Early antiretroviral therapy improves neurodevelopmental outcomes in infants

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Objectives: To evaluate the effect of early versus deferred antiretroviral therapy (ART) on the neurodevelopment of infants from Cape Town participating in the Children with HIV Early Antiretroviral Therapy (CHER) trial.

Design: HIV-infected infants were randomized to early (<3 months) or deferred ART. HIV-uninfected infants (HIV-exposed and HIV-unexposed) provide background data.

Methods: Neurological examination and Griffiths Mental Development Scales (GMDS) were administered between 10–16 months of age by testers blind to HIV status and randomized allocation. Mean quotients were compared using paired Student's *t*-tests.

Results: Sixty-four infants on early ART and 26 on deferred ART (of potential 77 and 38 respectively on CHER trial) were assessed at median age 11 months (range 10–16). On the GMDS, all scores were lower in the deferred arm and the General Griffiths and Locomotor Scores were significantly lower: mean (SD) = 100.1 (13.8) vs. 106.3 (10.6) $P = 0.02$; and 88.9 (16.3) vs. 97.7 (12.5), $P < 0.01$, respectively. Children with HIV who received early ART performed as well as children without HIV except on the Locomotor subscale. Both infected and uninfected mean GMDS scores were within the average range.

Conclusion: Infants initiated on early ART have significantly better Locomotor and general scores on the GMDS at median age 11 months compared to infants on deferred ART, despite careful monitoring and ready access to ART in the latter.

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Introduction

The prevalence of neurodevelopmental delay and/or HIV encephalopathy in HIV-infected children from predominantly well resourced countries has been reported to be between 13 and 23% [1]. Studies from resource-limited settings, wherein antiretroviral therapy (ART) is generally started later, have also reported neurodevelopmental delay [2–5]. However, few studies have prospectively evaluated the impact of early ART on the neurodevelopmental outcomes of HIV-infected infants, and there have been no randomized trials evaluating this outcome. Previous studies have frequently included infants exposed perinatally to other risk factors for poor neurodevelopmental outcome such as illicit drugs [6–8].

To determine the effect of early vs. deferred ART on early neurodevelopmental outcomes, we compared the neurodevelopmental profile on the Griffiths Mental Development Scales (GMDS) [9] of HIV-infected infants who started ART before 12 weeks of age with those for whom ART was deferred until they met immunological or clinical criteria. This was a substudy of the Children with HIV Early Antiretroviral Therapy (CHER) trial as previously described among children enrolled from the Cape Town clinical site [10].

Methods

This cross-sectional substudy compared neurodevelopmental outcomes among participants in CHER randomized to early versus deferred ART, and among HIV-uninfected infants (HIV-exposed and HIV-unexposed) participating in a linked vaccine study [11]. Children were eligible for inclusion if they had no dysmorphic syndromes or underlying non-HIV-related central nervous system abnormalities. The uninfected children were recruited from a concurrent study of pneumococcal conjugate vaccine to provide additional data on the GMDS for South African infants from low socioeconomic backgrounds.

In CHER, HIV-infected infants were randomly assigned to three arms: ART deferred until clinical or immunological progression; early ART commenced before 3 months and limited to 40 or 90 weeks. In this substudy, data from the two early ART arms have been combined. First-line ART included three drugs: zidovudine, lamivudine and lopinavir/ritonavir. Second-line ART was didanosine, abacavir and nevirapine.

Baseline viral load, CD4 cell count, time on ART and hospitalization were obtained from the study database. Birth history and maternal education were obtained from the charts and caregiver interviews. Hospital admissions prior to neurodevelopmental assessments were calculated as days in hospital including the days of admission and discharge. Head growth was plotted on Centers for Disease Control and Prevention (CDC) charts.

A neurological examination and the GMDS were performed at the study visit closest to 10–12 months of age by one of four pediatricians blinded to HIV status and randomized allocation. The GMDS 0–2 years was revised and re-standardized on 665 British children in 1996 [9]. The mean (SD) quotients for general quotient and subscales were 100.5 (11.8) and 100 (16), respectively. Significant impairment is regarded as more than 2 SDs below the mean. Quotients on the subscales and the general quotient were obtained from raw scores using data from normal British children. There are five subscales: Locomotor measures the earliest motor milestones; Personal-social assesses early adaptive behaviour using interaction with the environment and skill in dressing and feeding; Hearing and language measures early expressive language and the ability to follow commands and identify objects; Eye and hand coordination measures fine motor and visual abilities; Performance measures fine motor manipulative skill and visual spatial orientation. Standardized instructions, questions and comments were prepared in English, Afrikaans and Xhosa in accordance with the GMDS manual. A single translator assisted all Xhosa-speaking children.

