Cognitive function in young peope with and without perinatal HIV in the AALPHI cohort in England: the role of non-HIV related factors

Short title (40 characters): Cognition in youth with perinatal HIV

Ali Judd (MRC Clinical Trials Unit at University College London, London, UK)

Marthe Le Prevost (MRC Clinical Trials Unit at University College London, London, UK)

Diane Melvin* (Imperial College Healthcare NHS Trust, London, UK)

Alejandro Arenas-Pinto* (MRC Clinical Trials Unit at University College London, London, UK)

Francesca Parrott (MRC Clinical Trials Unit at University College London, London, UK)

Alan Winston (Imperial College London, London, UK)

Caroline Foster (Imperial College Healthcare NHS Trust, London, UK)

Kate Sturgeon (MRC Clinical Trials Unit at University College London, London, UK)

Katie Rowson (MRC Clinical Trials Unit at University College London, London, UK)

Di M. Gibb (MRC Clinical Trials Unit at University College London, London, UK)

on behalf of the Adolescents and Adults Living with Perinatal HIV (AALPHI) Steering Committee

*equal contribution status

Corresponding author:
Dr Ali Judd
MRC Clinical Trials Unit at UCL
University College London
Aviation House, 125 Kingsway, London WC2B 6NH
Tel: 020 7670 4830
Email: a.judd@ucl.ac.uk

Alternate corresponding author: Marthe Le Prevost, m.leprevost@ucl.ac.uk

40 word summary of main point of article:
In young people with perinatal HIV in England, cognitive impairment was relatively mild, and similar to HIV-negative affected controls, but lower than general population data. CDC stage C, worse depression, and black African ethnicity (likely associated with socio-economic status), predicted lower scores.

Key words: cognitive, perinatal, HIV, young people, adolescents, England
Main text word count: 2,999 (cannot exceed 3,000)
Funder: Monument Trust and PENTA Foundation

Cognitive function in young people with and without perinatal HIV in the AALPHI cohort in England: the role of non-HIV related factors

ABSTRACT

Background: There is limited evidence about the cognitive performance of older adolescents with perinatally-acquired HIV (PHIV+) compared to HIV-negative (HIV-) adolescents.
Methods: 296 PHIV+ aged 12-21 and 97 HIV- aged 13-23 completed 12 tests covering 6 cognitive domains. HIV- adolescents were siblings of PHIV+ and/or had an HIV positive mother. Domain-specific and overall (NPZ-6) z-scores were calculated for PHIV+ with and without CDC class C disease and HIV-. Linear regression explored predictors of NPZ-6.
Results: 125(42%) PHIV+ and 31(32%) HIV- were male, 251(85%) and 69(71%) were black African, and median age was 16[IQR 15,18] and 16[14,18] years respectively. In PHIV+, 247(86%) were on ART, and 76(26%) had a previous CDC C diagnosis. Mean NPZ-6 scores were -0.81 (standard deviation 0.99) in PHIV+ with a CDC C diagnosis, -0.45 (0.80) in PHIV+ without CDC C, and -0.32 (0.76) in HIV- ($p<0.001$). After adjustment, there was no difference in NPZ-6 between PHIV+ without a CDC C and HIV- participants (adjusted coefficient -0.01 (95%CI -0.22, 0.20) for PHIV+ no C versus HIV-). PHIV+ with CDC C scored below the HIV- group (adjusted coefficient -0.44 (-0.70, -0.19)). Older age predicted higher NPZ-6 score, whilst black African ethnicity and worse depression predicted lower NPZ-6. In a sensitivity analysis including PHIV+ only, no HIV-related factors apart from CDC C were associated with NPZ-6.
Conclusions: Cognitive performance was similar among PHIV+ without CDC C diagnoses and HIV-, and indicated relatively mild impairment compared to normative data. The true impact on day-to-day functioning needs further investigation.

Cognitive function in young people with and without perinatal HIV in the AALPHI cohort in England: the role of non-HIV related factors

INTRODUCTION

Previous research has described global and specific cognitive impairments in perinatally HIV-infected children in the era of combined antiretroviral therapy (cART).[1-3] This group typically does not perform as well as controls on general cognitive tasks, processing speed and visual-spatial tasks, and may have higher risk for behavioural problems and psychiatric disorders.[1, 4-7] Markers of HIV disease severity, including high viral replication,[5, 8] low CD4 cell counts,[7] and having a CDC C diagnosis,[3, 5, 9, 10] have been associated with poorer cognitive function.[2] In addition, encephalopathy (itself an AIDS-defining symptom) is associated with a rapidly progressive early disease and residual serious neurologic consequences.[11] Although the incidence of encephalopathy has declined with increased cART availability,[12] many children do not start ART in early life and are at risk of longer-term cognitive effects of HIV.

Knowledge about the cognitive performance of perinatally HIV-infected young people (PHIV+) is limited as most studies have small sample sizes and/or have recruited younger children or those just entering adolescence.[8, 13, 14] Some findings suggest similar cognitive impairment in PHIV+ to perinatally HIV exposed uninfected (PHEU) youth, but poorer scores in both groups compared to normative data,[3] highlighting the importance of having appropriate control groups for comparison, for two reasons. Firstly, non-HIV related factors may be contributing to lower cognitive performance in both PHIV+ and PHEU groups compared to normative data. In many settings, families affected by parental HIV are likely to have different environmental and psychosocial experiences and socioeconomic status to families not exposed to HIV, and these factors may influence cognitive performance.[15] For example, in the USA, many children with HIV (and PHEU siblings) are affected by poverty, trauma and parental drug use.[16] In the UK/Irish perinatal HIV cohort, a high proportion of PHIV+ are born abroad in sub-Saharan Africa, and so have key differences compared to the wider population of adolescents born to families residing permanently in the UK.[17] Secondly, many cognitive tests are validated on specific groups and so manufacturer normative data may not be applicable to young people,[18, 19] for whom critical changes in maturation take place during adolescence which may affect cognitive outcomes.[20, 21]

This study explored the association between HIV, psychosocial, environmental, lifestyle and mental health factors on cognition in a large cohort of older PHIV+, as well as a comparable control group of adolescents affected by HIV, in England. We asked a broader range of questions than have previously been studied, including psychosocial and environmental factors. We hypothesised that these broader factors, as well as CDC disease stage may be associated with cognitive performance.

