Association of early childhood Nevirapine-based ART regimens with poorer neuropsychological outcomes compared to Lopinavir/ritonavir in HIV-positive children

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BACKGROUND

IMPAACT P1104s compared neuropsychological outcomes over 96 weeks in children living with HIV (CLHIV) with matched HIV-unexposed (HU) and HIV-exposed uninfected (HEU) children, aged 5 to 11 years at 6 sites in Sub-Saharan Africa. Here, we explore associations with neuropsychological outcomes in the CLHIV cohort including clinical, immunological and medication-related factors.

METHODS

CLHIV had participated in IMPAACT P1060, comparing efficacy of nevirapine (NVP) and lopinavir/ritonavir (LPV/r) in young CLHIV < 3 years, also on lamivudine & zidovudine. P1104s was a follow-on study evaluating neuropsychological performance in CLHIV from P1060, HU and HEU children. 96% of eligible P1060 participants, enrolled in P1104s. Neuropsychological evaluations (KABC cognitive ability, BRIEF executive function - transformed to lower score being worse, TOVA attention-impulsivity and BOT-2 motor) were at 0, 48 and 96 weeks. In HIV+ children, clinical, antiretroviral and laboratory (immunological and virological) data from P1060 were combined with clinical and neuropsychological and caregiver data from P1104s to explore associations with neuropsychological outcomes. Linear mixed models with restricted maximum likelihood estimation (REML) and robust fixed effect error estimates were used to explore whether test scores were associated across time with the growth, clinical history, HIV disease severity and treatment markers (screening characteristics) and to estimate these associations. Personal and caregiver characteristics were controlled for. Slope estimates and adjusted means with 95% confidence intervals were presented. Tests of statistical significance were two-sided and 5% error rates were used.

RESULTS

The 246 CLHIV (45% male, mean age at P1104s entry 7.1 yrs (SD 1.2)) had median ART initiation at 15 months (IQR 8.2, 25.2), nadir CD4 count of 632 cells/mm^3 (IQR 427, 874); 233 (95%) had a peak viral load >100,000 copies/ml. 164 (67%), 7 (3%) and 71 (29%) were receiving LPV/r, efavirenz (EFV)- and NVP-based ART respectively at 1104s entry; 61% had ≥ stage 3 WHO clinical stage.

Risk factors for lower neuropsychological scores on all KABC, TOVA and BOT-2 domains included receiving NVP/EFV at P1104s entry rather than LPV/r.

Other risk factors included low birth weight, WHO stage 4 disease and serious illness, but these were not consistent across all domains

Elevated VL was not a risk factor.

Table 1. Risk factors for lower neuropsychological performance across cognitive domains

Variable	Level	KABC NVI	KABC MPI	BOT-2	BRIEF GEC	TOVA ADHD	DPrime
Growth							
Entry WHO Height for age Z score	n/a	1.0 (-0.4,2.4)	1.3 (0.2, 2.5)	1.3 (0.6, 2.0)	0.3 (-0.7,1.2)	-0.1 (-0.4,0.2)	0.3(-1.2,1.8)
WHO BMI Z score	n/a	0.4 (-0.7,1.6)	0.2 (-0.7,1.2)	-0.6 (-1.3,0.1)	-1.3 (-2.3, -0.3)	-0.4(-0.7,-0.2)	-1.6 (-3.0, -0.3)
Illness history							
Low birth weight	Yes vs. No	-5.7 (-10.5, -1.0)	-3.0 (-7.3, 1.4)	-1.4(-4.2,1.4)	0.5(-4.8,5.8)	-0.6 (-2.2,0.9)	1.0(-7.3,5.2)
Serious illness history	1 vs. none	-0.1(-3.3,3.1)	-0.2(-3.2,2.8)	-0.8(-2.6,0.9)	-3.4(-5.9,-0.9)	-0.3(-1.0,0.4)	-2.9(-6.3,0.5)
	2+vs. none	1.1(-3.1,5.2)	1.2(-2.7,5.1)	0.0(-2.6,2.7)	0.8(-3.1,4.6)	0.7(-2.0,0.6)	-0.7(-5.1,3.7)
HIV Illness characteristics							
Viremia within 9 mths of visit	Yes vs. No	-.8 (-3.1, 1.5)	-1.5 (-3.1, 0.1)	-0.1 (-1.4, 1.3)	0.0 (-2.0,2.0)	0.3 (-0.5, 1.1)	0.3 (-2.8,3.4)
Nadir CD4% <15	Yes vs. No	1.4 (-1.4,4.2)	2.4(-0.3,5.1)	-0.9 (-2.7,0.9)	2.8 (0.4,5.1)	-0.3 (-1.0,0.5)	-1.3 (-4.3,1.8)
Peak VL > 100K	Yes vs. No	-1.0 (-6.9,4.8)	2.0 (-2.9,7.0)	-3.4 (-6.4,-0.4)	1.2(-2.6,5.0)	-0.2 (-1.3, 1.0)	-0.1 (-6.4,6.2)
Log10 VL	n/a	0.4 (-0.9,1.6)	1.0 (0.0,2.0)	-0.2 (-1.0,0.6)	0.2 (-0.9,1.4)	0.3 (-0.1,0.7)	0.3 (-1.0,1.6)
WHO HIV Stage	II vs. I	-0.6 (-5.8, 4.6)	-0.5 (-5.5, 4.5)	-0.2 (-3.3,3.0)	4.0 (-0.3, 8.3)	-0.3 (-1.6, 1.0)	-1.5 (-8.6, 5.6)
	III vs. I	-0.7 (-5.4, 3.9)	-0.5 (-5.2, 4.2)	-0.1 (-3.1, 2.9)	4.4 (0.2, 8.6)	0.4 (-0.9, 1.6)	0.7 (-6.5, 8.0)
	IV vs.1	-10.2 (-17.1, -3.2)	-7.9 (-14.3, -1.4)	-2.3 (-6.5, 2.0)	2.1 (-3.2, 7.3)	-1.0 (-3.0, 1.0)	-5.6 (-14.5,3.3)