Statistical analysis was performed with Statistica 10 (Statsoft, Tulsa, Oklahoma, USA). Comparisons between groups were performed using either the paired Student's *t*-test or the Mann–Whitney *U* test for continuous variables and the χ^2 and Fishers test for discrete variables or using one-way analysis of variance using the Kruskal–Wallis test. Mean days in hospital was compared using a generalized linear model using the Poisson distribution and log link function. A 95% confidence interval was calculated where applicable and significance was established at *P* value less than 0.05.

The substudy protocol was approved by the Human Research Ethics Committee, Faculty of Health Sciences, Stellenbosch University, registration number N05/05/092. Written consent was obtained from the child's parent or guardian.

Results

A total of 115 HIV-infected infants from Cape Town participated in the parent study, 77 (67%) of whom were randomized to the two early ART arms and 38 to the deferred ART arm. Of these, eight infants died before assessment (all on the deferred arm); 10 (eight on early ART, two on deferred ART) were not enrolled as they

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withdrew from the parent study before scheduled neurodevelopmental assessments. Two infants on early ART with underlying neurological disorders (glutaric-aciduria, fetal alcohol syndrome) were excluded. Five infants (three on early ART and two on deferred) were also excluded because they were assessed after the cutoff age (two) or had unreliable scores (two) or repeatedly missed appointment dates (one). Our analysis included 64 infants on early ART and 26 on deferred treatment.

Demographic information is shown in Table 1. HIV-infected infants were predominantly girls and Xhosa-speaking and maternal education was comparable. Birth outcomes were comparable for weight, gestation and mode of birth. Demographics were comparable in the early treatment group and the unexposed uninfected infants, except for language and gestation. There were more Xhosa-speaking infants in the early treatment group (86 vs. 29%) and more infants with gestation more than 37 weeks in the HIV-infected groups. At enrollment into CHER, the treatment groups were comparable on mean absolute CD4 cell count (1746 vs. 2024 cells/μl, $P = 0.5$), CD4% (34.8 vs. 34.9%, $P = 1.0$) and plasma viral load (log10 RNA copies/ml: 5.66 vs. 5.64, $P = 0.8$).

Mean age of starting ART was 31.4 weeks in deferred and 8.4 weeks in early ART ($P < 0.01$). Twenty-four (92%) infants in deferred ART group were on ART at assessments. Mean time on ART before assessments was 18.7 weeks in deferred and 40.9 weeks in early ART ($P < 0.01$). According to the CHER protocol, treatment interruption was planned after 40 weeks of early ART for some participants [10]. Five infants on early ART, whose scores were included, had treatment interrupted (between 1 and 3 months) before neurodevelopmental assessments were performed. One infant, on early ART, was changed to second-line treatment at 6 months, (20 weeks before the GMDS) due to undisclosed treatment interruption by parent. Clinicians assumed treatment failure.

More infants on deferred ART compared with early ART experienced hospital admissions (46 vs. 30%). The deferred group stayed significantly longer in hospital than the early group (mean 9.4 vs. 2.4 days; $P < 0.01$). At assessment, head circumference was similar between the comparison arms.

On the GMDS, all scores were lower in the deferred vs. the early ART group (Table 2). General and Locomotor scores were significantly lower: mean (SD) = 100.1 (13.8) vs. 106.3 (10.6), $P = 0.02$ and 88.9 (16.3) vs. 97.7 (12.5), $P < 0.01$, respectively. All scores in the early ART arm were similar to those in both HIV-uninfected groups, except for Locomotor wherein the HIV-exposed uninfected arm performed better (Table 2).

Discussion

In this study, HIV-infected infants receiving early ART (<3 months old) scored higher on the GMDS scales, particularly on the General and Locomotor scores, compared to those on deferred ART. Children with HIV who received early ART performed as well as children without HIV except on the Locomotor subscale.

Our findings show that children with HIV who start ART earlier have better short-term neurodevelopmental outcomes than infants for whom treatment is deferred. The mean age starting ART in the deferred group was 31.4 weeks. Although this is early compared to many studies describing neurodevelopmental outcomes [3,4,12–15], even this delay is associated with poorer outcomes. The mean time on ART in infants receiving early ART compared to those on deferred ART was significantly longer (18.7 vs. 40.9 weeks), potentially influencing our findings.

