Cognitive performance, neuropsychiatric symptoms, and cerebrospinal fluid viral control following programmatic switch from efavirenz-based to dolutegravir-based antiretroviral therapy in South Africa (CONNECT): a prospective cohort study

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Summary

Background Both efavirenz and dolutegravir have been associated with neuropsychiatric side-effects and cognitive impairment. Furthermore, cerebrospinal fluid (CSF) HIV RNA escape has not been comprehensively studied in African populations. We aimed to examine changes in cognition, neuropsychiatric symptoms, and CSF viral control associated with the widespread switch from efavirenz-based to dolutegravir-based antiretroviral therapy (ART).

Methods This prospective cohort study of people with HIV and people without HIV recruited adults with HIV (aged 18–55 years) from the Gugulethu Community Health Centre in a low-income periurban area of Cape Town, South Africa. Eligible participants had been receiving efavirenz-based ART for at least 1 year and were identified by the clinic to switch to dolutegravir-based ART as part of the national programmatic switch. Participants were studied at baseline and followed up at 1 year after switch to dolutegravir. People without HIV were recruited from the same area, matched for age and gender, and followed up at the same time interval. People with HIV and people without HIV underwent comprehensive cognitive testing over seven domains and measures of functioning, mood, anxiety, and sleep. People with HIV had CSF sampling for HIV RNA quantification.

Findings Between Aug 12, 2019, and Sept 16, 2022, we recruited 178 people with HIV and 95 people without HIV. 145 (81%) of 178 people with HIV and 40 (66%) of 60 people without HIV who were offered underwent follow-up. Global cognitive performance was 2·57 T score points lower in people with HIV than in people without HIV at baseline (p=0·0008). At follow-up, cognition in people with HIV improved more than practice effects observed in people without HIV (coefficient 1·40, 95% CI 0·48–2·32, p=0·0028) and no significant difference in cognitive performance between groups was apparent (51·43 *vs* 52·73; p=0·22). Sleep quality improved following the switch (risk ratio 0·90, 95% CI 0·84–0·95; p=0·0002), driven mainly by indicators of disturbed sleep. There were nine incident cases of depression, although baseline differences were present. There was one case (1%) of CSF escape at baseline and three cases (4%) at follow-up; all were at low levels or resolved with repeated sampling.

Interpretation Improvements in cognition and sleep are probably related to switching from efavirenz. However, the possible increase in depression warrants further examination. Cognitive performance in virally supressed African people with HIV receiving dolutegravir-based therapy is similar to people without HIV. CSF escape is uncommon on both efavirenz-based and dolutegravir-based therapy.

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Introduction

In 2019, WHO changed their recommended first-line HIV treatment regimen from efavirenz-based to dolutegravir-based antiretroviral therapy (ART) on the basis of dolutegravir's superior efficacy and side-effect profile. The effects of this switch on the CNS are unknown. Efavirenz has been associated with clinical neuropsychiatric side-effects, including cognitive deficits, disturbed sleep, depressive symptoms, and suicidal ideation.[1–3] Dolutegravir has also been associated with neurotoxicity, with discontinuation rates due to neuropsychiatric side-effects of up to 6%.[4] However, some studies have found no increased risk of neurotoxicity with dolutegravir and the CNS effects of this drug remain to be fully elucidated.[5–9] CNS effects of the switch from efavirenz to dolutegravir have not been comprehensively studied in Africa, where the use of these drugs has been most widespread and risk factors, including drug metabolism and

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Research in context

Evidence before this study

In 2019, WHO changed their recommended first-line HIV treatment regimen from efavirenz-based to dolutegravir-based antiretroviral therapy (ART) affecting millions of people with HIV globally. The effects of this switch on the CNS are unknown. Additionally, the prevalence of cognitive impairment and cerebrospinal fluid (CSF) HIV RNA escape have not been comprehensively studied in African cohorts. We searched PubMed from database inception to Nov 1, 2023, for English language publications, using the search terms "efavirenz", "dolutegravir", "neurotoxicity", "cognitive impairment", "depression", "anxiety", "sleep", and "CSF escape". Efavirenz has been associated with cognitive deficits, disturbed sleep, depressive symptoms, and suicidal ideation. Dolutegravir has been associated with depression and insomnia, with discontinuation rates from neuropsychiatric side-effects of up to 6%. Few studies have been done in Africa and women are under-represented. Studies of CSF escape in Africa are scarce, with reported rates of 9–28%. To our knowledge, no study has specifically examined the effect of the programmatic ART switch on rates of CSF escape.