METHODS

The Adolescents and Adults Living with Perinatal HIV (AALPHI) cohort is a prospective study evaluating the impact of HIV infection and ART exposure on perinatally HIV-infected and (predominantly sibling) HIV negative young people. Participants were approached in 18 HIV clinics and 4 community services in England between 2013-2015, and underwent a two hour face–to--face interview with a trained research nurse. PHIV+ were aged 13-21 years and were all included in the national UK and Ireland Collaborative HIV Paediatric Study (CHIPS), with perinatal HIV confirmed through the National Study of HIV in Pregnancy and Childhood.[17, 22, 23] HIV negative (HIV-) young people were: aged 13-23 years; HIV negative on a point-of-care test at interview; lived in the same household as a PHIV+ participant in AALPHI, or had a sibling, friend or partner who was a PHIV+ in AALPHI, or had an HIV-infected parent (non-mutually exclusive categories); and awareness of HIV in the family (where appropriate). All participants had lived in the UK for ≥6 months, and could speak and understand English. Full ethical approval was obtained from Leicester Research Ethics Committee.

The cognitive assessment measured 12 tests across six domains (Supplementary Table 1), giving a comprehensive overview of the domains found to be affected in HIV-infected adults and children. Interviewers completed full training and had ongoing supervision (from D. Melvin, chartered Clinical Psychologist) to maintain standards and minimise intra-interviewer variability.

Seven tests were administered via the computerised CogState^{TM} battery (Melbourne, Australia),[24, 25] validated in HIV-infected adult patients, and largely non-language based.[26] Participants completed one full practice test prior to each task to obtain optimal performance at baseline.[27] Five tests were paper-based, including *Color Trails 1 and 2* for speed of information processing and executive function respectively, *WAIS-IV coding/ digit symbol* for attention and working memory,[28] and *Grooved Pegboard* for dominant/non-dominant hand fine motor skills.[29] The Hospital Anxiety and Depression Scale (HADS) was chosen as a measure of anxiety and depression as it has been used widely in the UK, was self-report and easy to complete.

ART was defined as receipt of ≥3 ART drugs from ≥2 classes. The Centers for Disease Control and Prevention (CDC) clinical classification system[30] was used to indicate class B moderately symptomatic infection and class C past history of an AIDS-defining illness.

Statistical analysis

Data were analysed using STATA version 13 (Stata Corp, College Station, Texas, USA). Scoring of CogState^{TM} tests followed manufacturer recommendations. For each test, z-scores were calculated using manufacturer normative data, adjusted for age where appropriate (Supplementary Table 1), and then averaged to give mean z-scores for each domain compared to the reference mean. Normative data were not available for WAIS IV and so only the CogState^{TM} Identification Task contributed to the attention/working memory domain. Summary NPZ-6 score was calculated as the mean z-score across all domains. Cognitive impairment was defined as the proportion of participants with a z-score <-1 in ≥2 domains.[19, 31]

Mean z-scores were compared using t-tests and ANOVA, proportions using χ^2 test, and medians using Wilcoxon rank sum. The effect of potential predictors on NPZ-6 score was explored using linear regression and Wald p-values. Factors considered *a priori* to be associated with NPZ-6 for all participants were HIV status and CDC disease stage (HIV-, PHIV+ CDC N/A/B, PHIV+ CDC C), sex, age, ethnicity, and being born outside of the UK. Other variables considered were: psychosocial (death of one/both parents, currently living with parents, occupation, having a parent or carer in work; ever excluded from school); environmental (fostered/adopted; number of main carers (different adults taking responsibility for and living with the participant during childhood); main language spoken at home (English only v other); residential deprivation score (Income Deprivation Affecting Children Index (IDACI), ranging from 0-1; higher score = more severe deprivation)); lifestyle (tobacco, alcohol, drugs); and mental health (HADS,[32] ranging from 0-21; higher scores indicate more severe anxiety or depression)).

A sensitivity analysis excluding PHIV+ with CDC C encephalopathy explored whether any differences by CDC C stage were sustained for other CDC C diagnoses, and another sensitivity analysis allowed for clustering by sibling pairs. An additional analysis included HIV-related indicators for PHIV+ young people only (with pre-AALPHI data collected through the CHIPS cohort): year first presented to treatment, age diagnosed with HIV, age starting ART, current ART status, current efavirenz (EFV) use, nadir and most recent CD4 cell count, most recent viral load, median cumulative years with viral load<400 copies/ml, CDC stage, ever diagnosed with encephalopathy. Variables attaining a *p* value of less than 0.15 in univariable analyses were considered in multivariable analysis using backwards selection. Additionally characteristics of PHIV+ in AALPHI were compared to perinatally HIV-infected young people aged 13-21 years not in AALPHI but in the national UK/Ireland CHIPS cohort by 31 October 2013.[17, 22]

RESULTS

A total of 296 PHIV+ participants and 97 HIV- completed cognitive testing. Of the 97 HIV- participants: 50 (52%) had an HIV-infected mother; 37 (38%) were siblings of PHIV+ in the study; 6 (6%) had PHIV+ siblings who were not in the study; and 4 (4%) had a close friend who was a PHIV+ (non-mutually exclusive categories). Sociodemographic characteristics of PHIV+ and HIV- young people were similar (Table 1). There were more females than males in each group, the median age for both groups was 16 years, most were black African and born outside of the UK, and most attended school and lived with their parents at the time of interview. Around a quarter (24%) of HIV- participants had experienced the death of one or both parents, compared to 36% of PHIV+, and median age at first parent death was 6 years (IQR 2, 10) and 7 years (4, 10) respectively. Similar proportions reported having ever smoked and used alcohol, and mean anxiety and depression HADS scores were similar. The median age at which PHIV+ became aware of their HIV diagnosis was 12 years [IQR 11, 13].

