AIDS Care

Psychological and Socio-medical Aspects of AIDS/HIV

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/caic20

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To cite this article: Kirsten Rowe, Mihaela Duta, Nele Demeyere, Ryan G. Wagner, Audrey Pettifor, Kathleen Kahn, Stephen Tollman, Gaia Scerif & Alan Stein (2020): The relationship between executive function, risky behaviour and HIV in young women from the HPTN 068 study in rural South Africa, AIDS Care, DOI: 10.1080/09540121.2020.1851016

To link to this article: https://doi.org/10.1080/09540121.2020.1851016

AIDS CARE
https://doi.org/10.1080/09540121.2020.1851016

The relationship between executive function, risky behaviour and HIV in young women from the HPTN 068 study in rural South Africa

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ABSTRACT

Executive function (EF) may predict sexual risk-taking and HIV risk in young women in rural South Africa. We tested associations between EF and seven risky behavioural outcomes: binge drinking, illicit substance use, unprotected vaginal sex, concurrent sexual relationships, transactional sex, herpes simplex virus type 2 (HSV-2) infection, and HIV infection. We compared EF in young women with HIV to matched controls. 1080 young women underwent cognitive assessments. Better verbal short-term memory was associated with a lower risk of HSV-2 (OR 0.77; 95% CI 0.69, 0.86; $p < 0.001$). Uncorrected trends ($p < 0.05$) were better verbal working memory being associated with a lower risk of concurrency, better planning with a lower risk of illicit drug use, and better affective inhibition with a lower risk of transactional sex. 78 participants with sexually acquired HIV were matched with 153 HIV-negative controls and had poorer verbal working memory than controls (Hedge's $g = -0.38$; 95% CI -0.66, -0.10; $p = 0.0076$), but this was non-significant after adjustment. EF's contribution to young women's risky behaviour in this context does not hold when stringent statistical corrections are applied, with only verbal short term memory reaching statistical significance as predictor. Replication in other samples is recommended.

ARTICLE HISTORY
Received 11 February 2020
Accepted 10 November 2020

KEYWORDS
Risky behaviour; HIV; executive function; adolescent girls and young women; sub-Saharan Africa

Background

Executive functioning (EF) involves the top-down control of attention and the ability to suppress short-term impulses to achieve long-term goals. Three core EFs are generally described (working memory, inhibition, set-shifting) (Miyake & Friedman, 2012); higher-order EFs include planning (Diamond, 2013; Miyake et al., 2000). EF continues to develop during adolescence and the early twenties (Casey et al., 2008; Luna, 2009; Tau & Peterson, 2010), an extension of adolescence (Sawyer et al., 2018). Protracted development of prefrontal-subcortical EF neural circuits has been linked to sexual behaviour decision-making (Ross et al., 2016; Spinella, 2007). Poorer EF in adolescence may be associated with more sexual risk-taking (Bornovalova et al., 2008; Derefinko et al., 2014; Khurana et al., 2012, 2015; Lejuez et al., 2002, 2007; Ross et al., 2015, 2016). EF deficits may thus increase risk for acquiring HIV. 15–24-year-old females in sub-Saharan Africa are one of the most high-risk groups for acquiring HIV (Shisana et al., 2014; UNAIDS, 2018). A previous small cognitive study in rural South Africa found some associations between poorer EF and risk-taking outcomes (Rosenberg et al., 2018). The aim was to test these findings in a larger sample in which confounders were controlled for and to include a more extensive EF battery including hot EF tasks under emotionally significant conditions.

Adolescents with sexually acquired HIV may have had pre-existing EF deficits predisposing them to HIV acquisition (Chen et al., 2018; Hosain et al., 2012). After infection, HIV itself may lead to impaired EF (Clifford & Ances, 2013; Phillips et al., 2016). Markers of advanced or poorly controlled HIV may also be associated with poorer EF in adolescents with HIV (Jeremy et al., 2005; Nichols et al., 2016). Poorer EF may be associated with poorer academic and functional outcomes, poorer adherence to treatment with resultant poorer disease control, and risky sexual behaviour resulting in HIV transmission (Best et al., 2011; Hinkin et al., 2002; Ross et al., 2016; Sirois et al., 2016; Wilson &

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Supplemental data for this article can be accessed https://doi.org/10.1080/09540121.2020.1851016

Vassileva, 2016). A better understanding of EF in adolescents with sexually acquired HIV and whether it is associated with markers of advanced or poorly controlled disease is needed. Very few studies have focused specifically on adolescents with sexually acquired HIV. The ATN 071 study, comprising a predominantly male American cohort, found higher rates of set-shifting deficits in sexually acquired HIV compared to population norms (Nichols et al., 2013). There have been no large studies looking at EF in young women with sexually acquired HIV in sub-Saharan Africa. We aimed to address this gap by determining if young women with sexually acquired HIV in rural South Africa have similar EF deficits to those found in high-income countries and whether EF in this population is related to markers of advanced or poorly controlled HIV.