Our study is limited by small sample sizes for the deferred ART and uninfected groups. Given the trend to better outcomes for hearing and speech, eye–hand coordination and performance in the group on early ART, larger sample sizes may have provided a more precise estimate. Eight infants in the deferred group died before assessment. Five of these infants had CDC stage C disease. Had they lived to be assessed, they may have lowered the scores in the deferred ART group further, increasing the differences between arms. Literature has established that neurodevelopmental outcomes in children with AIDS-defining illness are worse than in those without such diagnosis [7–8]. There was an imbalance in primary language; there were more Xhosa-speaking infants in the HIV-infected groups than in the uninfected groups. This may indicate differences in cultural and child-rearing practices but our experience of this age group is that early childhood stimulation is similar in the two language groups, as shown in the comparable results. The study is further limited by the cross-sectional nature of neurodevelopmental assessments. Also, viral loads and CD4 cell counts were measured at varying times in relation to neurodevelopmental assessment and ART status, thus not being comparable. We, therefore, cannot comment on the changes over time and response to ART initiation.

The deferred arm had a higher incidence of illness and hospitalization. The degree to which this may have contributed to the neurodevelopmental delay is not clear. More children in the deferred arm than the early arm required hospitalization (46 vs. 30%) and the mean hospital duration for those admitted was 9.4 vs. 2.4 days. This confirms that early ART prevents morbidity, which may have implications for large ART programmes in developing countries.

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Table 1. Demographic data of study participants.

	HIV infected deferred ART ($N=26$)	HIV infected early ART ($N=64$)	HIV-exposed uninfected ($N=28$)	HIV-unexposed uninfected ($N=34$)	*P*-value comparing 4 groups
Sex: male	10 (39%)	28 (44%)	17 (61%)	19 (56%)	0.7
Mean birth weight, g (range)	3019 (2000–3640)	2989 (2188–3790)	3057 (2166–3798)	3139 (2172–4294)	0.8
Gestation					
>37 weeks	24 (96%)	50 (78%)	11 (71%)	21 (62%)	0.2[b]
≤37 weeks	1 (1 unknown)	11 (3 unknown)	17	13	
Mode of birth					
NVD	20 (77%)	55 (86%)	21 (75%)	29 (85%)	0.4
Caesarean section	6	9	7	5	
Mean (SD) head circumference at assessment, centimetres (range)	46 (1.6) (44–52)	46 (1.5) (43–52)	46 (1.5) (42–48)	46 (1.9) (42–50)	0.4
Primary language					
Xhosa	24 (92%)	55 (86%)	19 (68%)	11 (29%)	0.5
Afrikaans	2	9	6	21	
English	0	0	3	2	
Maternal education: median years of formal schooling (range)	11.0 (4–12)	10.0 (1–12)	10.5 (5–12)	10.0 (6–12)	0.4
Mean (SD) absolute CD4 cell count on enrolment to CHER (range)	1746 (582); (746–2926); (*n=24*)	2024 (1065); (358–5255); (*n=63*)	n/a	n/a	0.5
Mean (SD) CD4% on enrolment to CHER (range)	34.8 (7.9); (17.4–51.3); (*n=24*)	34.9 (8.2); (21.6–53.9); (*n=63*)	n/a	n/a	1.0
Mean viral load (log10 RNA copies/ml) on enrolment to CHER (range)	5.66 (0.42); (4.21–5.88)	5.64 (0.41); (3.78–5.88)	n/a	n/a	0.8
Least square mean (SD) age starting ART, weeks (range)	31.4 (16); (8–76)[a]	8.4 (1.6); (6–12)	n/a	n/a	<0.01
Mean (SD) time on ART in weeks (range)	18.7 (12.7); (0–40)	40.9 (5.1); (33–60)	n/a	n/a	<0.01
Hospital admissions: number participants admitted (% of group)	12 (46%)	19 (30%)	5 (18%)	6 (18%)	0.1
Mean days in hospital ± SE (range)	9.4 ± 0.06 (0–87)	2.4 ± 0.08 (0–25)	0.8 ± 1.5 (0–4)	0.9 ± 1.4 (0-6)	<0.01[c]

ART, antiretroviral therapy; CHER, Children with HIV Early Antiretroviral Therapy.
[a]Three participants who started ART after GMDS were included.
[b]Fisher test.
[c]Wald test (Poisson distribution with log link function).

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Table 2. Comparison of mean scores and standard deviations on the Griffiths Mental Development Scales.