Table 2 presents HIV-related clinical markers for PHIV+ participants, stratified by CDC class C diagnosis. For the 76 (27%) with a CDC C diagnosis, the median age at the first CDC C event was 2.8 years (interquartile range, IQR 0.5, 6.4), and 11 diagnoses were encephalopathy (median age at diagnosis 2.5 years (IQR 0.8,3.5)). Those with a CDC C were more likely to present to HIV care at a younger age and in earlier calendar years, and initiate ART at a younger age. Around three-quarters in each group had a suppressed viral load <50c/ml at interview, whilst CD4 nadir and CD4 at interview were similar between the groups at around 200 cells/mm^3 and 600 cells/mm^3 respectively.

In terms of comparability to young people with perinatal HIV in the UK and Ireland CHIPS cohort who were not in AALPHI, slightly less PHIV+ in AALPHI were male (p=0.005), and a higher proportion were born abroad (p<0.001), but the median age and proportion who were black were similar (both p values >0.1, Table 1). For HIV clinical markers, the median age at first presentation was lower in AALPHI (p<0.001), and more PHIV+ in AALPHI presented in earlier calendar years (p=0.031, Table 2). A higher proportion of the national cohort remained ART naïve at most recent follow-up (p=0.014), but there was no difference in the age at ART initiation (p=0.90). A similar proportion in AALPHI to the national cohort had suppressed viral load at last follow-up, and although nadir CD4 count was lower in AALPHI, there was no difference in CD4 at last follow-up (p=0.038, p=0.13 respectively).

Figure 1 and Supplementary Table 2 present mean z-scores for each cognitive domain and NPZ-6 scores, by HIV and CDC C status. For each domain and for NPZ-6 overall, PHIV+ participants with CDC C had the poorest performance, and most mean z-scores for all three groups (and all for PHIV+ with CDC C) were below reference means. For executive function, speed of information processing memory, and fine motor skills, PHIV+ with CDC C had poorer mean z-scores than PHIV+ without CDC C and HIV- participants, and the latter two groups had similar scores. Scores for attention were similar for all three groups, while for learning, both groups of PHIV+ scored more poorly than HIV- participants. Only for fine motor skills were mean z-scores for PHIV+ without CDC C and HIV- groups above the mean score. However for most domains and groups, mean

scores and 95% confidence intervals were within one standard deviation below the reference mean.

The NPZ-6 reflected the general trend of PHIV+ with CDC C scoring significantly worse than PHIV+ without a CDC C and HIV- participants (mean z-score (SD) -0.81 (0.99), -0.45 (0.80), -0.32 (0.76) respectively, p<0.001). Forty-six (61%) PHIV+ young people with CDC C were classified as having cognitive impairment, compared to 100 (46%) PHIV+ with no CDC C, and 36 (40%) of HIV- participants (p=0.024).

Table 4 presents univariable and multivariable predictors of improved NPZ-6 scores, for all *a priori* factors as well as those with univariable $p<0.15$ or multivariable $p<0.05$. There was no difference in NPZ-6 score between PHIV+ without CDC C and HIV- participants overall, although PHIV+ with a CDC C scored more poorly both before and after adjustment for other variables. Both before and after adjustment for other factors, NPZ-6 score improved with each year increase in age (multivariable coefficient 0.06, 95% CI 0.02, 0.09), and was lower in black African young people (multivariable coefficient -0.46, 95% CI -0.68, -0.24) and those with worse depression scores (multivariable coefficient -0.04, 95% CI -0.06, -0.01). Having been born outside the UK/Ireland, parent death, number of adult carers, IDACI deprivation score, never having alcohol or drugs were all associated with lower NPZ-6 in univariable analyses but not in multivariable analyses (all multivariable p values >0.05). Black African participants were more likely to have been born outside of the UK/Ireland, experienced the death of a parent, had more adult carers and a greater deprivation score, and so univariable associations between these factors and NPZ-6 were weakened after multivariable adjustment for ethnicity (data not shown). In a sensitivity analysis excluding ethnicity, greater deprivation score was associated with lower NPZ-6 after adjustment for other factors (p=0.032), but not death of parents (data not shown).

Additional sensitivity analyses excluding participants who had experienced encephalopathy found a similar trend of PHIV+ with CDC C performing more poorly than the other two groups, and allowing for clustering of sibling pairs also did not change the overall model results (data not shown). A separate model for PHIV+ only found similar results to the overall model, and no other HIV-related health factors were associated with NPZ-6 scores (data not shown).

DISCUSSION

In our study we found no difference in cognitive scores between PHIV+ without a CDC C diagnosis and HIV- participants. The young people included represent many different countries of origin, with around two-thirds having been born outside of the UK/Ireland, predominantly in sub-Saharan Africa. They will have experienced varying education in childhood, and different levels of familial cultural adjustment to life in England. Findings have relevance to the many PHIV+ young people living in countries across Europe,[33] many of whom similarly started ART after infancy and/or are from sub-Saharan Africa.[17, 34, 35]

In our study domains with the poorest scores were executive function and information processing speed, similar to previous findings.[3, 5, 7, 36] Many young people had domain-specific and summary NPZ-6 cognitive scores within one standard deviation below the mean for the normative data, which may not have any functional significance. Further, the differences in individual domain and overall scores between HIV- and PHIV+ without a CDC diagnosis were relatively small. This finding suggests that contemporary cohorts of HIV positive children who avoid severe disease prior to starting ART are at similar risk of cognitive problems as their HIV uninfected peers, and that some problems may be subtle.