We hypothesised that:

(1) Poorer EF is associated with increased risky substance use and sexual behaviour in young women in rural South Africa;
(2) Cases with sexually acquired HIV have poorer EF than socio-demographically matched controls;
(3) In participants with sexually acquired HIV, those with biological markers of more advanced disease (CD4 counts < 350 cells/mm^3) or uncontrolled disease (viral load ≥ 1000 copies/ml) (WHO, 2016) have poorer EF than those with less advanced disease (CD4 count ≥ 350 cells/mm^3) or better controlled disease (viral load < 1000 copies/ml), respectively.

Methods

Study design and population

This cognitive substudy was nested within HPTN 068, a longitudinal cohort study after an individually randomised controlled trial in which there was no intervention effect (Pettifor et al., 2016; Pettifor et al., 2016). A subset of 1080 17–26-year-old young women underwent cognitive testing in October-November 2016 4–5 years after study initiation in the second post-intervention round of data collection. The study took place in the Agincourt sub-district of Bushbuckridge Municipality in rural Mpumalanga, South Africa within the MRC (Medical Research Council of South Africa)/Wits (University of the Witwatersrand) Rural Public Health and Health Transitions (Agincourt) Research Unit (Kahn et al., 2012). HIV prevalence here is high amongst young women with incidence increasing rapidly as women reach their early twenties (Gomez-Olive et al., 2013). Full inclusion criteria for the cohort study are detailed elsewhere (Pettifor et al., 2016). Adolescents who had HIV at baseline (i.e., possible perinatal transmission) were included but they were excluded from the analysis examining HIV as an outcome, and the case–control substudy which focused on sexually acquired HIV. Ethics approval for the study was obtained from the Institutional Review Board at the University of Witwatersrand, the University of Oxford and the University of North Carolina. Written informed consent and assent (from minors under 18-years-old) were obtained from all participants and caregivers (for minors under 18-years-old).

Data collection

Data were collected on electronic tablets by trained fieldworkers in Tsonga, the local language, using instruments translated from English by the MRC/Wits Agincourt Research Unit staff. We used data from the baseline and 2016 visits which included a household sociodemographic interview with caregivers using Computer Assisted Personal Interview (CAPI). Similarly, adolescents completed electronic questionnaires, partly fieldworker-administered using CAPI and partly self-administered (for sensitive questions e.g., sexual behaviour) using Audio Computer Assisted Self Interview (ACASI). Participants received group pre-test counselling prior to venous blood sampling for rapid HIV testing (using two test kits from separate companies), herpes simplex virus type 2 (HSV-2) testing, and additional confirmatory laboratory serum HIV testing (along with serum CD4 cell count and viral load) if one or both HIV rapid tests were reactive. They received individual post-test counselling. Testing occurred at all visits. Details regarding biological testing are reported elsewhere. Adolescent cognitive testing was done by trained fieldworkers using the Oxford Cognitive Screen – Executive Function (OCS-EF) software (© The University of Oxford) on Windows Surface Pro tablets with most tests undertaken in individual testing rooms; a few tests were performed at participants' homes if they were unable to come to the office. The battery took about 30 minutes to administer. Test conditions for each cognitive task were selected by the fieldworker on-screen from a predefined list: no issue, no speech, visual problems, motor problems, auditory problems, fatigue, refused, technical problems, ran out of time, interruptions, examiner error, other. If there were any issues that compromised the validity of test conditions, that participant's task data were excluded from analysis.

Outcome measures

We measured seven risky behavioural outcomes, two related to substance abuse (binge drinking and illicit substance use) and five related to risky sexual behaviour (unprotected vaginal sex, concurrent relationships, transactional sex, HSV-2 infection, HIV infection, (the latter two of which were biological)).

Primary behavioural outcomes measured were:

- Substance use:
  - Binge drinking: self-reported drinking of five or more standard alcoholic drinks during drinking episodes. Standard drink was defined as a small glass of wine, a 330 ml can of regular beer, a tot of spirits, or a mixed drink.
  - Drug use: self-reported past (ever) use of drugs e.g., cannabis or methamphetamine.
- Risky sexual behaviour:
  - Unprotected sex: present if participant self-reported at least one episode of unprotected (without a condom) vaginal sex in the past 3 months.
  - Concurrent relationships: ongoing relationship with at least two of up to five most recent sexual partners.
  - Transactional sex: present if participant self-reported engagement in transactional sex (defined as becoming, staying or feeling like one had to have sex or be sexually involved with a partner in the hope that he would or because he did provide you with money or things like groceries, airtime or clothes) with any of up to five of the most recent sexual partners.

Primary biological outcomes were:

- HSV-2 infection: testing positive on HSV-2 testing at baseline or subsequent study visits.
- Behavioural HIV infection: testing positive on confirmatory HIV testing in a subsequent study visit in participants who tested negative on two HIV rapid tests at study baseline.

