Title

Absence of neurocognitive disadvantage associated with paediatric HIV subtype A infection in children on antiretroviral therapy

Journal

Journal of the International AIDS Society, 20(2)

ISSN

1758-2652

Authors

Bangirana, Paul
Ruel, Theodore D
Boivin, Michael J
et al.

Publication Date

2017-10-01

DOI

10.1002/jia2.25015

Peer reviewed

Bangirana P et al. *Journal of the International AIDS Society* 2017, **20**:e25015
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25015/full | https://doi.org/10.1002/jia2.25015

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

SHORT REPORT

Absence of neurocognitive disadvantage associated with paediatric HIV subtype A infection in children on antiretroviral therapy

Paul Bangirana[1], Theodore D Ruel[2], Michael J Boivin[3], Satish K Pillai[4,5], Leila B Giron[6], Alla Sikorskii[3,7], Asish Banik[7] and Jane Achan[8]

Corresponding author: Paul Bangirana, Makerere University, Department of Psychiatry, Upper Mulago Hill Road, Box 7072, Kampala, Uganda. Tel: +256 772 673831. (pbangirana@yahoo.com)

Abstract

Introduction: Infection with HIV subtype A has been associated with poorer neurocognitive outcomes compared to HIV subtype D in Ugandan children not eligible for antiretroviral therapy (ART). In this study, we sought to determine whether subtype-specific differences are also observed among children receiving ART.

Materials and Methods: Children were recruited from a clinical trial in which they were randomized to receive either lopinavir (LPV)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)- based ART (NCT00978068). Age at initiation of ART ranged from six months to six years. HIV subtype was determined by PCR amplification and population sequencing of the *pol* region derived from peripheral blood mononuclear cell DNA, followed by application of the REGA and Recombinant Identification Programme algorithms. General cognition was assessed using the Kaufman Assessment Battery for Children (Second Edition), attention using the Test of Variables of Attention, and motor skills using the Bruininks-Oseretsky Test of Motor Proficiency (Second Edition). Home environment was assessed using the Home Observation for the Measurement of the Environment (HOME). Age-adjusted test z-scores were entered into a regression model that adjusted for sex, socio-economic status score, HOME score, years of schooling, and ART treatment type.

Results: One hundred and five children were tested; median (interquartile range) age was 7.05 years (6.30 to 8.44), CD4 count was 867.7 cells/mm^3 (416.0 to 1203.5), and duration on ART was 4.03 years (3.55 to 4.23). Seventy-eight children had HIV subtype A and 27 had subtype D; the groups had comparable home and socio-economic status, except that there were more males among children infected with subtype A than D (64.7% vs. 35.3%, $p = 0.02$). There were no differences between the subtypes in general cognition (estimated mean difference: 0.20; 95% CI: −0.11 to 0.50); $p = 0.21$), attention (−0.18, 95% CI: −0.60 to 0.24, $p = 0.41$) and motor skills (1.60, 95% CI: −0.84 to 4.04, $p = 0.20$).

Conclusions: Our results imply that ART may diminish the neurocognitive disadvantage seen in treatment-naïve HIV-infected children with subtype A.

Keywords: HIV subtype; neurocognition; children; antiretroviral therapy

Received 11 April 2017; **Accepted** 28 September 2017

1 | INTRODUCTION

Access to antiretroviral therapy (ART) in low and middle-income countries has increased over the years and contributed to improved health outcomes in HIV-infected children including neurocognitive outcomes [1,2]. However, neurocognitive deficits are still observed in children receiving ART, underscoring the need to optimize treatment [3,4]. Studies evaluating neurocognitive outcomes in HIV-infected children have identified key factors associated with poor outcome including high viral load, low CD4 counts, and high levels of soluble P-selectin and fibrinogen [5–7]. The time between sample collection and neurocognitive testing varies in these studies [8,9].

Data describing the influence of HIV-subtype on neurocognitive function are conflicting. Our group previously reported that HIV subtype A was associated with poorer neurocognitive outcomes than subtype D in ART naïve children [8]. The poorer neurocognitive outcomes in children with subtype A was speculated to be a consequence of increased CCR5 affinity associated with HIV subtype A, that could in turn lead to increased ability to infect macrophages and enter the central nervous system (CNS) [8]. Our study above in children contrasted with observations by Sacktor *et al.* in HIV-infected adults with advanced immune suppression where subtype D and not A was associated with poorer neurocognitive outcomes [10]. Another study by Sacktor el al. found no

differences by subtype in adults with moderate immune suppression [11].