	HIV infected deferred ART ($N=26$)	HIV infected early ART ($N=64$)	HIV-exposed uninfected ($N=28$)	HIV-unexposed uninfected ($N=34$)	*P*-value comparing 4 groups
Median age, months, (range)	11.1 (10–14)	11.0 (10–16)	11.5 (10–16)	11.5 (10–14)	0.11
General quotient, mean ± 1 SD (range)	100.1 ± 13.8[b] (55–125)	106.3 ± 10.6[c] (71–125)	105.6 ± 9.9 (82–128)	106.9 ± 11.7 (81.0–125)	0.14[#]
Locomotor quotient, mean ± 1 SD (range)	88.9 ± 16.3[a] (48–112)	97.7 ± 12.5[a] (58–124)	105.3 ± 14.1 (68–137)	101.6 ± 3.6 (69–129)	<0.01
Personal-Social quotient, mean ± 1 SD (range)	107.7 ± 15.9 (63–138)	111.3 ± 13.6[a] (79–138)	106.6 ± 12.1 (81–134)	107.4 ± 17.2 (60–136)	0.46
Hearing and speech quotient, mean ± 1 SD (range)	108.4 ± 13.2 (75–131)	112.5 ± 10.4 (85–131)	108.0 ± 13.9 (71–127)	112.3 ± 13.9 (85–139)	0.55
Eye and hand co-ordination quotient, mean ± 1 SD (range)	102.0 ± 16.1 (50–128)	107.4 ± 15.8[a] (67–128)	107.1 ± 10.6 (84–128)	108.8 ± 15.1 (63–133)	0.24
Performance quotient, mean ± 1 SD (range)	95.0 ± 15.9[a] (58–128)	100.3 ± 13.1 (62–128)	99.8 ± 12.7 (63–123)	102.7 ± 15.5 (61–128)	0.16

ART, antiretroviral therapy.
[#]Posthoc deferred ART vs. early ART *P*-value = 0.02.
[a]No data for 1 participant.
[b]No data for 2 participants.
[c]No data for 3 participants.

The GMDS has not been standardized for South African children, but is widely used [16–18] and scores show good correlation with British children from different race and language groups [19]. Our results support the GMDS as an appropriate tool in our setting. The mean scores on all subscales between the unexposed uninfected and the early ART groups were similar (Table 2). Although there is a significant difference in the mean General and Locomotor scores between the early therapy and deferred therapy groups, the means are still within the normal developmental range (within 1 SD) for the GMDS.

Strengths of this study include that this was performed in a setting in which there is limited prenatal recreational drug exposure. The study population is from a poor socioeconomic background, representative of infants accessing public health system and the demographics of HIV infection. Results should be generalizable to the relevant South African population. The study is further strengthened by the inclusion of uninfected groups from similar cultural and socioeconomic backgrounds, which contextualizes the information on performance on the GMDS.

This study provides evidence of the neurodevelopmental benefits of early ART. In infants tested at a median age of 11 months on the GMDS, those initiated at a mean of 8.4 weeks of age had significantly better Locomotor and General scores than when ART was deferred, despite careful monitoring and ready access to ART. It is plausible that the true difference may be larger based on deaths before assessments. In addition, we found little neurodevelopmental difference between infants who received early ART and infants who were uninfected with HIV. These findings support the earliest possible diagnosis of HIV and initiation of ART in infants. However, caution should be exercised in extrapolating to long-term predictions.

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B.L.: Substudy design, assessments of participants, interpretation of data and lead author.

M.C.: Major contribution in producing manuscript.

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D.G.: Substudy design, primary statistical analysis.

M.K.: Statistical analysis.

P.E.S.: Substudy design, assessment of participants, assistance with interpretation of results and contribution to manuscript.

E.D.: Investigator on parent study and contribution to manuscript.

A.J.v.R.: Study Coordinator.

A.V.: Parent study design and implementation and contribution to manuscript.

A.G.B.: Parent study design and trial statistician.

S.A.M.: Parent study design and contribution to manuscript.

P.J.P.: Parent study design and contribution to manuscript.

D.M.G.: Parent study design and contribution to manuscript.

M.F.C.: Parent study design and implementation and senior author.

All authors have read the final text and approved of submission to AIDS. All authors have signed Authorship Responsibility, Financial Disclosure, and Copyright Transfer.

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Conflicts of interest

There are no conflicts of interest.