Primary cognitive predictors were scores on the seven OCS-EF cognitive tasks, validated in this sample (Rowe, 2020) administered in a fixed order (see Supplement 1 for full task descriptions):

(1) Trails: baseline accuracy (planning); switch accuracy cost (set-shifting) (Demeyere et al., 2020; Humphreys et al., 2017).
(2) Iowa Gambling Task: net score (implicit learning, decision-making and hot inhibition (Burdick et al., 2013; Cassotti et al., 2014; Kerr & Zelazo, 2004)).
(3) Emotional go/no-go: d-prime (hot inhibition (Schulz et al., 2007)).
(4) Rule-finding: accuracy score (set-shifting, visuospatial pattern recognition and problem-solving) (Demeyere et al., 2020; Humphreys et al., 2017).
(5) Figure drawing: copy (constructional ability) and immediate recall accuracy scores (visuospatial working memory and planning) (Demeyere et al., 2020).
(6) Selection: visible (selective attention) and invisible accuracy scores (visuospatial working memory and planning) (Demeyere et al., 2020).
(7) Digit recall: forwards (verbal short-term memory) and backwards span (verbal working memory) (Baddeley, 2003).

Socio-demographic and control variables:

- Age: calculated using date of birth (self-reported).
- Relationship status: has a boyfriend or main partner (self-reported).
- Socio-economic status (SES): absolute asset index (based on number of baseline household durable goods owned as reported by caregiver in household interview) quartiles derived and used to divide participants into low (lowest quartile), middle (middle two quartiles), and high (highest quartile) SES categories.
- Education level: summarised into three levels (some secondary school, completed secondary school, and post-secondary) based on highest level of education completed (self-reported in cognitive visit).

Biological predictor variables only used in participants with HIV:

- CD4 cell count (at 2016 visit)
- Viral load (at 2016 visit).

Statistical analysis

Analysis was performed in Stata 14. p-values are two-tailed. Alpha was set to $p = 0.001$ to correct for multiple comparisons. Histograms were inspected to assess distributions. There was no collinearity or multicollinearity.

Missing data were handled using pairwise deletion. Simple logistic regressions were initially used to examine the associations between the EF variables as predictors of the seven risky behavioural outcomes. Multivariable logistic regression was then performed controlling for SES, education level and age in the full cognitive sample. In the analysis examining HIV as an outcome, we excluded the 22 participants who had HIV at study entry.

For the case–control substudy, a subsample of controls was randomly matched to cases with HIV acquired during the original study based on age and SES using Stata's "ccmatch" module. This process was repeated to select a second set of matched controls to produce a final case:control ratio of 1:2 to increase statistical power (Kang et al., 2009). After initial group mean comparisons testing (paired t tests or Wilcoxon signed-rank tests depending on outcome distribution), linear multivariable regression analyses controlling for potential confounders (age, SES, education level) were done to detect differences between the cases and controls on the cognitive outcomes. Assumptions were checked to ensure that the use of linear regression models was appropriate. Q-plots of residual variances were inspected to ensure that the residuals were normally distributed. Homogeneity of residual variances was assessed using box-and-whisker plots or scatterplots. Residual-versus-fit plots were also inspected to check for non-linearity, unequal residual variances and outliers. There were no extreme outliers that had not already been excluded through the examiner invalidation process.

For HIV-related sub-analyses, after initial group mean comparisons testing (paired t tests or Wilcoxon signed-rank tests depending on outcome distribution), multivariable linear regression models were used to assess HIV-related factors (CD4 cell count < 350; viral load >1000 copies/ml) in the sexually acquired HIV group (controlling for age, SES, education level). Assumptions were checked as described above.

Results

Sample characteristics

1080 participants underwent cognitive assessments. 22 (2.0% of original cognitive sample) participants were excluded due to missing or duplicate cognitive data files. The full sociodemographic characteristics of the 1058 participants with cognitive data available are listed in Table 1. The mean age was 19.8 years old at the time of the assessment. 71.6% of the sample had completed secondary school with 39.2% having completed additional post-secondary training. 638 (60.5%) participants had a boyfriend or main partner. 100 (9.5%) participants tested HIV-positive, with 22 (2.1%) having tested positive at study entry and 78 (7.4%) having acquired HIV at any point during the cohort study. The number of participants with invalid cognitive test conditions was highest for trails ($n = 90$, 8.5%), selection ($n = 36$, 3.4%) and digit recall ($n = 29$, 2.7%) tasks and mostly due to examiner error, technical error or interruptions. The other four tasks each

Table 1. Sociodemographic characteristics and frequency of risky behavioural outcomes of the full cognitive sample (N = 1058).