In addition to diseases like HIV, malaria and meningitis, environmental variables like child and parental education, socio-economic status of the family, quality of the home environment and the child's nutritional status affect cognition in children in sub-Saharan Africa [12–14]. These variables need to be accounted for when studying cognitive function in children with HIV or other CNS infections.

Adverse drug reactions, e.g. toxicities are one of the main factors influencing ART regimen choice and adherence [15,16]. Subtype-specific differences in neurocognitive outcomes could also have implications for clinical management of children infected with subtype A, requiring administration of drugs with better CNS penetration to mitigate the virus' effect on the brain. Current WHO guidelines recommend that all HIV-infected children are initiated on ART regardless of the disease stage, promoting universal ART coverage [17]. To better inform ART regimen decision-making, we investigated whether variations in neurocognitive outcomes associated with HIV subtype are also observed in HIV-infected children on ART. In this study, we compared neurocognitive outcomes between HIV subtype A-infected and HIV subtype D-infected children on suppressive ART.

2 | METHODS

The study was conducted between December 2013 and May 2015 in Tororo district, eastern Uganda. Participants were recruited from a cohort of children who had participated in the PROMOTE-Paediatrics trial conducted from September 2009 to July 2011 which recruited children aged two months to five years not yet on ART or receiving the standard first-line ART as per national guidelines at that time [18]. Participants in the PROMOTE-Paediatrics trial were randomized to receive either protease inhibitors (PI) (lopinavir-ritonavir plus two nucleoside reverse transcriptase inhibitors (NRTIs)) or non-nucleoside reverse transcriptase inhibitors (NNRTI) nevirapine (for children less than three years of age) or efavirenz (for children ≥3 years of age) – plus two NRTIs. Lamivudine and zidovudine were the NRTIs used, with stavudine or abacavir replacing zidovudine in children who had anaemia. Majority of the children (71%) were HAART naive at the start of the study [19]. Children who were already receiving ART were randomly assigned to continue their current regimen or to switch to lopinavir-ritonavir while continuing the same NRTIs. Children were followed up for six months to two years to record malaria incidence [18]. At the conclusion of the study, the majority of children randomized to LPV/r were changed to NNRTI-based treatment.

This study began two years after the parent trial had closed [18]. Inclusion criteria for this study included: a) age 5 years to 12 years, b) no history of malnutrition or other CNS infection as reported by the mother, c) currently or formerly enrolled in the PROMOTE-Paediatrics trial. Children were traced and those meeting eligibility criteria were assessed for general cognition, working memory (sequential processing), visual-spatial processing (simultaneous processing), Learning, and planning (reasoning) using the Kaufman Assessment Battery for Children (Second Edition) (KABC-II) [20]. Attention was assessed using the D' Prime score of the Test of Variables of Attention (TOVA) [21], and motor skills using the Total Score of the Bruininks-Oseretsky Test of Motor Proficiency (Second Edition) (BOT-2) [22]. The battery of tests used in this study had previously been used in HIV-infected Ugandan children [5,8,23]. The KABC-II and TOVA have been validated for use in Uganda and in similar settings where they demonstrated stable construct validity and were sensitive to education exposure and health indicators [24–26].

Home environment was assessed using the Home Observation for the Measurement of the Environment (HOME) [27] and nutrition was assessed using height- and weight-for-age z scores (Epi Info version 3.5.3; Centers for Disease Control and Prevention). Socio-economic status was assessed using a checklist of material possessions, housing quality, cooking resources and water accessibility [12]. HIV subtype and recombinant status were determined by PCR amplification and population sequencing of the *pol* region [28] derived from peripheral blood mononuclear cell (PBMC) DNA, followed by application of the REGA subtyping tool v2.0 and Recombinant Identification Programme algorithm [29,30]. Viral load and CD4 data were obtained from the PROMOTE-Paediatrics trial data.

Written informed consent was provided by the parents and caregivers of the children prior to enrolment. Assent was also provided by children aged seven years and older. The study was approved by the Research and Ethics Committee at Makerere University School of Medicine and the Uganda National Council for Science and Technology.