Whilst PHIV+ without CDC C diagnoses scored similarly to HIV- participants, both groups scored worse than available normative data, similar to a USA study,[3] and 31% and 23% respectively had a z-score lower than -2 in at least one domain This is not unexpected, as young people in our study are not representative of the surrounding adolescent population where they live, either ethnically or culturally. Indeed, normative data for CogState comprise largely male Caucasian Australian adults;[37] had we not carefully recruited a comparative control population in our study we may have concluded that cognitive impairment was more prevalent in all adolescents with perinatally acquired HIV. Conversely, in this cohort of long-term survivors of perinatal HIV, PHIV+ participants with CDC C diagnoses had the poorest cognition. Most of the CDC C events were experienced in early life, indicating the importance of early initiation of ART to minimise disease severity and long-term sequelae.[3, 13, 38, 39]

Other independent risk factors for poorer NPZ-6 were younger age, black African ethnicity, and worse depression, but not HIV-related factors. As NPZ-6 is age-adjusted, findings may suggest recovery as PHIV+ mature and develop other compensatory skills. Poorer results for those of black African ethnicity are unlikely to be due to linguistic fluency, as many were born in the UK or in English-speaking countries. Additionally many of the CogState tests were non-verbal, but the predominance of Caucasian males in the normative dataset may inhibit complete adjustment for ethnicity in our study. These potential problems highlight the importance of recruiting study-specific control groups as well as careful adjustment for demographic variables;[19, 40] our sensitivity analysis showed a separate effect of deprivation score on lower NPZ-6, and socio-economic status has itself been associated with cognitive function.[41] Depression has been associated with poorer cognition in studies of HIV-infected adults, consistent with the association found in our study.[42, 43] We found that parent death, more adult carers, ever having alcohol

and ever taking recreational drugs were associated with NPZ-6 in univariable analyses, but their effect was weakened after adjustment for ethnic group.

Our study has a number of limitations. Firstly, its cross-sectional nature means that we are unable to draw causal inferences about the direction of associations found with NPZ-6. Secondly, the study could not differentiate the effect of HIV versus ART exposure on cognition, or the specific effects of individual ART drugs. Thirdly, although all PHIV+ young people were invited to join AALPHI, those with severe cognitive impairment may not have been referred to the study. However those included were quite representative of the national adolescent cohort in the UK/Ireland, and stratification by CDC C stage controlled for some differences. Fourthly, among HIV- participants, prenatal ART exposure was not measured as two-thirds were born outside the UK/Ireland. Fifth, we did not have the statistical power to investigate multiplicative effects of combined variables on cognitive function. However to our knowledge ours is the first study to recruit a substantial number of PHIV+ as well as HIV- affected older adolescents about to embark on adult life.

In conclusion, our study of older adolescents with PHIV and a comparable group of HIV- young people affected by HIV found that cognitive scores over a range of domains were similar for PHIV+ without a CDC C diagnosis and HIV- participants, and indicated mild rather than severe impairment. Although the drive to halt all new infections in infants and to provide early ART for those infected may prevent severe cognitive complications in the future, there are still many children globally with HIV who did not start treatment in early life and for whom cognitive issues may be relevant. The day-to-day impact of cognitive problems on educational and employment outcomes in adulthood warrants further investigation.

Acknowledgements

We thank all PHIV+ and HIV- young people, parents and staff from all the clinics and voluntary services in AALPHI.

Project team: S. Brice, A. Judd, M. Le Prevost, A. Mudd, A. Nunn, K. Rowson, K. Sturgeon.

Investigators: M. Conway, K. Doerholt, D. Dunn, C. Foster, D.M. Gibb, A. Judd (PI), S. Kinloch, N. Klein, H. Lyall, D. Melvin, K. Prime, T. Rhodes, C. Sabin, M. Sharland, C. Thorne, P. Tookey.

MRCC CTU Data Services: C. Diaz Montana, K. Fairbrother, M. Rauchenberger, N. Tappenden, S. Townsend.

Neurocognitive subgroup: A. Arenas-Pinto, C. Foster, A. Judd, M. Le Prevost, D. Melvin, A. Winston.

Steering Committee chairs: D. Gibb, D. Mercey (2012-2015), C. Foster (2016-).

NHS clinics (named alphabetically): LONDON: Chelsea and Westminster NHS Foundation Trust, F. Boag, P. Seery; Great Ormond Street Hospital NHS Foundation Trust, M. Clapson, V. Noveli; Guys and St Thomas' NHS Foundation Trust, A. Callahgan, E. Menson; Imperial College Healthcare NHS Trust, C. Foster, A. Walley; King's College Hospital NHS Foundation Trust, E. Cheserem, E. Hamlyn; Mortimer Market Centre, Central and North West London NHS Foundation Trust, R. Gilson, T. Peake; Newham University Hospital, S. Liebeschuetz, R. O'Connell; North Middlesex University Hospital NHS Trust, J. Daniels, A. Waters; Royal Free London NHS Foundation Trust, T. Fernandez, S. Kinloch de Loes; St George's University Hospitals NHS Foundation Trust, S. Donaghy, K. Prime. REST OF ENGLAND: Alder Hey Children's NHS Foundation Trust, S. Paulus, A. Riordan; Birmingham Heartlands, Heart of England NHS Foundation Trust J. Daglish, C. Robertson; Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust, J. Bernatonlene, L. Hutchinson, University Hospitals Bristol NHS Foundation Trust, M. Gompel, L. Jennings; Leeds Teaching Hospitals NHS Trust, M. Dowie, S. O'Riordan; University Hospitals of Leicester NHS Trust, W. Ausalut, S. Bandi; North Manchester General Hospital, Pennine Acute Hospitals NHS Trust, P. McMaster, K. Rowson; Royal Liverpool and Broadgreen University Hospitals NHS Trust, M. Chaponda, S Paulus. Voluntary services (named alphabetically): Blue Sky Trust, C. Dufton, B. Oliver; Body and Soul, A. Ash, J. Marsh; Faith in People, I. Clowes, M. Overton; Positively UK, M. Kiwanuka, A. Namiba; Positive Parenting & Children, N. Bengtsson, B. Chipalo. Funding: Monument Trust and PENTA Foundation.

