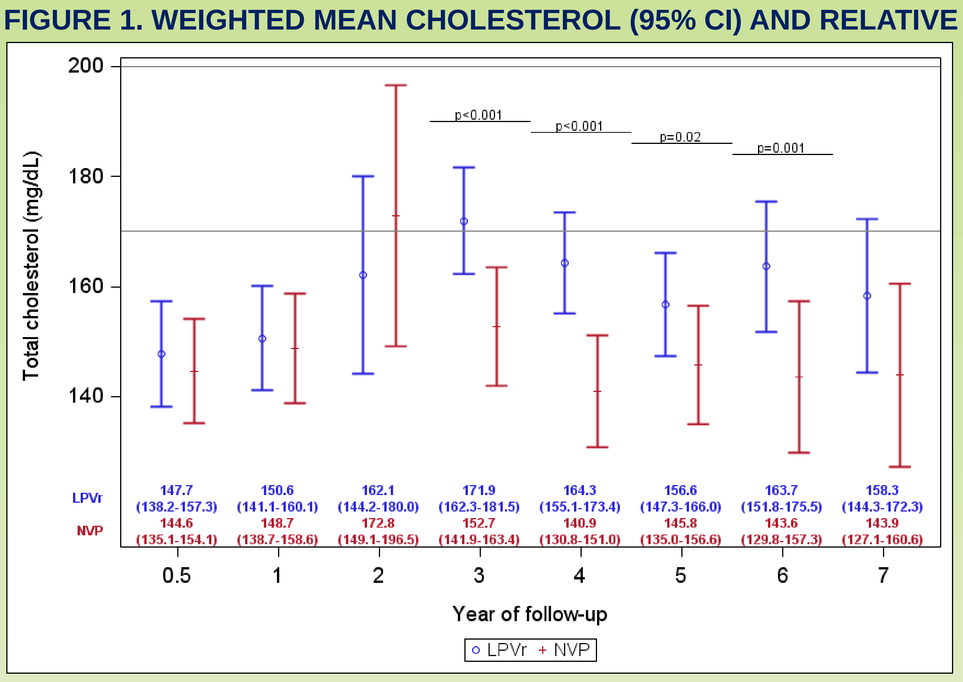
RESULTS

TABLE 1. BASELINE CHARACTERISTICS BY RANDOMIZED TREATMENT

Characteristic	LPV/r/ZDV/3TC* (N=222)	NVP/ZDV/3TC* (N=227)
Age (years)	1.2 (0.5, 2.5)	1.2 (0.5, 2.6)
Male Sex	110 (50%)	103 (45%)
South Africa	101 (45%)	112 (49%)
Breast-fed	134 (60%)	131 (58%)
CD4%	16.6 (8.0, 28.1)	16 (9.1, 27.1)
<15	90 (41%)	96 (42%)
15-24	91 (41%)	97 (43%)
≥25	41 (18%)	34 (15%)
Plasma HIV RNA ($\log_{10}$ copies/mL)	5.8 (4.8, 6.0)	5.8 (4.9, 6.0)
WHO Disease Stage		
1	43 (19%)	36 (16%)
2	49 (22%)	49 (22%)
3	115 (52%)	118 (52%)
4	15 (7%)	24 (10%)
WHO Height-for-age Z-score	-2.2 (-4.2, -0.3)	-2.4 (-4.3, -0.2)
WHO Weight-for-age Z-score	-1.6 (-3.5, 0.2)	-1.5 (-3.7, 0.4)
Total cholesterol (mg/dL)	108 (73.9, 146.9)	100.5 (61.9, 143.1)
<170	212 (95%)	220 (97%)
170-199	4 (2%)	7 (3%)
≥200	6 (3%)	0 (0%)
Triglycerides (mg/dL)	154.6 (87.0, 309.1)	150.6 (74.4, 270.1)
>150	116 (52%)	114 (50%)
In P1060 Extended Follow-up (V5)	175 (79%)	172 (76%)