2.1 | Statistical analyses

The primary outcomes were general cognition, attention and motor skills. Their distributions were evaluated, and no outlying values were detected. Age adjusted z-scores (with a mean of 0 and standard deviation of 1) were derived from age-matched community controls (N = 210) from the same region for general cognition, working memory, visual spatial processing, planning and attention as previously described [31]. These controls were participating in another study that administered the KABC-II and TOVA. Z scores less than or equal to −1 were categorized as mild neurocognitive impairment. Age-adjusted standard scores based on US norms, with a mean of 50 and standard deviation of 10, were used for motor skills since there were no appropriate controls assessed with the BOT-2. Chi-square and T tests were used to compare baseline socio-demographic and clinical measures between the groups. Test scores were compared between the HIV subtypes using analysis of covariance (ANCOVA) while controlling for sex, socio-economic status score, HOME score, years of schooling, and ART regimen. Weight-for age z-score, viral load and CD4 were not included to avoid potential co-linearity with HIV subtype. Least square (LS) means and their standard errors (SE) were derived from the ANCOVA and compared by subtype using t-tests. Chi-square or Fisher's exact tests were used to compare the rates of mild neurocognitive impairment between the groups.

In our previous study of cognition by subtype in ART naïve children [8], 37 children infected with subtype A had a mean sequential processing score of 29.11 (SD=5.33) while the 16

children infected with subtype D had a mean (SD) of 31.81 (6.36). These differences corresponded to an effect size of Cohen's d = 0.48. In this study, the available sample sizes of 78 and 27 in the subtype groups allowed detection of differences corresponding to d = 0.63 or greater as statistically significant in two-tailed tests with power of 0.80 or greater and 0.05 level of significance. In addition to statistical significance testing, we estimated the magnitude of the effect sizes in this study. The adjusted effect sizes were computed as the difference between LS means divided by the square root of the mean squared error in the ANCOVA model.

Table 1. Socio-demographic characteristics and baseline laboratory measures of the study participants

Variable	Subtype A (N = 78)	Subtype D (N = 27)	*p*
Age (years)	7.32 (1.42)	7.57 (1.21)	0.41
Sex (male) N (%)	33 (42.31)	18 (69.23)	0.02
Years in school	2.17 (1.33)	2.11 (0.75)	0.84
Weight for age Z score	−1.07 (1.05)	−1.14 (1.10)	0.75
Height for age Z score	−0.76 (1.17)	−1.20 (0.94)	0.09
HOME score	−0.06 (0.99)	−0.41 (0.99)	0.12
SES score	9.08 (3.60)	8.63 (3.28)	0.57
Treatment arm, (PI) N (%)	43 (55.1)	12 (44.4)	0.34
Treatment duration (years)	4.05 (0.51)	3.98 (0.52)	0.53
Number of malaria episodes	3.82 (5.68)	4.04 (4.48)	0.86
Viral load			
≤400, N (%)	67 (85.9%)	23 (85.2%)	0.99[a]
>400, N (%)	11 (14.1%)	4 (14.8%)	
CD4 count	1026.09 (445.30)	1057.78 (433.84)	0.75

All figures are Mean (SD) unless otherwise stated. HOME, Home Observation for the Measurement of the Environment; PI, protease inhibitors; SES, socio-economic status score.
[a]Fisher's exact test.

3 | RESULTS

3.1 | Demographic characteristics by HIV Subtype

Of the 163 children who completed the parent trial, 162 were traced and screened for enrolment; 158 met eligibility criteria and were enrolled into this study. Viral subtype could not be determined for 49 children due to sample unavailability, and four children had subtype C or AD infection. We therefore analysed data for 105 children; 78 had subtype A and 27 had subtype D with a higher proportion of males seen with D versus A (69.2% vs. 42.3%, $p = 0.02$). The mean age (SD) was 7.38 (1.37) with a range of 5.01 to 10.21 (Table 1). There were no differences by subtype with respect to age, child's education, nutritional status, quality of the home environment, socio-economic status, number of malaria episodes during the parent trial, latest viral load, latest CD4 count, or duration of ART (median 4.16 years). There was no statistical difference in the proportion of children who received PIs versus NNRTIs between children infected with subtype A and D.