Characteristic Sociodemographic	*N* (%) unless specified
Mean age (SD) in years	19.79 (1.38)
Has a boyfriend or main partner	638 (60.47)
Highest level of education, *n* (%)	
Some secondary school	300 (28.38)
Completed secondary school	343 (32.45)
Post-secondary	414 (39.17)
Missing	1 (0.00)
Socio-economic status, *n* (%)	
Low	280 (27.16)
Middle	507 (49.18)
High	244 (23.67)
Missing	1 (0.00)
HIV status, *n* (%)	
Negative	932 (88.09)
Positive	100 (9.45)
Missing	26 (2.46)
Risky behavioural outcome	
Binge drinking	16 (1.51)
Missing	1 (0.09)
Illicit drug use	44 (4.28)
Missing	5 (0.47)
Unprotected vaginal sex	207 (20.06)
Concurrent relationships	52 (5.04)
Transactional sex	233 (22.02)
HSV-2 infection	213 (20.13)
Missing	27 (2.55)
HIV-1 infection during study	78 (7.37)
Past HIV-1 infection	22 (2.08)
HIV status missing	26 (2.46)

Table 2. Executive function summary scores of the full cognitive sample (N = 1058).

EF task	N with valid data	Measure of central tendency	Measure of dispersion	Min; max	Distribution
DF	1029	Mean 5.37	SD 1.47	0; 9	Normal
DB	1029	Mean 3.62	SD 1.53	0; 9	Normal
TB	968	Median 0.86	IQR 0.64; 1	0; 1	Negative skew
TS	968	Median 0.57	IQR 0.29; 0.87	0; 1	Negative skew
RF	1057	Mean 0.46	SD 0.23	0; 1	Normal
IGT	1056	Median 0.13	IQR −0.07; 1	−1; 1	Bimodal (central & positive peaks)
d′	1055	Mean 2.15	SD 0.97	−1.58; 4.87	Normal
FC	1046	Median 0.92	IQR 0.83; 0.95	0; 1	Negative skew
FR	1046	Median 0.82	IQR 0.70; 0.90	0.03; 1	Negative skew
SV	1022	Median 0.97	IQR 0.93; 1	0.07; 1	Negative skew
SI	1022	Median 0.83	IQR 0.77; 0.90	0; 1	Negative skew

Key: EF = executive function; N = number; Min = minimum; Max = maximum; SD = standard deviation; IQR = interquartile range; DF = digit recall forwards; DB = digit recall backwards; TB = trails baseline; TS = trails switch accuracy cost; RF = rule-finding; IGT = Iowa Gambling Task net score; d′ = go/no-go d-prime; FC = figure copy; FR = figure recall; SV = selection visible; SI = selection invisible.

had only 0–1% with invalid test conditions. EF scores are summarised in Table 2.

The relationship between executive function and risky behavioural outcomes

Risky behavioural outcomes varied in frequency within the sample (see Table 1). Unprotected vaginal sex, HSV-2 infection and transactional sex were more frequent than HIV acquired during the study, concurrent relationships, past illicit drug use and binge drinking.

There was only one significant association between cognition and behaviour that remained significant after adjustment for potential confounders and multiple comparisons. Better verbal short-term memory/attention (on digit recall forwards) was associated with a significantly decreased risk of HSV-2 infection (Odds Ratio (OR) 0.77; 95% CI 0.69, 0.86; $p < 0.001$) (see Table 6). Prior to correction for multiple comparisons and adjustment for confounders, there were a few other significant associations (see Tables 3–6). Although a stringent correction for multiple comparisons is beneficial in the context of multiple predictor and outcome variables, it is worth noting that this study is unique in its composition, size and depth of cognitive measures, so we highlight the uncorrected trends in an exploratory fashion and as useful guidance for future replications. Better verbal working memory (on digit recall backwards) was associated with a decreased risk of concurrent relationships (OR 0.74; 95% CI 0.61, 0.91; $p = 0.004$) (see Table 4). Better planning/sequencing ability (on trails baseline task) was associated with a decreased risk of illicit drug use (OR 0.21; 95% CI 0.06, 0.72; $p = 0.012$) (see Table 3). Better inhibitory control under emotional conditions (on emotional go/no-go d-prime) was associated with a decreased risk of transactional sex (OR 0.83; 95% CI 0.72, 0.97; $p = 0.018$) (see Table 5).

Case-control substudy

We matched 77 17–24-year-old cases with sexually acquired HIV (acquired in the last few years during the cohort study) to 153 HIV-negative controls to examine associations between sexually acquired HIV infection and EF. Cases and controls were similar in terms of the matching variables (age; SES), as well as other sociodemographic variables (see Table 7). Median CD4 cell count of cases was 635 cells/mm^3 and median viral load was 6120 copies/ml (see Table 8). The cases had poorer verbal working memory (digit span backwards) than controls (Hedge's $g = -0.38$; 95% CI -0.66, -0.10; $p = 0.0076$), but this was no longer

Table 3. Results from logistic regression analyses examining executive function as a predictor of risky substance use.