Added value of this study

Our data show that South African people with HIV who are adherent to dolutegravir-based ART have cognitive performance similar to that in people without HIV, which is a reassuring counterpoint to previously reported high prevalence of cognitive impairment in African people with HIV. Our majority female Black African cohort from a low-income area is broadly representative of the demographic of HIV in southern Africa, a group under-represented in neuro-HIV research. Inclusion of a control cohort of people without HIV allowed us to show that improvements in cognitive performance following the ART switch, which have been observed in other studies, were not related to practice effects alone. The study of people without HIV also revealed the high false-positive rate from measures of cognitive symptoms and functioning in this population, highlighting the subjective nature of these complaints. Rates of CSF escape were lower than previously reported and, where present, CSF HIV RNA was at a low level (ie, <200 copies per mL) or transient.

Implications of all the available evidence

Our findings should lead to updates to public health messaging to reassure people with HIV of the low risk of cognitive impairment and CSF escape on modern ART. Our results support WHO advice on switching from efavirenz-based to dolutegravir-based therapy due to neuropsychiatric side-effects. However, the apparent increase in depression in this population warrants further examination.

comorbid conditions, can differ from non-African cohorts.[10,11]

The effect of the programmatic switch from efavirenz-based to dolutegravir-based ART on the prevalence of cerebrospinal fluid (CSF) escape and the effect on cognition have not been determined. CSF HIV RNA escape describes the occurrence of HIV RNA at higher concentrations in CSF than plasma.[12] CSF escape can indicate compartmentalised HIV in the CNS, which has been associated with neurological deterioration,[13,14] or can be asymptomatic or secondary to other CNS conditions.[13] The prevalence of CSF escape varies depending on population and setting. Studies of CSF escape in Africa have reported rates of 9–28%,[15,16] but have not been done in populations with high plasma HIV RNA suppression, which now represent the majority of people with HIV in South Africa.

We sought to examine the effect of this widespread programmatic ART switch on cognitive performance, neuropsychiatric symptoms, and CSF viral control.

Methods

Study design and participants

The Cognition, Neuropsychiatric Symptoms and Neuroinflammation Switching to Dolutegravir in Cape Town (CONNECT) study recruited a prospective cohort of adults with HIV (aged 18–55 years) from the Gugulethu Community Health Centre in a low-income periurban area of Cape Town, South Africa. Eligible participants had been receiving efavirenz-based ART for at least 1 year and were identified by the clinic to switch to dolutegravir-based ART as part of the national programmatic switch. After evaluation and adherence support, the South African Department of Health ART guideline recommended switching adults on first-line ART from oral once-daily efavirenz 600 mg with tenofovir 300 mg and emtricitabine 200 mg to oral once-daily dolutegravir 50 mg with tenofovir 300 mg and lamivudine 300 mg if they had HIV RNA fewer than 50 copies per mL, or had two samples with fewer than 1000 copies per mL taken 3 months apart.[17]

Individuals with factors that could confound cognitive testing were excluded, including: current substance use (Drug Use Disorders Identification Test using a standard cutoff score of >5 for men and >1 for women), high-risk or harmful alcohol use (Alcohol Use Disorders Identification Test score >15), history of CNS infection or major head injury (loss of consciousness for >30 min), uncontrolled neurological conditions, such as seizure disorders or established cerebrovascular disease, history of learning difficulty or severe intellectual disability, fewerthan 7 years total education, or history of severe mental health disorder (schizophrenia, psychosis, or bipolar disorder). We excluded those with vertical HIV