3.2 | Neurocognitive outcomes by subtype

No differences in neurocognitive outcome were observed between children infected with subtypes A versus D for both primary and secondary outcomes after controlling for confounding variables (Table 2). Though it was not statistically significant, only the difference in visual-spatial processing between subtypes A versus D corresponded to a practically meaningful effect size of 0.42. The frequency of mild neurocognitive impairment was not different between the groups (Table 3). 33.3% of the children had mild cognitive impairment in at least one of the areas tested (except motor skills for which no appropriate controls were present). In addition, there were no differences in neurocognitive outcomes between children receiving PIs versus NNRTIs. Years in school, nutritional status (WAZ and HAZ scores), HOME score and SES score were associated with a number of neurocognitive outcomes (Table 4). There was a sex difference in test performance with males performing better than females on tests for motor skills and visual-spatial processing. Viral load and absolute CD4 count were not significantly correlated with any of the outcomes.

Table 2. Comparison of age-adjusted z-scores between subtypes A and D, adjusted for sex, socio-economic status, quality of the home environment, years of schooling, and trial arm

Variable	Subtype A LS mean (SE)	Subtype D LS mean (SE)	Mean difference (95% confidence interval)	*p*	Adj. effect size
Overall cognition	0.05 (0.07)	−0.14 (0.13)	0.20 (−0.11 to 0.50)	0.20	0.31
Attention	0.08 (0.10)	0.25 (0.18)	−0.18 (−0.60 to 0.24)	0.41	0.20
Motor skills[a]	32.66 (0.60)	31.06 (1.04)	1.60 (−0.84 to 4.04)	0.20	0.31
Working memory	−0.18 (0.08)	−0.24 (0.13)	0.06 (−0.26 to 0.37)	0.73	0.08
Visual-spatial processing	0.06 (0.07)	−0.19 (0.12)	0.25 (−0.03 to 0.54)	0.08	0.42
Learning	0.20 (0.14)	−0.18 (0.25)	0.38 (−0.19 to 0.95)	0.19	0.32
Reasoning	0.13 (0.10)	0.04 (0.18)	0.10 (−0.32 to 0.51)	0.65	0.11

[a]Standard scores were used since z-scores were not available for this domain.

4 | DISCUSSION

This study compared neurocognitive outcomes between HIV subtype A-infected and subtype D-infected Ugandan children on ART. We did not find a difference in neurocognitive outcomes by subtype in this cohort of ART-treated children, in contrast to our prior study of ART-naïve children [8]. We speculate that suppression of viral replication by ART relieves neurocognitive deficits in both groups of children to near normal levels, effectively eliminating subtype-specific differences. We had previously observed that high HIV viral load was associated with neurocognitive impairment in Ugandan children who were not on ART [5]. In that same cohort, children infected with subtype A who had poorer neurocognitive outcomes also had higher HIV viral load than subtype D-infected children [8]. In this study, there was no difference in viral load between children infected with subtype A versus subtype D.

This current study adds to mounting evidence about the benefits of ART on neurocognitive outcomes. Brahmbhatt *et al*. showed that Ugandan children aged zero to six years who had been on ART for 24 to 60 months had decreased impairments in fine motor, receptive language, expressive language and in overall neurodevelopment compared to those who had been on ART for <12 months [32]. A later study by Brahmbhatt *et al*. among children aged 7 to 14 years showed that longer duration on ART significantly reduced the risk of impairment in working memory assessed using the KABC-II [23]. However, they observed higher rates of disability measured by the KABC-II in Ugandan HIV-infected children who were receiving ART compared to controls [23]. We similarly observed in this study that despite being on ART, 33.3% of the children had mild cognitive impairment in the KABC-II and TOVA. Neurocognitive impairment in HIV-infected children who are on ART highlights the need for comprehensive services for school going HIV-infected children that may include educational, neurocognitive and behavioural interventions [23,33].

The present study's correlations between the socio-demographic variables and neurocognitive outcome are consistent with earlier studies in Uganda and elsewhere in sub-Saharan Africa [12,14,34]. Bangirana *et al*. observed that education level of the child was associated with more neurocognitive abilities than other socio-demographic factors as was observed in the present study [12]. Similarly, nutritional factors (WAZ and HAZ) and the HOME score correlated with a number of abilities in this study as was observed in the earlier study [12]. These findings have implications for interventions to improve neurocognitive outcome in HIV-infected children. For example, Boivin *et al*. provided an intervention that enhanced the quality of the mother-child interaction that resulted in improved cognitive scores in Ugandan HIV-infected children [35].