	Binge drinking						Illicit drug use					
EF task	OR (95% CI)	p	n	aOR (95% CI)	p	N	OR	p	n	aOR	p	n
DF	0.92 (0.65, 1.30)	0.646	1028	0.94 (0.65, 1.237)	0.758	1028	0.95 (0.77, 1.16)	0.598	1024	0.96 (0.78, 1.18)	0.677	1024
DB	1.02 (0.73, 1.42)	0.912	1028	1.03 (0.74, 1.45)	0.852	1028	0.87 (0.70, 1.07)	0.184	1024	0.87 (0.70, 1.09)	0.227	1024
TB	0.13 (0.02, 0.91)	0.040*	967	0.13 (0.02, 1.03)	0.053	967	0.21 (0.06, 0.72)	0.012*	963	0.22 (0.06, 0.80)	0.022*	963
TS	1.69 (0.27, 10.45)	0.573	940	1.82 (0.28, 11.64)	0.530	940	0.67 (0.26, 1.78)	0.426	936	0.69 (0.26, 1.84)	0.459	936
RF	1.74 (0.22, 13.96)	0.601	1056	1.27 (0.15, 10.53)	0.823	1056	2.05 (0.58, 7.33)	0.268	1052	2.17 (0.61, 7.80)	0.233	1052
IGT	0.52 (0.22, 1.21)	0.130	1055	0.53 (0.23, 1.24)	0.144	1055	0.68 (0.40, 1.15)	0.152	1051	0.68 (0.41, 1.41)	0.143	1051
d′	0.79 (0.48, 1.28)	0.334	1054	0.78 (0.47, 1.29)	0.330	1054	0.77 (0.57, 1.04)	0.092	1050	0.77 (0.57, 1.04)	0.09	1050
FC	1.37 (0.01, 158.50)	0.896	1045	1.20 (0.01, 170.09)	0.941	1045	0.48 (0.04, 5.52)	0.561	1041	0.59 (0.05, 7.16)	0.681	1041
FR	0.61 (0.02, 16.84)	0.771	1045	0.52 (0.02, 15.53)	0.708	1045	0.86 (0.11, 6.58)	0.883	1041	1.03 (0.13, 8.38)	0.975	1041
SV	71.90 (0.00, 908.33)	0.838	1021	1.66 (0.00, 699.74)	0.870	1021	2.58 (0.05, 139.82)	0.642	1017	2.75 (0.05, 160.97)	0.625	1017
SI	0.12 (0.01, 1.18)	0.070	1021	0.12 (0.01, 1.23)	0.073	1021	0.68 (0.11, 4.33)	0.680	1017	0.67 (0.10, 4.51)	0.678	1017

Key: EF = executive function; OR = odds ratio; CI = confidence interval; aOR = adjusted odds ratio (adjusted for age, socio-economic status and highest level of education); DF = digit recall forwards; DB = digit recall backwards; TB = trails baseline; TS = trails switch accuracy cost; RF = rule-finding; IGT = Iowa Gambling Task net score; d′ = go/no-go d-prime; FC = figure copy; FR = figure recall; SV = selection visible; SI = selection invisible; $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

Table 4. Results from logistic regression analyses examining executive function as a predictor of risky sexual behavioural self-reported outcomes.

	Unprotected vaginal sex						Concurrent relationships					
EF task	OR	*p*	*N*	aOR	*p*	*N*	OR	*P*	*n*	aOR	*P*	*n*
DF	0.91 (0.82, 1.01)	0.087	1029	0.92 (0.83, 1.03)	0.148	1028	0.85 (0.71, 1.03)	0.094	1029	0.86 (0.71, 1.04)	0.129	1028
DB	0.94 (0.85, 1.04)	0.238	1029	0.95 (0.86, 1.06)	0.373	1028	0.74 (0.61, 0.91)	0.004**	1029	0.75 (0.61, 0.92)	0.007**	1028
TB	1.12 (0.56, 2.24)	0.742	968	1.19 (0.58, 2.44)	0.628	967	0.40 (0.13, 1.28)	0.122	968	0.43 (0.13, 1.44)	0.170	967
TS	1.19 (0.72, 1.96)	0.491	941	1.22 (0.74, 2.02)	0.430	940	0.64 (0.26, 1.60)	0.344	941	0.67 (0.27, 1.68)	0.390	940
Rule	1.02 (0.54, 1.95)	0.941	1057	1.12 (0.58, 2.15)	0.734	1056	0.52 (0.15, 1.76)	0.293	1057	0.51 (0.15, 1.74)	0.282	1056
IGT	1.19 (0.92, 1.56)	0.191	1056	1.18 (0.90, 1.53)	0.230	1055	0.82 (0.51, 1.32)	0.415	1056	0.82 (0.51, 1.33)	0.421	1055
d′	1.12 (0.95, 1.31)	0.178	1055	1.11 (0.95, 1.30)	0.197	1054	0.86 (0.65, 1.13)	0.277	1055	0.85 (0.64, 1.12)	0.247	1054
FC	2.53 (0.58, 11.12)	0.219	1046	3.22 (0.72, 14.50)	0.127	1045	0.86 (0.07, 9.98)	0.902	1046	0.95 (0.08, 11.42)	0.968	1045
FR	2.56 (0.87, 7.56)	0.088	1046	3.13 (1.03, 9.49)	0.043*	1045	0.42 (0.07, 2.50)	0.340	1046	0.46 (0.07, 2.79)	0.396	1045
SV	1.26 (0.22, 7.18)	0.798	1022	1.47 (0.25, 8.63)	0.667	1021	7.61 (0.08, 693.18)	0.378	1022	8.03 (0.07, 865.42)	0.383	1021
SI	2.18 (0.74, 6.40)	0.155	1022	2.39 (0.81, 7.05)	0.114	1021	1.66 (0.22, 12.67)	0.623	1022	1.70 (0.22, 12.84)	0.609	1021