References

1. Wolters PL, Brouwers P. **Neurobehavioral function and assessment of children and adolescents with HIV-1 infection.** In: Zeichner SL, Read JS, editors. *Handbook of pediatric HIV care*. Cambridge: Cambridge University Press; 2006. pp. 309–331.
2. Bagenda D, Nassali A, Kalyesubula I, Sherman B, Drotar D, Boivin MJ, *et al*. **Health, neurologic, and cognitive status of HIV-infected, long-surviving, and antiretroviral-naive Ugandan children.** *Pediatrics* 2006; **117**:729–740.
3. Puthanakit T, Aurpibul L, Louthrenoo O, Tapanya P, Nadsasarn R, Insee-ard S, *et al*. **Poor cognitive functioning of school-aged children in thailand with perinatally acquired HIV infection taking antiretroviral therapy.** *AIDS Patient Care STDS* 2010; **24**:141–146.
4. Smith L, Adnams C, Eley B. **Neurological and neurocognitive function of HIV-infected children commenced on antiretroviral therapy.** *S Afr J Child Health* 2000; **2**:108–113.
5. Van Rie A, Harrington PR, Dow A, Robertson K. **Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: a global perspective.** *Eur J Paediatr Neurol* 2007; **11**:1–9.
6. Chase C, Ware J, Hittelman J, Blasini I, Smith R, Llorente A, *et al*. **Early cognitive and motor development among infants born to women infected with human immunodeficiency virus. Women and Infants Transmission Study Group.** *Pediatrics* 2000; **106**:E25.
7. Chiriboga CA, Fleishman S, Champion S, Gaye-Robinson L, Abrams EJ. **Incidence and prevalence of HIV encephalopathy in children with HIV infection receiving highly active antiretroviral therapy (HAART).** *J Pediatr* 2005; **146**:402–407.
8. Smith R, Malee K, Leighty R, Brouwers P, Mellins C, Hittelman J, *et al*. **Effects of perinatal HIV infection and associated risk factors on cognitive development among young children.** *Pediatrics* 2006; **117**:851–862.
9. Huntley R. *The Griffiths Mental Development Scales from birth to 2 years*. Oxford: The Test Agency Limited; 1996.
10. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, *et al*. **Early antiretroviral therapy and mortality among HIV-infected infants.** *N Engl J Med* 2008; **359**:2233–2244.
11. Madhi SA, Adrian P, Cotton MF, McIntyre JA, Jean-Philippe P, Meadows S, *et al*. **Effect of HIV infection status and antiretroviral treatment on quantitative and qualitative antibody responses to pneumococcal conjugate vaccine in infants.** *J Infect Dis* 2010; **202**:355–361.
12. Berk DR, Falkovitz-Halpern MS, Hill DW, Albin C, Arrieta A, Bork JM, *et al*. **Temporal trends in early clinical manifestations of perinatal HIV infection in a population-based cohort.** *JAMA* 2005; **293**:2221–2231.
13. Foster CJ, Biggs RL, Melvin D, Walters MD, Tudor-Williams G, Lyall EG. **Neurodevelopmental outcomes in children with HIV infection under 3 years of age.** *Dev Med Child Neurol* 2006; **48**:677–682.
14. Puthanakit T, Vonthanak S, Ananworanich J, Kosaralaksa P, Hansudewechakul R, Vibol U, *et al*. **Randomized clinical trial of immediate versus deferred antiretroviral therapy initiation in children older than one year with moderate immunodeficiency: the PREDICT Study.** Poster Presentation: *6th Annual Conference of the International AIDS Society*. Rome, Italy; 2011.
15. Faye A, Le Chenadec J, Dollfus C, Thuret I, Douard D, Firtion G, *et al*. **Early versus deferred antiretroviral multidrug therapy in infants infected with HIV type 1.** *Clin Infect Dis* 2004; **39**:1692–1698.
16. Amod Z, Cockroft K, Soellaart B. **Use of the 1996 Griffiths Mental Development Scales for infants: a pilot study with a Black, South African sample.** *J Child Adolesc Mental Health* 2007; **19**:123–130.
17. Cockroft K, Amod Z, Soellaart B. **Level of maternal education and performance of Black, South African infants on the 1996 Griffiths Mental Development Scale.** *Afr J Psychiat* 2008; **11**:44–50.
18. Perez EM, Hendricks MK, Beard JL, Murray-Kolb LE, Berg A, Tomlinson M, *et al*. **Mother-infant interactions and infant development are altered by maternal iron deficiency anemia.** *J Nutr* 2005; **135**:850–855.
19. Allan MA. **A Comparison of the performance of normal preschool South African and British children on the Griffiths Scales of Mental Development.** *Port Elizabeth: Unpublished Master's Thesis, Psychology Department, University of Port Elizabeth*; 1988.

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