This study has several limitations. There was a time lag of four years in evaluating the children after randomization during which time, number of malaria episodes and viral load that could affect neurocognitive outcome were not measured. Without pretreatment data, it is impossible to know the extent of subtype differences in the cohort, as well as to determine changes in neurocognitive outcomes after treatment and whether these differed by subtype. In addition, viral load levels and CD4 counts were measured during the PROMOTE-Paediatrics trial and not at the time when neurocognitive testing was performed. Therefore, definite associations between neurocognitive outcome and viral load/immune status cannot be assessed using our findings. Of the 163 children who completed the PROMOTE-Paediatrics trial, we were only able to analyse data for 105 children. These 105 children may represent a group that has slower disease progression and better neurocognitive outcomes than those who were not

Table 3. Frequency of mild neurocognitive impairment among the participants[a]

Variable	Total	Subtype A(N = 78)	Subtype D (N = 27)	*p*
Overall cognition	6 (5.7)	5 (6.4)	1 (3.7)	1.00[b]
Attention	14 (13.3)	12 (15.4)	2 (7.4)	0.51[b]
Working memory	13 (12.4)	10 (12.8)	3 (11.1)	1.00[b]
Visual-spatial processing	7 (6.7)	5 (6.4)	2 (7.4)	1.00[b]
Learning	18 (17.1)	12 (15.4)	6 (22.2)	0.55[b]
Reasoning	9 (8.6)	8 (10.3)	1 (3.7)	0.44[b]
Any impairment	35 (33.3)	26 (33.3)	9 (33.3)	1.00

Figures are n (%).
[a]Mild neurocognitive impairment refers to a z score of ≤−1.
[b]Fisher's exact test.

Table 4. Association between neurocognitive outcome and socio-demographic variables

	CD4 count	Viral load	Sex[a]	Years in school	WAZ	HAZ	HOME	SES score
Overall cognition	−0.08	−0.08	0.03	0.50***	0.23*	0.37***	0.34***	0.22*
Attention	0.003	−0.11	0.13	0.32***	0.19*	0.47***	0.20*	0.13
Motor skills	−0.14	−0.01	4.53***	0.31**	0.34***	0.42***	0.20*	0.19
Working memory	0.06	−0.15	0.23	0.36***	0.33***	0.38***	0.20*	0.18
Visual-spatial processing	−0.09	−0.05	0.41**	0.45***	0.30**	0.44***	0.39***	0.33***
Learning	−0.04	−0.06	0.48	0.41***	0.02	0.17	0.24*	0.09
Reasoning	−0.18	−0.01	0.08	0.44***	0.23*	0.33***	0.32***	0.20*

All values are correlation coefficients unless otherwise stated.
[a]Mean difference in test scores between males and females.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

located during follow-up, which may affect our results. Finally, the sample size was not adequate to detect differences between the groups that corresponded to effect sizes below d = 0.63. While there is no consensus on the cutoff for clinical significance, differences between groups exceeding 1/3 or 1/2 of the standard deviation (effect sizes exceeding 0.33 or 0.5) are often deemed clinically significant [36,37]. In the present study, only one of the effect sizes (0.42 for visual-spatial processing) was in this range, but statistical significance was not reached with the available sample size.

5 | CONCLUSIONS

We observed no differences in neurocognitive outcomes between subtype A and D in children who were on ART. A probable explanation for this observation could be optimal viral load suppression by ART in the majority. This study provides additional support for the current WHO guidelines to treat all HIV-infected children.

AUTHORS' AFFILIATIONS

[1]Department of Psychiatry, Makerere University College of Health Sciences, Kampala, Uganda; [2]Department of Pediatrics, University of California, San Francisco, CA, USA; [3]Department of Psychiatry, Michigan State University, East Lansing, MI, USA; [4]Blood Systems Research Institute, San Francisco, CA, USA; [5]Department of Laboratory Medicine, University of California, San Francisco, CA, USA; [6]Federal University of São Paulo, São Paulo, Brazil; [7]Department of Statistics and Probability, Michigan State University, East Lansing, MI, USA; [8]Disease Control and Elimination Theme, Medical Research Council Unit, Banjul, The Gambia

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

PB conceived the study, wrote the manuscript and approved the final manuscript as submitted. TDR and JA participated in the design of the study, reviewed and revised the manuscript and approved the final manuscript as submitted. MJB, AS and AB analysed the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. SKP and LBG analysed the samples for subtyping, reviewed and revised the manuscript, and approved the final manuscript as submitted.