Key: EF = executive function; OR = odds ratio; CI = confidence interval; aOR = adjusted odds ratio (adjusted for age, socio-economic status and highest level of education); DF = digit recall forwards; DB = digit recall backwards; TB = trails baseline; TS = trails switching; RF = rule-finding; IGT = Iowa Gambling Task net score; d′ = go/no-go d-prime; FC = figure copy; FR = figure recall; SV = selection visible; SI = selection invisible; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 5. Results from logistic regression analyses examining executive function as a predictor of risky sexual behavioural self-reported outcomes.

	Transactional sex					
EF task	OR	*P*	*N*	aOR	*p*	*n*
DF	0.97 (0.88, 1.07)	0.563	1029	1.00 (0.90, 1.11)	0.978	1028
DB	0.93 (0.84, 1.02)	0.107	1029	0.95 (0.86, 1.05)	0.348	1028
TB	0.49 (0.26, 0.92)	0.027*	968	0.56 (0.29, 1.08)	0.082	967
TS	0.91 (0.57, 1.47)	0.710	941	0.95 (0.59, 1.54)	0.850	940
Rule	0.56 (0.30, 1.05)	0.073	1057	0.62 (0.33, 1.17)	0.072	1056
IGT	0.91 (0.71, 1.17)	0.473	1056	0.89 (0.69, 1.15)	0.369	1055
d′	0.83 (0.72, 0.97)	0.018*	1055	0.82 (0.70, 0.95)	0.011*	1054
FC	0.96 (0.26, 3.52)	0.951	1046	1.39 (0.36, 5.28)	0.631	1045
FR	1.19 (0.44, 3.22)	0.416	1046	1.56 (0.56, 4.34)	0.811	1045
SV	0.34 (0.08, 1.49)	0.339	1022	0.40 (0.09, 1.81)	0.541	1021
SI	1.52 (0.56, 4.11)	0.760	1022	1.79 (0.65, 4.93)	0.261	1021

Key: EF = executive function; OR = odds ratio; CI = confidence interval; aOR = adjusted odds ratio (adjusted for age, socio-economic status and highest level of education); DF = digit recall forwards; DB = digit recall backwards; TB = trails baseline; TS = trails switching; RF = rule-finding; IGT = Iowa Gambling Task net score; d′ = go/no-go d-prime; FC = figure copy; FR = figure recall; SV = selection visible; SI = selection invisible; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 6. Results from logistic regression analyses examining executive function as a predictor of risky sexual behavioural biological outcomes.