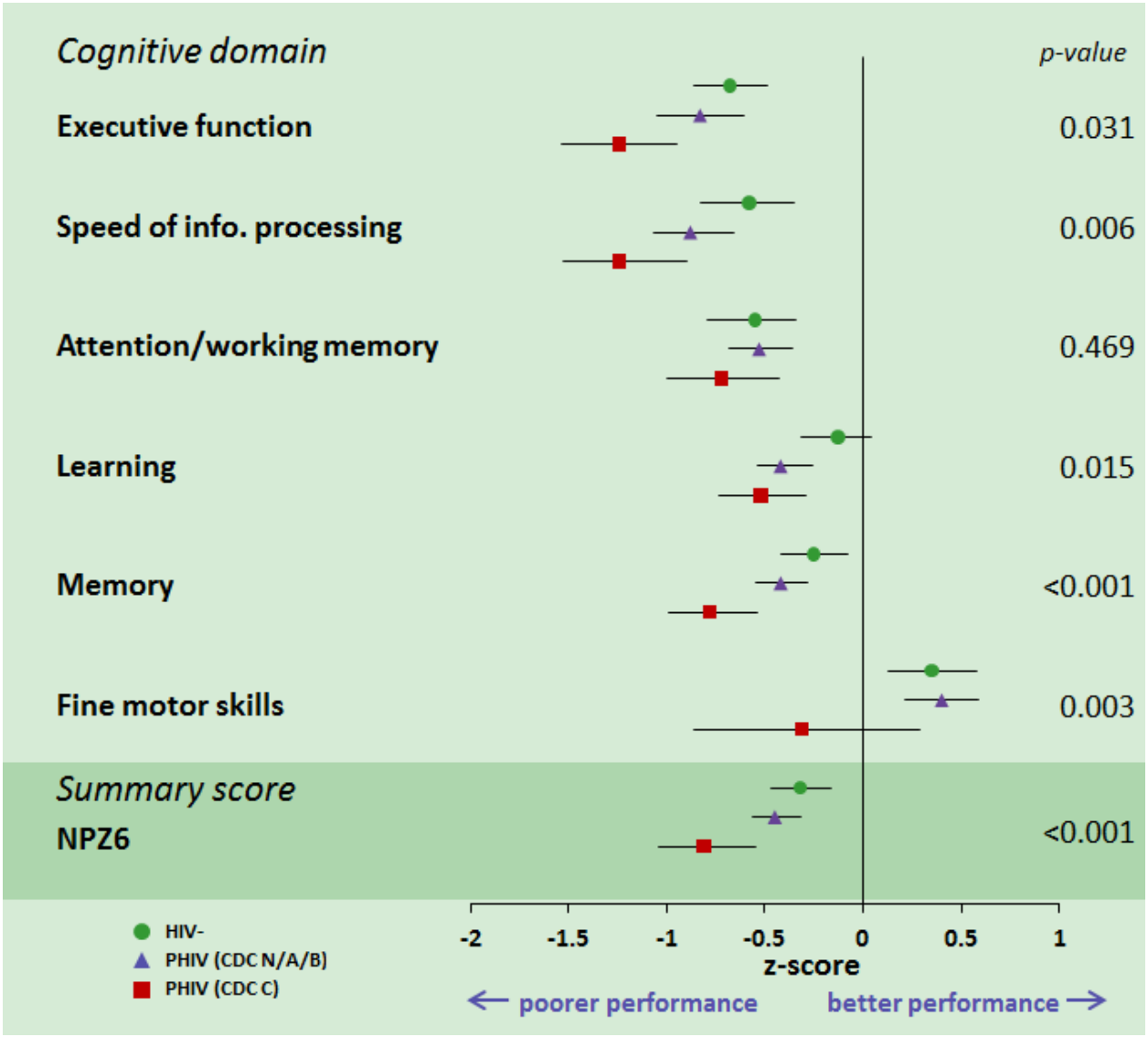
Role of the funding sources

The funding sources had no role in the study design, collection, analysis and interpretation of data, writing of the report or decision to submit the paper for publication.

Conflict of interest

All authors - none declared.

Figure 1: Neurocognitive performance by domain, HIV status and CDC class



Notes: Data points are means with 95% confidence intervals. P values compare the three groups (HIV-, PHIV CDC N/A/B), PHIV CDC C) using ANOVA.

Table 1: Characteristics of PHIV+ and HIV- participants in AALPHI, and comparison to PHIV+ in UK/Ireland

	AALPHI			UK/Ireland+	
	HIV- (n=97)	PHIV+ (n=296)	P value*	PHIV+ (n=698)	P value**
	n (%) or median [IQR] or mean [SD]				
Sociodemographics:					
Sex (male)	31 (32%)	125 (42%)	0.073	363 (52%)	0.005
Age					
≤15 years	41 (42%)	116 (39%)	0.768	264 (38%)	0.900
16-18 years	35 (36%)	119 (40%)		283 (41%)	
≥19 years	21 (22%)	61 (21%)		151 (22%)	
Median	16 [14,18]	16 [15,18]	0.820	16 [14,18]	0.689
Ethnicity (black)	69 (71%)	251 (85%)	0.003	560 (81%)	0.115
Born outside UK/Ireland	59 (61%)	228 (77%)	0.002	445 (64%)	<0.001
Psychosocial:					
Death of one/both parents	22 (24%)	101 (36%)	0.023		
Live with parents	86 (89%)	269 (92%)	0.402		
Occupation					
School	89 (92%)	273 (92%)	0.734		
Employment	4 (4%)	8 (3%)			
Not in education or	4 (4%)	15 (5%)			
Parent/ carer in work	56 (58%)	210 (71%)	0.043		
Ever excluded from school	23 (24%)	51 (17%)	0.165		
Environmental:					
Fostered/adopted	0 (0%)	14 (11%)	0.019		
Number of adult carers	1 [1,2]	1 [1,2]	0.318		
Language at home					
English only	44 (45%)	154 (52%)	0.391		
English and another	49 (51%)	134 (45%)			
Language other than	4 (4%)	7 (2%)			
Mean IDACI deprivation	0.45 [0.14]	0.39 [0.18]	0.012		
Lifestyle:					
Ever smoked	24 (26%)	52 (18%)	0.122		
Ever alcohol	42 (45%)	115 (40%)	0.428		
Ever recreational drugs	25 (28%)	40 (14%)	0.003		
Mental health:					
Mean HADS anxiety score	6.1 [4.1]	6.5 [4.0]	0.279		
Mean HADS depression	3.5 [3.0]	3.9 [3.2]	0.069		