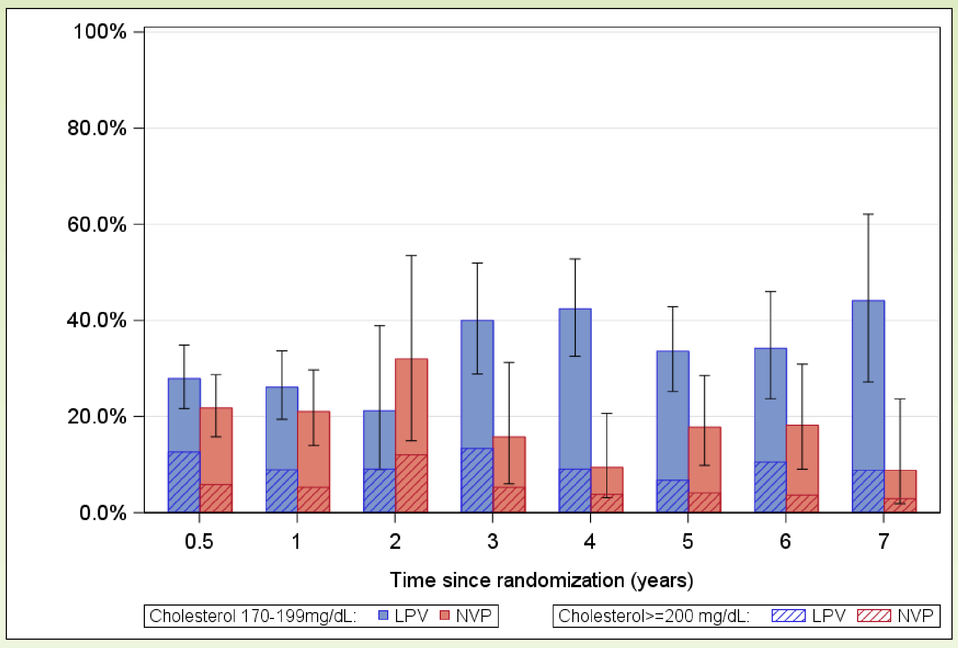
*Median (10^{th}, 90^{th}) or N (%)

FIGURE 1. WEIGHTED MEAN CHOLESTEROL (95% CI) AND RELATIVE DIFFERENCES



Follow-up Year	Mean Difference (95% CI)
0.5	3.2 (-5.3, 11.6)
1	1.9 (-7.1, 11.0)
2	-10.7 (-29.2, 7.9)
3	19.3 (9.3, 29.3)
4	23.4 (14.5, 32.3)
5	10.9 (1.9, 19.9)
6	20.1 (7.8, 32.4)
7	14.5 (-0.6, 29.5)

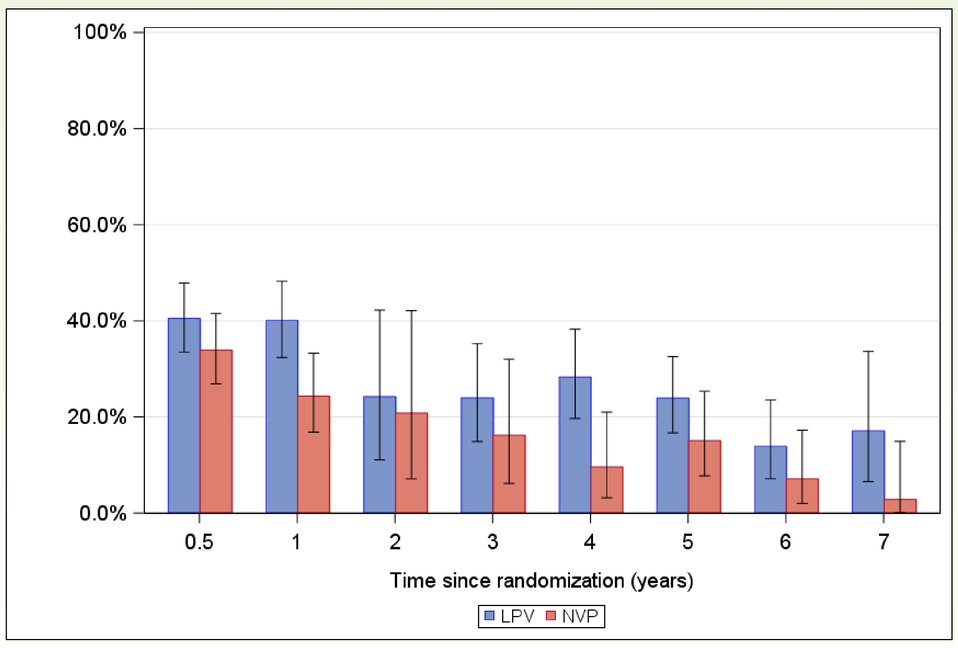
FIGURE 2. PERCENT WITH BORDERLINE/HIGH CHOLESTEROL (95% CI) AND RELATIVE RISKS



Follow-up Year	Relative Risk* (95% CI)
0.5	1.2 (0.8, 1.7)
1	1.2 (0.8, 1.9)
2	0.3 (0.1, 1.1)
3	2.6 (1.3, 5.3)
4	4.1 (1.8, 9.6)
5	1.6 (0.9, 2.8)
6	1.7 (0.9, 3.2)
7	4.3 (1.2, 15.3)