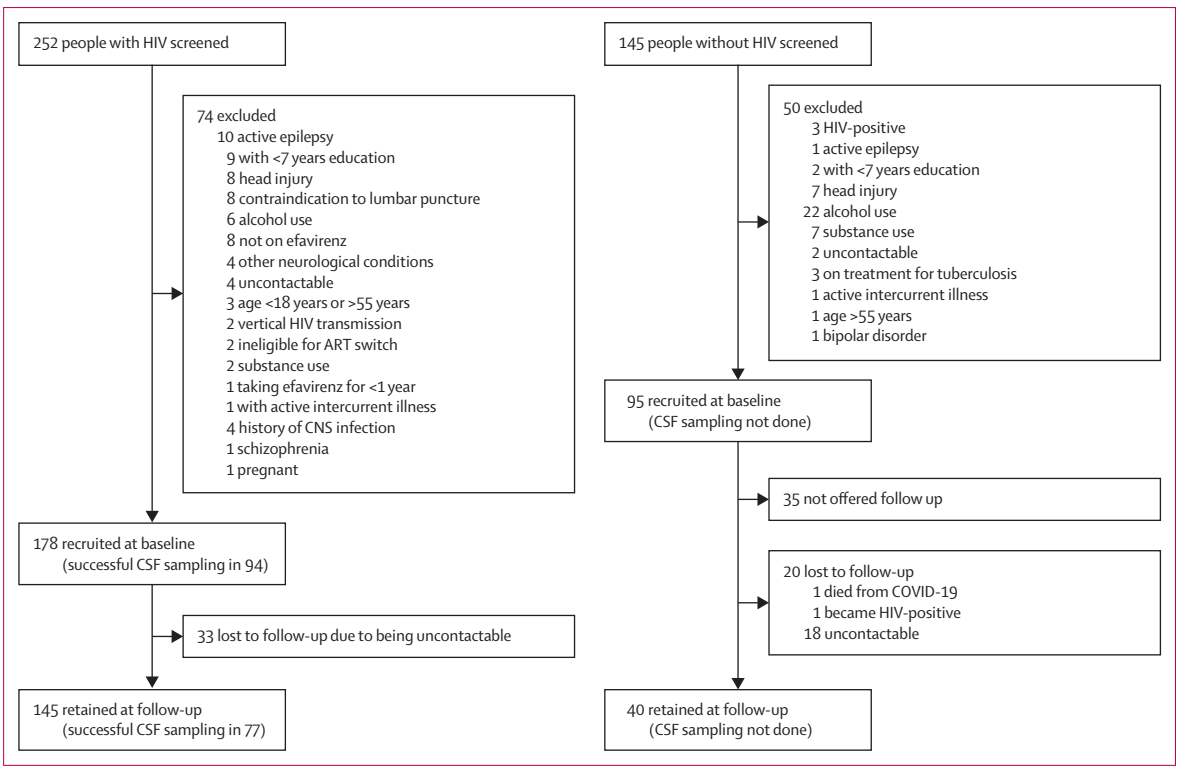

Figure 1: **Study recruitment and retention**
ART=antiretroviral therapy.

acquisition, currently being investigated or treated for active intercurrent illness such as infection or carcinoma, currently receiving treatment for tuberculosis, known or suspected to be pregnant, not fluent in English or isiXhosa, or with a contraindication to lumbar puncture.

People without HIV had the same inclusion and exclusion criteria as people with HIV. People with HIV were matched with people without HIV by age band and gender (self-identified man or woman). To target an HIV-negative group with a similar sociodemographic background to people with HIV, people without HIV were recruited from the friends, relatives, and associates of people attending the Gugulethu HIV clinic. Negative HIV status was confirmed by rapid test. Participants were asked to self-report as a man, woman, or other gender identity.

The study was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (017/2019). Written informed consent was obtained in the language of participant preference (English or isiXhosa).

Procedures

Baseline study visits were done while people with HIV were receiving efavirenz-based ART. A follow-up visit was performed 12 months later once the participant had been receiving dolutegravir-based ART for at least 3 months. The first 60 people without HIV recruited at baseline were offered follow-up at 12 months to assess magnitude of practice effects (ie, the improvement in cognitive test scores due to repeated evaluation).

Comprehensive cognitive testing was done with a standard battery of validated tests that assess seven cognitive domains: executive functioning, verbal learning and memory, visuospatial learning and memory, verbal fluency, attention and working memory, information processing speed, and motor skills. This battery of tests takes approximately 2 h. Domains, tests, and outcome variables are described in more detail in the appendix (p 1). Tests were administered in either English or isiXhosa by a bilingual neuropsychology technician. A registered clinical neuropsychologist (AJD) supervised test administration and scoring protocols.