+ UK/Ireland numbers are for PHIV+ aged 13-21 years in the national CHIPS cohort who are not in AALPHI

* P value comparing HIV- to PHIV+ in AALPHI

**P value comparing PHIV+ in AALPHI to PHIV+ aged 13-21 years in the national CHIPS cohort.

The grey shaded area represents variables not measured in CHIPS, hence no comparison was possible.

Table 2: HIV clinical markers for PHIV+ with and without a CDC C diagnosis in AALPHI, and comparison to PHIV+ in UK/Ireland

	PHIV+ in AALPHI			PHIV+ in UK/Ireland[+]	
	No CDC C (n=210)	**CDC C (n=76)**	**Total (n=286)**	**PHIV+ (n=698)**	**P value***
	n (%) or median [IQR]				
Age at first presentation					
Birth	18 (9%)	6 (8%)	24 (8%)	46 (7%)	0.030
<1 year	27 (13%)	25 (33%)	52 (18%)	88 (13%)	
1-4 years	52 (25%)	25 (33%)	77 (27%)	170 (24%)	
5-9 years	67 (32%)	14 (18%)	81 (28%)	217 (31%)	
≥10 years	46 (22%)	6 (8%)	52 (18%)	176 (25%)	
Median age	5 [1,9]	1.5 [0,5]	4.0 [0.0,8.0]	6 [2,10]	0.001
Year of first presentation					
Up to 1996	33 (16%)	16 (21%)	49 (17%)	78 (11%)	0.040
1997-2000	43 (20%)	26 (34%)	69 (24%)	177 (25%)	
2001 onwards	134 (64%)	34 (45%)	168 (59%)	443 (63%)	
ART status at interview					
Naïve	24 (8%)	0 (0%)	24 (8%)	104 (15%)	0.006
On ART	175 (83%)	72 (95%)	247 (86%)	541 (78%)	
Off ART (previous ART exposure)	11 (5%)	4 (5%)	15 (5%)	53 (8%)	
Age at initiation of ART (on or off ART only)	8.0 [5.1,11.8]	3.8 [1.3,6.2]	6.8 [3.5,10.9]	7.1 [3.0,11.1]	0.775
Year initiated ART (on or off ART only)					
Up to 1996	0 (0%)	1 (1%)	1 (<1%)	31 (5%)	0.002
1997-2000	41 (22%)	37 (49%)	78 (30%)	158 (27%)	
2001 onwards	144 (78%)	38 (50%)	182 (70%)	405 (68%)	
Taking efavirenz at interview (on ART only)	61 (29%)	16 (21%)	77 (27%)	183 (34%)	0.042
Viral load <50c/ml at interview (on ART only)	138 (79%)	49 (68%)	187 (76%)	204 (71%)	0.205
Median cumulative years VL<400c/ml	5.7 [2.5,8.4]	7.5 [4.4,10.7]	5.9 [3.1,9.2]	4.7 [2.0,7.9]	<0.001
CD4 nadir (cells/mm^3)	226 [131,370]	197 [43,325]	220 [120,354]	260 [153,375]	0.001
CD4 at interview (cells/mm^3)	582 [406,769]	641 [422,873]	599 [407,790]	620 [477,810]	0.057

+ UK/Ireland numbers are for PHIV+ aged 13-21 years in the national CHIPS cohort who are not in AALPHI

*P value comparing all PHIV+ in AALPHI to CHIPS aged 13-21 years.

Table 4: Univariable and multivariable predictors* of improved NPZ-6 scores

Variable	Univariable predictors of NPZ-6			Multivariable predictors of NPZ-6		
	Coefficient	95% CI	p value	Coefficient	95% CI	p value
Constant	-0.32	-0.48,-0.15		-0.73	-1.36, -0.10	
HIV/CDC status (*v.* HIV-)			<0.001			<0.001
PHIV+ no C	-0.13	-0.33, 0.07		-0.01	-0.22, 0.20	
PHIV+ C	-0.50	-0.75, -0.24		-0.44	-0.70, -0.19	
Sociodemographics:						
Sex, female (*v.* male)	0.06	-0.11, 0.24	0.472	0.01	-0.16, 0.19	0.867
Age, per year increase	0.05	0.02, 0.08	0.004	0.06	0.02, 0.09	0.002
Ethnicity, black African (*v.* other)	-0.44	-0.66, -0.23	<0.001	-0.46	-0.68, -0.24	<0.001
Born outside of UK/Ireland	-0.16	-0.35, 0.03	0.090	-0.10	-0.29, 0.09	0.292
Psychosocial:						
Parent death (*v.* both parents alive)			0.015			
One parent died	-0.08	-0.28, 0.11		-		
Both parents died	-0.62	-1.04, -0.20		-		
Environmental:						
No. adult carers, per 1 carer increase	-0.04	-0.09, 0.01	0.138	-		
IDACI deprivation score, per unit inc.	-0.49	-1.03, 0.06	0.079	-		
Lifestyle:						
Ever alcohol	0.33	0.16, 0.50	<0.001	-		
Ever recreational drugs	0.39	0.17, 0.62	<0.001	-		
Mental health:						
Depression score, per unit worse	-0.04	-0.06, -0.01	0.014	-0.04	-0.06, -0.01	0.011

Notes

*All *a priori* variables, as well as those with univariable $p<0.15$ are presented here.