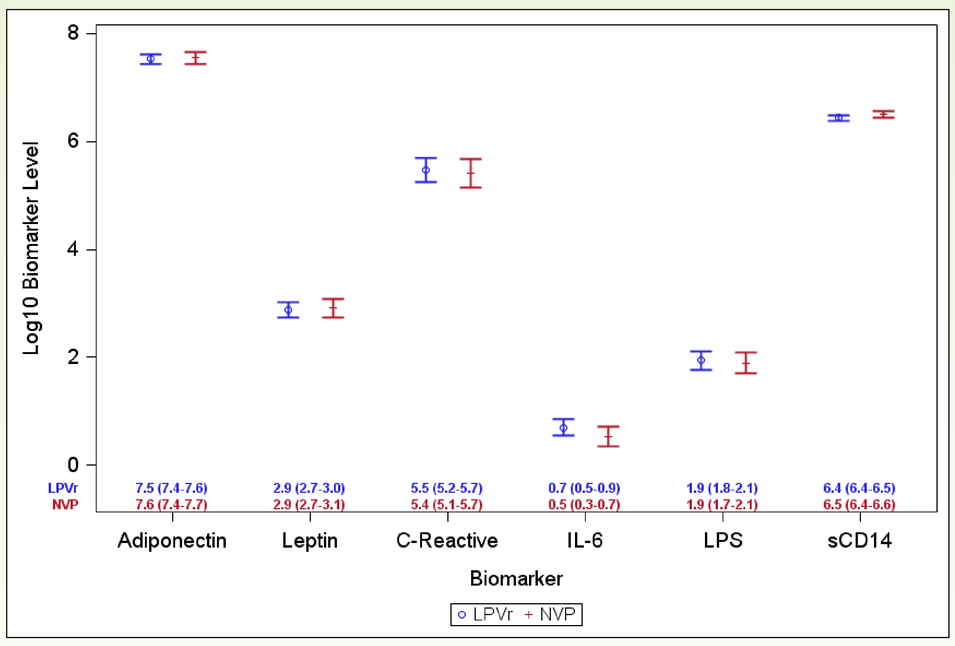
*cholesterol ≥ 170 mg/dL

FIGURE 3. PERCENT WITH HIGH TRIGLYCERIDES (95% CI) AND RELATIVE RISKS



Follow-up Year	Relative Risk (95% CI)
0.5	1.2 (0.9, 1.6)
1	1.8 (1.3, 2.7)
2	1.5 (0.5, 4.7)
3	1.8 (0.8, 3.9)
4	2.2 (0.9, 5.4)
5	1.3 (0.7, 2.5)
6	1.7 (0.5, 6.2)
7	Not estimable

FIGURE 4. MEAN $\log_{10}$ BIOMARKERS LEVELS (95% CI)



- LPV/r predictor of lower sCD14: RD (95% CI): -0.07 (-0.12, -0.01).
- High triglycerides predictor of higher leptin: RD (95% CI): 0.20 (0.03, 0.37)
- Weight for age < 2 SD predictor of higher LPS: RD (95% CI): 0.61 (0.30, 0.92)

CONCLUSIONS

- Long-term monitoring of total cholesterol among young children initiating a LPV/r-based regimen may be warranted as it is associated with higher total cholesterol after 3 years of follow-up compared to initiating a NVP-based regimen.
- Initiation of a LPV/r-based regimen in young children is not consistently associated with high triglycerides over follow-up.
- Initiation of a LPV/r-based regimen in young children is not a strong predictor of markers of metabolic syndrome, inflammation, microbial translocation, or immune activation.
- Study strengths include long follow-up after initiation of LPV/r and adjustment for censoring over follow-up, while limitations include only non-fasting lipid measures and lack of lipid subsets.

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). Funding for biomarker assays was provided by NICHD. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Presented at the
9th IAS Conference on HIV Science (IAS 2017)
Paris. FRANCE - July 23-26, 2017
Poster Number: TUPEB0448