	HSV-2 infection						HIV-1 infection					
EF task	OR	*p*	*n*	aOR	*p*	*n*	OR	*p*	*n*	aOR	*p*	*n*
DF	0.77 (0.69, 0.86)	<0.001***	1002	0.81 (0.72, 0.91)	<0.001***	1001	0.95 (0.81, 1.11)	0.532	981	1.00 (0.85, 1.18)	0.975	980
DB	0.91 (0.82, 1.01)	0.071	1002	0.99 (0.89, 1.10)	0.816	1001	0.85 (0.72, 1.00)	0.048*	981	0.90 (0.76, 1.06)	0.196	980
TB	0.47 (0.25, 0.92)	0.027*	942	0.88 (0.43, 1.81)	0.732	941	0.53 (0.20, 1.43)	0.208	923	1.00 (0.35, 2.86)	0.993	922
TS	1.39 (0.84, 2.30)	0.195	915	1.69 (0.99, 2.89)	0.054	914	1.12 (0.53, 2.41)	0.762	897	1.16 (0.54, 2.50)	0.710	896
Rule	0.97 (0.51, 1.86)	0.932	1030	1.37 (0.69, 2.69)	0.367	1029	0.71 (0.26, 1.95)	0.506	1009	0.93 (0.34, 2.56)	0.892	1008
IGT	1.10 (0.84, 1.43)	0.481	1029	1.04 (0.79, 1.37)	0.766	1028	0.79 (0.53, 1.18)	0.241	1008	0.79 (0.53, 1.17)	0.242	1007
d′	0.90 (0.77, 1.05)	0.186	1029	0.89 (0.75, 1.05)	0.157	1028	0.93 (0.73, 1.18)	0.536	1008	0.94 (0.74, 1.19)	0.597	1007
FC	0.64 (0.17, 2.34)	0.498	1020	1.79 (0.43, 7.48)	0.428	1019	0.22 (0.04, 1.21)	0.082	999	0.40 (0.07, 2.35)	0.310	998
FR	0.46 (0.17, 1.26)	0.131	1020	1.03 (0.35, 3.04)	0.950	1019	0.33 (0.08, 1.40)	0.132	999	0.60 (0.13, 2.84)	0.521	998
SV	0.19 (0.04, 0.82)	0.026*	995	0.21 (0.04, 1.00)	0.050	994	0.19 (0.03, 1.26)	0.085	974	0.19 (0.03, 1.43)	0.108	973
SI	0.40 (0.16, 0.99)	0.047*	995	0.55 (0.20, 1.49)	0.238	994	1.39 (0.29, 6.70)	0.680	974	2.10 (0.40, 11.01)	0.380	973

Key: EF = executive function; OR = odds ratio; CI = confidence interval; aOR = adjusted odds ratio (adjusted for age, socio-economic status and highest level of education); DF = digit recall forwards; DB = digit recall backwards; TB = trails baseline; TS = trails switch accuracy cost; RF = rule-finding; IGT = Iowa Gambling Task; d′ = go/no-go d-prime; FC = figure copy; FR = figure recall; SV = selection visible; SI = selection invisible; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

significant after correction for multiple comparisons or adjustment for covariates ($p = 0.010$). There were no other significant differences in EF between cases and controls (see Table A, Supplement 2). In the cases with HIV, we were unable to examine associations between CD4 count and EF as there were too few ($n = 10$) participants with a CD4 count <350. Viral load was not associated with EF (see Table B, Supplement 2).

Discussion

Key findings

In this sample of young women from rural South Africa, better EFs were sometimes associated with less risky sexual and substance use behaviour (particularly short-term memory); however, most associations did not hold after adjustment for age, socio-economic status and education level and correction for multiple comparisons.

Our findings differ from those of an earlier cognitive substudy on another subset of young women from the HPTN 068 cohort which found some weak associations between EF and risky sexual behaviour; however, the earlier substudy did not adjust for education level or maternal education both of which were associated with EF because the researchers felt these factors were potentially causal factors influencing EF and that controlling for them might decrease the observed association between EF and sexual risk inappropriately (Rosenberg et al., 2018). These discrepant findings could also be due to differences in variable definitions with our study referring to the last five sexual partners (versus last three); including HSV-2 infection occurring at any time (versus recently); and using continuous scores (versus dichotomous).

In the case–control study, participants with sexually acquired HIV had poorer verbal working memory; the effect size was small. This association was no longer significant after correction for multiple comparisons. Performance on other EF tasks was similar to healthy controls. This suggests that young women with HIV acquired sexually in the last five years during adolescence have fewer EF deficits than late adolescents with perinatally acquired HIV (Willen et al., 2017). This is similar to ATN 071, a predominantly male American adolescent cohort with sexually acquired HIV, who also only had limited EF deficits; however, they had set-shifting not verbal working memory deficits. Amongst the participants with sexually acquired HIV, viral load was not associated with EF. There were too few participants with a low CD4 count to assess the association between CD4 count and EF.

Table 7. Sociodemographic characteristics of matched cognitive subsample.

Characteristic	Cases with HIV ($n = 77$)	HIV-negative controls ($n = 153$)	Mean comparisons and p-value	Whole subsample ($n = 230$)
Mean age (SD) in years	20.29 (1.45)	20.27 (1.43)	$t = -0.09$ $p = 0.93$	20.27 (1.44)
Highest level of education, *n* (%)				
Some secondary school	29 (37.66)	37 (24.18)	$\text{chi}^2 = 4.73$;	66 (28.70)
Completed secondary school	20 (25.97)	44 (28.76)	$p = 0.094$	64 (27.83)
Post-secondary	28 (36.36)	72 (47.06)		100 (43.48)
Socio-economic status, *n* (%)				
Low	15 (19.48)	30 (19.61)	$\text{chi}^2 = 0.00$;	45 (19.57)
Middle	41 (53.25)	81 (52.94)	$p = 1.00$	122 (53.04)
High	21 (27.27)	42 (27.45)		63 (27.39)
Marital status, *n* (%)				
Unmarried	74 (96.10)	147 (96.73)	$\text{chi}^2 = 0.56$;	222 (96.52)
Married	3 (3.90)	6 (3.27)	$p = 0.76$	8 (3.48)

Since EF, particularly short-term memory, has some associations with important behavioural outcomes, interventions aiming to improve EF may be useful. Although some interventions (e.g., computerised cognitive rehabilitation therapy) have been tested amongst younger children and adolescents in sub-Saharan African contexts (Boivin et al., 2016), research on interventions amongst late adolescents and young adults is limited.