Supplementary Table 1: Neurocognitive domains, tools and tests

Domain	Tool	Test
Executive function	Cogstate	Groton Maze
	Color Trails Test	Color Trails 2 (normative data for age 18-29 years, with 7-9 years of education)
Speed of info. Processing	Cogstate	Detection task (age adjusted)
	Color Trails Test	Color Trails 1 (normative data for age 18-29 years, with 7-9 years of education)
Attention/working memory	Cogstate	Identification Task (age adjusted)
	WAIS-IV	Coding (raw no. correct) (normative data not available so omitted from NPZ-6)
Learning	Cogstate	One card learning (age adjusted)
	Cogstate	International shopping list
Memory	Cogstate	International shopping list delayed
	Cogstate	One back task
Fine motor skills	Grooved pegboard	Pegboard dominant hand (age/sex adjusted)
	Grooved pegboard	Pegboard non-dominant hand (age/sex adjusted)

Supplementary Table 2: Mean z-scores by neurocognitive domain in PHIV+ with a CDC C diagnosis, PHIV+ with no CDC C diagnosis, and HIV- participants

Domain	Mean z-score (standard deviation)			
	HIV- (n=97)	PHIV+ no C (n=210)	PHIV+ C (n=76)	p
Executive function	-0.68 (0.92)	-0.83 (1.61)	-1.24 (1.34)	0.031
Speed of information processing	-0.58 (1.23)	-0.88 (1.39)	-1.24 (1.29)	0.006
Attention/concentration	-0.55 (1.19)	-0.53 (1.13)	-0.72 (1.18)	0.469
Learning	-0.13 (0.94)	-0.42 (0.95)	-0.52 (0.92)	0.015
Memory	-0.25 (0.87)	-0.42 (0.91)	-0.78 (0.90)	<0.001
Fine motor skills	0.35 (1.09)	0.40 (1.41)	-0.31 (2.41)	0.003
NPZ-6	-0.32 (0.76)	-0.45 (0.80)	-0.81 (0.99)	<0.001

Notes: P values compare the three groups (HIV-, PHIV CDC N/A/B), PHIV CDC C) using ANOVA.

REFERENCES

1. 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.
2. Laughton B, Cornell M, Boivin M, Van Rie A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. *J Int AIDS Soc* 2013,**16**:18603.
3. Smith R, Chernoff M, Williams PL, Malee KM, Sirois PA, Kammerer B*, et al.* Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. *Pediatr Infect Dis J* 2012,**31**:592-598.
4. Mellins CA, Elkington KS, Leu CS, Santamaria EK, Dolezal C, Wiznia A*, et al.* Prevalence and change in psychiatric disorders among perinatally HIV-infected and HIV-exposed youth. *AIDS Care* 2012,**24**:953-962.
5. Ruel TD, Boivin MJ, Boal HE, Bangirana P, Charlebois E, Havlir DV*, et al.* Neurocognitive and motor deficits in HIV-infected Ugandan children with high CD4 cell counts. *Clinical Infectious Diseases* 2012,**54**:1001-1009.
6. Koekkoek S, de Sonneville LM, Wolfs TF, Licht R, Geelen SP. Neurocognitive function profile in HIV-infected school-age children. *Eur J Paediatr Neurol* 2008,**12**:290-297.
7. Nachman S, Chernoff M, Williams P, Hodge J, Heston J, Gadow KD. Human immunodeficiency virus disease severity, psychiatric symptoms, and functional outcomes in perinatally infected youth. *Arch Pediatr Adolesc Med* 2012,**166**:528-535.
8. Crowell CS, Huo Y, Tassiopoulos K, Malee KM, Yogev R, Hazra R*, et al.* Early viral suppression improves neurocognitive outcomes in HIV-infected children. *AIDS* 2015,**29**:295-304.
9. Garvie PA, Zeldow B, Malee K, Nichols SL, Smith RA, Wilkins ML*, et al.* Discordance of cognitive and academic achievement outcomes in youth with perinatal HIV exposure. *Pediatr Infect Dis J* 2014,**33**:e232-238.
10. Rutstein Lazarus J, Rutstein RM, Lowenthal ED. Treatment initiation factors and cognitive outcome in youth with perinatally acquired HIV infection. *HIV Med* 2015,**16**:355-361.
11. Webb KM, Mactutus CF, Booze RM. The ART of HIV therapies: dopaminergic deficits and future treatments for HIV pediatric encephalopathy. *Expert Rev Anti Infect Ther* 2009,**7**:193-203.
12. Patel K, Ming X, Williams PL, Robertson KR, Oleske JM, Seage GR, 3rd. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. *AIDS* 2009,**23**:1893-1901.
13. Wood SM, Shah SS, Steenhoff AP, Rutstein RM. The impact of AIDS diagnoses on long-term neurocognitive and psychiatric outcomes of surviving adolescents with perinatally acquired HIV. *AIDS* 2009,**23**:1859-1865.
14. Paramesparan Y, Garvey LJ, Ashby J, Foster CJ, Fidler S, Winston A. High rates of asymptomatic neurocognitive impairment in vertically acquired HIV-1-infected adolescents surviving to adulthood. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*,**55**:134-136.
15. Hackman DA, Farah MJ. Socioeconomic status and the developing brain. *Trends Cogn Sci* 2009,**13**:65-73.
16. Mellins CA, Smith R, O'Driscoll P, Magder LS, Brouwers P, Chase C*, et al.* High rates of behavioral problems in perinatally HIV-infected children are not linked to HIV disease. *Pediatrics* 2003,**111**:384-393.
17. Judd A, Doerholt K, Tookey PA, Sharland M, Riordan A, Menson E*, et al.* Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with