Legend: Table 1 presents regression slopes at 95% CIs. The orange shading indicates significance at p < 0.05

Table 2: HIV treatment as a risk factor for lower neuropsychological scores

ARV (time varying)	KABC NVI	KABC MPI	BOT-2	BRIEF GEC	TOVA ADHD	TOVA DPrime
NRTI+EFV vs. NRTI+PI	-6.6 (-10.4, -2.7)	-3.1 (-7.3, 1.0)	-2.7 (-4.9,-0.4)	-1.8 (-6.2,2.6)	-0.9 (-2.3 (0.5)	-6.1 (-10,-2.2)
NRTI+NVP vs. NRTI+PI	-4.9 (-7.8, -2.0)	-3.5 (-5.7, -1.2)	-3.5 (-5.2, -1.7)	-0.3 (-2.7, 2.1)	-1.2 (-1.9, -0.4)	-7.5 (-10.3, -4.7)
Non-HAART vs. NRTI+PI	3.0 (-0.7, 6.6)	4.1 (0.3, 7.8)	-0.2 (-2.6, 2.2)	0.2 (-3.4, 3.8)	0.6 (-0.7, 1.8)	4.0 (-1.2, 9.2)

Legend: Table 2 regression slopes (95% CIs). Shading indicates significance at p < 0.05

Figure 1: Adjusted Means for Selected Neuropsychological Outcomes across Time by Entry ARV Regimen

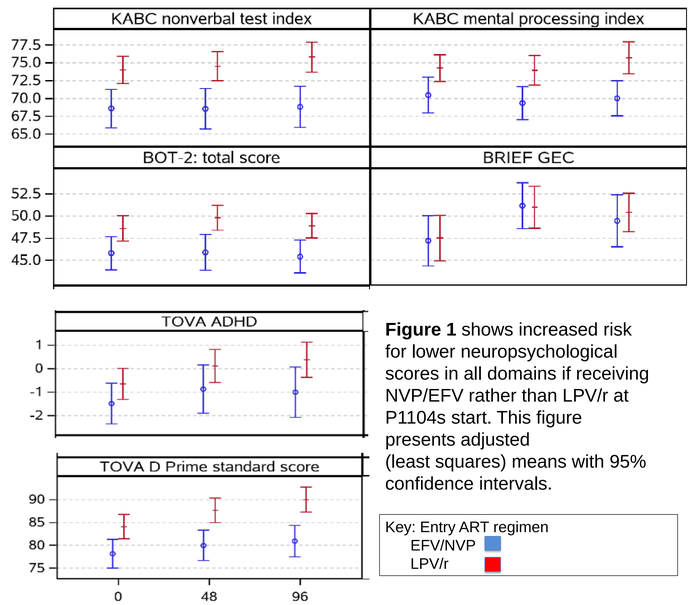

Figure 1 shows increased risk for lower neuropsychological scores in all domains if receiving NVP/EFV rather than LPV/r at P1104s start. This figure presents adjusted (least squares) means with 95% confidence intervals.

SUMMARY

NVP or EFV at P1104s study start or during follow-up were associated with lower neuropsychological scores than LPV/r (Figure 1), which persisted when controlling for nadir CD4 percent and time-varying HIV viral load (data not shown). Other predictors of poorer scores in KABC domains included low birth weight, WHO stage 4 disease and serious illness history but not elevated VL on P1060 or P1104 due to loss of viral suppression from treatment failure.

CONCLUSIONS

Children receiving nevirapine or efavirenz while on P1104s had poorer neuropsychological scores as assessed by the KABC, BOT-2 and TOVA than those on lopinavir/ritonavir. Lopinavir/ritonavir is the preferred option for young children initiating ART. NVP may be related to poorer neuropsychological outcomes.

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