Strengths

To our knowledge, this was one of the first large-scale studies to look at the association between EF subtypes (including both hot and cool EF) as cognitive predictors of risky sexual and substance use behavioural outcomes in young women in sub-Saharan Africa. Strengths of this study include the large sample size and detailed sociodemographic, behavioural and biological data collected. We included an array of EF tests spanning core EFs (working memory, inhibition, set-shifting), complex EFs (planning or sequencing, problem-solving), and hot EFs (affective decision-making, emotional inhibition). This allowed us to explore potential associations with EF subtypes which is important because EFs may be differentially affected in the context of HIV-associated neurocognitive disorder or relate to risky behaviour in different ways (Walker & Brown, 2018). In turn, to mitigate for the large number of outcome and predictor measures included, we corrected for multiple comparisons, a strength in statistical terms.

Table 8. Disease-related characteristics of cases with HIV in case-control substudy.

Characteristic	*N* (%)	Median (IQR)
CD4 cell count (cells/mm3)		
Full sample	68 (88.31)	635 (447–815)
<350	10 (12.99)	306 (251–329)
≥350	58 (75.32)	679 (490–838)
Missing	9 (11.69)	
Viral load (copies/ml)		
Full sample	75 (96.10)	6120 (30–45,920)
<1000	25 (32.47)	30 (30–30)
≥1000	49 (63.64)	22880 (7650–73,230)
Missing	3 (3.90)	

Limitations

Limitations included not knowing whether participants were currently pregnant and whether participants with HIV were on antiretroviral therapy, both of which may affect EF (Al-Khindi et al., 2011; Davies et al., 2018). As our cognitive data were cross-sectional, it was not possible to determine directionality of associations and likely causality. Due to eligibility criteria for inclusion in the full study, some of the potentially most vulnerable adolescents (those who were pregnant, or not enrolled in school at baseline) were excluded. The stringency of correction for multiple comparisons may have masked trends to be followed in future large scale replication studies. Power to detect differences between subgroups was limited by the small sample size within the sexually acquired HIV group overall ($n = 77$) and even smaller numbers in subgroups.

Conclusions

Verbal working memory was poorer in young women with sexually acquired HIV than healthy controls but this association was not significant after adjustment for confounders and correction for multiple comparisons. Their EF was otherwise similar. Although better EF was sometimes associated with a lower risk of risky behavioural outcomes in young women in rural South Africa, all but one of these associations disappeared after adjustment for age, education level, socio-economic status and correction for multiple comparisons. This suggests that although young women with poorer EF may be at higher risk for certain risky behavioural outcomes, risk is not generally conferred by poorer EF itself, but rather by associated factors such as age, education level and/or socio-economic status. Keeping adolescent girls in secondary school, enabling further post-secondary education and training, and creating employment opportunities for young women in rural South Africa are likely to be useful interventions to reduce risky behaviour. Interventions to improve EF may also be useful and should be tested in this age group and context.

Acknowledgements

The authors would like to thank the study site team at the MRC/Wits Agincourt Research Unit, the project managers Linda Kimaru and Busisiwe Mayindi who supervised cognitive data collection for this study, the fieldworkers who administered the assessments, as well as all the participants and caregivers who volunteered their time to participate. The copyright for the Oxford Cognitive Screen – Executive Function (OCS-EF) and the OCS-Plus are claimed by the University of Oxford. For permission to use the tools, please approach the authors in the first instance. KR is funded by the Rhodes Trust, the Africa-Oxford initiative (AfiOx-32), and the Society for Education and Music Psychology Research (SEMPRE) Gerry Farrell scholarship. Overall support for the HIV Prevention Trials Network (HPTN) was provided by the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Mental Health (NIMH) and the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH) under Award Numbers UM1AI068619 (HPTN Leadership and Operations Centre), UM1AI068617 (HPTN Statistical and Data Management Centre), and UM1AI068613 (HPTN Laboratory Centre). The study was also funded under Award Number 5R01MH087118-02 and R24 HD050924 to the Carolina Population Centre. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by National Institute of Allergy and Infectious Diseases [grant number UM1AI068613, UM1AI068617, UM1AI068619]; National Institute of Mental Health [grant number 5R01MH087118-02]; National Institute on Drug Abuse [grant number R24 HD050924]; Africa-Oxford Initiative [AfiOx-32]; Rhodes Scholarships; Society for Education, Music and Psychology Research.

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