ACKNOWLEDGEMENTS

We are grateful for the mothers and caregivers and their children for participating in this study. We also appreciate the efforts of the research team who traced the participants and carried out the neurocognitive assessments.

FUNDING

Funding for this study was made possible in part by a Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) grant from the International AIDS Society, supported by ViiV Healthcare and by an NICHD grant of the National Institutes of Health under award number (R01HD070723). The views presented in this report do not necessarily reflect the official policies of the International AIDS Society, ViiV Healthcare or the National Institutes of Health.

REFERENCES

1. Van Rie A, Dow A, Mupuala A, Stewart P. Neurodevelopmental trajectory of HIV-infected children accessing care in Kinshasa, Democratic Republic of Congo. J Acquir Immune Defic Syndr. 2009;52(5):636–42.
2. Le Doare K, Bland R, Newell ML. Neurodevelopment in children born to HIV-infected mothers by infection and treatment status. Pediatrics. 2012;130(5):e1326–44.
3. Lowick S, Sawry S, Meyers T. Neurodevelopmental delay among HIV-infected preschool children receiving antiretroviral therapy and healthy preschool children in Soweto, South Africa. Psychol Health Med. 2012;17(5):599–610.
4. Potterton J, Hilburn N, Strehlau R. Developmental status of preschool children receiving cART: a descriptive cohort study. Child Care Health Dev. 2016;42(3):410–4.
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. Clin Infect Dis. 2012;54:1001–9.
6. Banks LM, Zuurmond M, Ferrand R, Kuper H. The relationship between HIV and prevalence of disabilities in sub-Saharan Africa: systematic review (FA). Tropical Med Int Health. 2015;20(4):411–29.
7. Laughton B, Cornell M, Boivin M, Van Rie A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. J Int AIDS Soc. 2013;16:186903.
8. Boivin MJ, Ruel TD, Boal HE, Bangirana P, Cao H, Eller LA, et al. HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children. AIDS. 2010;24(8):1163–70.
9. Kapetanovic S, Leister E, Nichols S, Miller T, Tassiopoulos K, Hazra R, et al. Relationships between markers of vascular dysfunction and neurodevelopmental outcomes in perinatally HIV-infected youth. AIDS. 2010;24(10):1481–91.
10. Sacktor N, Nakasujja N, Skolasky RL, Rezapour M, Robertson K, Musisi S, et al. HIV subtype D is associated with dementia, compared with subtype A, in immunosuppressed individuals at risk of cognitive impairment in Kampala, Uganda. Clin Infect Dis. 2009;49(5):780–6.
11. Sacktor N, Nakasujja N, Redd AD, Manucci J, Laeyendecker O, Wendel SK, et al. HIV subtype is not associated with dementia among individuals with moderate and advanced immunosuppression in Kampala, Uganda. Metab Brain Dis. 2014;29(2):261–8.
12. Bangirana P, John CC, Idro R, Opoka RO, Byarugaba J, Jurek AM, et al. Socioeconomic predictors of cognition in Ugandan children: implications for community interventions. PLoS One. 2009;4(11):e7898.
13. Abubakar A, Holding P, Van de Vijver FJR, Newton C, Van Baar A. Children at risk for developmental delay can be recognised by stunting, being underweight, ill health, little maternal schooling or high gravidity. J Child Psychol Psychiatry. 2010;51(6):652–9.
14. Abubakar A, Van de Vijver F, Van Baar A, Mbonani L, Kalu R, Newton C, et al. Socioeconomic status, anthropometric status, and psychomotor development of Kenyan children from resource-limited settings: a path-analytic study. Early Hum Dev. 2008;84(9):613–21.
15. Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, Renaud-Théry F, Shaffer N, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. AIDS. 2013;27(9):1403–12.
16. Mocroft A, Phillips AN, Soriano V, Rockstroh J, Blaxhult A, Katlama C, et al. Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen: increased incidence of stopping due to toxicity or patient/physician choice in patients with hepatitis C coinfection. AIDS Res Hum Retroviruses. 2005;21(9):743–52.
17. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015.
18. Achan J, Kakuru A, Ikilezi G, Ruel T, Clark TD, Nsanzabana C, et al. Antiretroviral agents and prevention of malaria in HIV-Infected Ugandan children. N Engl J Med. 2012;367(22):2110–8.
19. Ruel TD, Kakuru A, Ikilezi G, Mwangwa F, Dorsey G, Rosenthal PJ, et al. Virologic and immunologic outcomes of HIV-infected Ugandan children randomized to lopinavir/ritonavir or nonnucleoside reverse transcriptase inhibitor therapy. J Acquir Immune Defic Syndr. 2014; 65(5):535–41.
20. Kaufman AS, Kaufman NL. Kaufman Assessment Battery for Children Manual, 2nd edn. Circle Pines, MN: American Guidance Service; 2004.
21. Leark RA, Greenberg LM, Kindschi CL, Dupuy TR, Hughes SJ. Test of variables of attention continuous performance test. Los Alamitos, CA: The TOVA Company; 2007.
22. Bruininks RH, Bruininks BD. BOT2: Bruininks-Oseretsky Test of Motor Proficiency. 2nd ed. Minneapolis, MN: Pearson Assessments; 2005.
23. Brahmbhatt H, Boivin M, Ssempijja V, Kagaayi J, Kigozi G, Serwadda D, et al. Impact of HIV and atiretroviral therapy on neurocognitive outcomes among school aged children. J Acquir Immune Defic Syndr. 2017;75:1–8.