perinatally acquired HIV infection during 1996-2006: planning for teenage and adult care. *Clinical Infectious Diseases* 2007,**45**:918-924.
18. Cohen S, Ter Stege JA, Geurtsen GJ, Scherpbier HJ, Kuijpers TW, Reiss P*, et al.* Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls. *Clin Infect Dis* 2015,**60**:1111-1119.
19. Winston A, Arenas-Pinto A, Stohr W, Fisher M, Orkin CM, Aderogba K*, et al.* Neurocognitive function in HIV infected patients on antiretroviral therapy. *PLoS One* 2013,**8**:e61949.
20. Steinberg L. Cognitive and affective development in adolescence. *Trends Cogn Sci* 2005,**9**:69-74.
21. Colver A, Longwell S. New understanding of adolescent brain development: relevance to transitional healthcare for young people with long term conditions. *Arch Dis Child* 2013,**98**:902-907.
22. Gibb DM, Duong T, Tookey PA, Sharland M, Tudor-Williams G, Novelli V*, et al.* Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *British Medical Journal* 2003,**327**:1019-1024.
23. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS* 2008,**22**:973-981.
24. Winston A, Duncombe C, Li PC, Gill JM, Kerr SJ, Puls R*, et al.* Does choice of combination antiretroviral therapy (cART) alter changes in cerebral function testing after 48 weeks in treatment-naive, HIV-1-infected individuals commencing cART? A randomized, controlled study. *Clin Infect Dis* 2010,**50**:920-929.
25. Garvey LJ, Yerrakalva D, Winston A. Correlations between computerized battery testing and a memory questionnaire for identification of neurocognitive impairment in HIV type 1-infected subjects on stable antiretroviral therapy. *AIDS Res Hum Retroviruses* 2009,**25**:765-769.
26. Cysique LA, Maruff P, Darby D, Brew BJ. The assessment of cognitive function in advanced HIV-1 infection and AIDS dementia complex using a new computerised cognitive test battery. *Arch Clin Neuropsychol* 2006,**21**:185-194.
27. Collie A, Maruff P, Darby DG, McStephen M. The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. *J Int Neuropsychol Soc* 2003,**9**:419-428.
28. Wechsler D. Wechsler Adult Intelligence Scale - Fourth Edition. In. San Antonio, TX, USA: Pearson Ecuation, Inc; 2008.
29. Lafayette Instrument Company Inc. Grooved Pegboard test user instructions. In. Lafayette, IN, USA: Lafayette Instrument Company, Inc; 2002.
30. Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *Morbidity and Mortality Weekly Report* 1994,**43**:1-10.
31. Su T, Schouten J, Geurtsen GJ, Wit FW, Stolte IG, Prins M*, et al.* Multivariate normative comparison, a novel method for more reliably detecting cognitive impairment in HIV infection. *AIDS* 2015,**29**:547-557.
32. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983,**67**:361-370.
33. Writing group for the Kids to Adults Working Group and Data Management and Harmonisation Group in EuroCoord. Children and young people with perinatal HIV in Europe: epidemiological situation in 2014 and implications for the future. *Eurosurveillance* 2016,**21**:ppi=30162.

34. Cohen S, van Bilsen WP, Smit C, Fraaij PL, Warris A, Kuijpers TW*, et al.* Country of birth does not influence long-term clinical, virologic, and immunological outcome of HIV-infected children living in the Netherlands: a cohort study comparing children born in the Netherlands with children born in Sub-Saharan Africa. *J Acquir Immune Defic Syndr* 2015,**68**:178-185.
35. de Jose MI, Jimenez de Ory S, Espiau M, Fortuny C, Navarro ML, Soler-Palacin P*, et al.* A new tool for the paediatric HIV research: general data from the Cohort of the Spanish Paediatric HIV Network (CoRISpe). *BMC Infect Dis* 2013,**13**:2.
36. Martin SC, Wolters PL, Toledo-Tamula MA, Zeichner SL, Hazra R, Civitello L. Cognitive functioning in school-aged children with vertically acquired HIV infection being treated with highly active antiretroviral therapy (HAART). *Dev Neuropsychol* 2006,**30**:633-657.
37. Garvey L, Surendrakumar V, Winston A. Low Rates of Neurocognitive Impairment Are Observed in Neuro-Asymptomatic HIV-Infected Subjects on Effective Antiretroviral Therapy. *HIV Clinical Trials* 2011,**12**:333-338.
38. Laughton B, Cornell M, Grove D, Kidd M, Springer PE, Dobbels E*, et al.* Early antiretroviral therapy improves neurodevelopmental outcomes in infants. *AIDS* 2012,**26**:1685-1690.
39. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA*, et al.* Early antiretroviral therapy and mortality among HIV-infected infants. *New England Journal of Medicine* 2008,**359**:2233-2244.
40. Manly JJ, Smith C, Crystal HA, Richardson J, Golub ET, Greenblatt R*, et al.* Relationship of ethnicity, age, education, and reading level to speed and executive function among HIV+ and HIV- women: the Women's Interagency HIV Study (WIHS) Neurocognitive Substudy. *J Clin Exp Neuropsychol* 2011,**33**:853-863.
41. Brito NH, Noble KG. Socioeconomic status and structural brain development. *Front Neurosci* 2014,**8**:276.
42. Fellows RP, Byrd DA, Morgello S. Major depressive disorder, cognitive symptoms, and neuropsychological performance among ethnically diverse HIV+ men and women. *J Int Neuropsychol Soc* 2013,**19**:216-225.
43. Grant I, Franklin DR, Jr., Deutsch R, Woods SP, Vaida F, Ellis RJ*, et al.* Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology* 2014,**82**:2055-2062.