24. Bangirana P, Musisi S, Allebeck P, Giordani B, John C, Opoka O, et al. A preliminary examination of the construct validity of the KABC-II in Ugandan children with a history of cerebral malaria. Afr Health Sci. 2009;9(3):186–92.
25. Giordani B, Boivin MJ, Opel B, Dia Nseyila D, Diawaku N, Lauer RE. Use of the K-ABC with children in Zaire, Africa: an evaluation of the sequential-simultaneous processing distinction within an intercultural context. Int J Disabil Dev Educ. 1996;43(1):5–24.
26. Boivin MJ, Chounramany C, Giordani B, Xaisida S, Choulamountry L, Pholsena P, et al. Validating a cognitive ability testing protocol with Lao children for community development applications. Neuropsychology. 1996;10(4):588–99.
27. Caldwell BM, Bradley RH. Home inventory administration manual. 3rd ed. Little Rock, AR: University of Arkansas; 2001.
28. Zhou Z, Wagar N, DeVos JR, Rottinghaus E, Diallo K, Nguyen DB, et al. Optimization of a low cost and broadly sensitive genotyping assay for HIV-1 drug resistance surveillance and monitoring in resource-limited settings. PLoS One. 2011;6(11):e28184.
29. de Oliveira T, Deforche K, Cassol S, Salminen M, Paraskevis D, Seebregts C, et al. An automated genotyping system for analysis of HIV-1 and other microbial sequences. Bioinformatics. 2005;21(19):3797–800.
30. Siepel AC, Halpern AL, Macken C, Korber BT. A computer program designed to screen rapidly for HIV type 1 intersubtype recombinant sequences. AIDS Res Hum Retroviruses. 1995;11(11):1413–6.
31. Bangirana P, Opoka RO, Boivin MJ, Idro R, Hodges JS, Romero RA. Severe malarial anemia is associated with long-term neurocognitive impairment. Clin Infect Dis. 2014;59:336–44.
32. Brahmbhatt H, Boivin M, Ssempijja V, Kigozi G, Kagaayi J, Serwadda D, et al. Neurodevelopmental benefits of antiretroviral therapy in Ugandan children aged 0-6 years with HIV. J Acquir Immune Defic Syndr. 2014;67(3):316–22.
33. Bangirana P. Cognitive outcome of malaria and HIV infection in children in sub-Saharan Africa. In: Musisi S, Jacobson S, editors. Brain degeneration and dementia in sub-Saharan Africa. New York: Springer; 2015. p. 165–81.
34. Richter LM, Grieve KW. Home environment and cognitive development of black infants in impoverished South African families. Infant Ment Health J. 1991;12:89–102.
35. Boivin MJ, Bangirana P, Nakasujja N, Page CF, Shohet C, Givon D, et al. A year-long caregiver training program improves cognition in preschool Ugandan children with human immunodeficiency virus. J Pediatr. 2013;63(5):1409–16.e1401–1405.
36. Sloan JA, Cella D, Hays RD. Clinical significance of patient-reported questionnaire data: another step toward consensus. J Clin Epidemiol. 2005;58(12):1217–9.
37. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. Mayo Clin Proc. 2002;77(4):371–83.