See Online for appendix

Functional impairment was determined by an adapted version of the Patient's Assessment of Own Functioning Inventory (PAOFI), which predominantly assesses cognitive symptoms, and the Charter Instrumental Activities of Daily Living scale (CTADL); higher scores for both of these scales indicate worse functional impairment. Modifications to the PAOFI for this study are described in the appendix (p 2). The cutoff for impairment on the PAOFI was three or more items endorsed either "almost always", "very often", or "fairly often". Impairment on CTADL was two or more items with current scores higher than a participant's recalled best functioning (ie, the difference between now and best).

	Participants with HIV (N=178)	Participants without HIV (N=95)	p value
Demographics			
Gender			0·54
Women	142 (80%)	72 (76%)	
Men	36 (20%)	23 (24%)	
Age at consent, years			0·51*
Median (IQR)	39·60 (35·35–46·61)	39·20 (34·39–46·67)	
Years of education			0·0005*
Mean (SD)	10·67 (1·26)	11·19 (1·21); n=94	
Median (IQR)	11·00 (10·00–12·00)	11·00 (11·00–12·00); n=94	
Self-identified ethnicity			0·35
Black	178 (100%)	94 (99%)	
Coloured	0	1 (1%)	
First language			0·058†
isiXhosa	164 (92%)	87 (92%)	
English	2 (1%)	5 (5%)	
Other	12 (7%)	3 (3%)	
Marital status			0·0010
Single	82 (46%)	66 (69%)	
Married or living together	69 (39%)	20 (21%)	
Divorced, separated, or widowed	27 (15%)	9 (9%)	
Medical and HIV history			
Type 2 diabetes	7 (4%)	5 (5%)	0·61
Hypertension	25 (14%)	13 (14%)	0·94
Hyperlipidaemia	3 (2%)	4 (4%)	0·24†
Smoker			0·072
Never	135/177 (76%)	60 (63%)	
Current	32/177 (18%)	27 (28%)	
Ex-smoker	10/177 (6%)	8 (8%)	
Myocardial infarction	1 (1%)	0	..
Minor head injury	5 (3%)	3 (3%)	1†
Psychiatric disorder	4 (2%)	5 (5%)	0·28†
Previous tuberculosis	59 (33%)	13 (14%)	0·0005
WHO clinical stage			..
1	32/69 (46%)	..	
2	14/69 (20%)	..	
3	14/69 (20%)	..	
4	9/69 (13%)	..	
Mean (SD) most recent CD4 count, cells per µL	528·36 (258·83)	..	..
Mean (SD) duration of antiretroviral therapy at enrolment, years	8·79 (3·95)	..	..

(Table 1 continues on next page)

Symptoms of mood, anxiety, and sleep were assessed using the Centre for Epidemiological Studies-Depression (CES-D) scale, State Trait Anxiety Inventory-Trait (STAI-Trait), and Pittsburgh Sleep Quality Index (PSQI; higher score indicates worse sleep), respectively. The standard cutoff of 16 or higher on the CES-D was used to indicate depressive symptoms. On the PSQI, the global score was calculated by summing subscale scores and a cutoff of 5 or higher indicated poor sleep quality. Current diagnosis of major depressive disorder (MDD), panic disorder, post-traumatic stress disorder (PTSD), generalised anxiety disorder (GAD), and suicide risk (low, moderate, or high) was by the Mini International Neuropsychiatric Interview (Mini), version 7.0. Adherence to ART was determined by participant self-report ("in the last 30 days, how often did you take your antiretrovirals in the way you were supposed to?" 1: Never, 2: rarely, 3: sometimes, 4: usually, 5: almost always, 6: always) and pharmacy refill data (number of tablets used divided by the number of days between prescriptions).

Lumbar puncture was done in people with HIV using a Sprotte atraumatic lumbar puncture needle (Pajunk; Alpharetta, GA, USA). Blood was drawn as soon as feasible after the lumbar puncture procedure. Participants were contacted the day after the procedure to assess for complications.

Given the occurrence of the COVID-19 pandemic shortly after recruitment commenced, additional measures were added to assess the psychological, economic, and health impacts on participants. These measures are described in the appendix (p 3).

CSF and plasma HIV-1 RNA were quantified in plasma and CSF by the Alinity m HIV-1 assay (Abbott Molecular; Des Plaines, IL, USA) (lower detection limit 20 copies per mL for 1 mL input).

Statistical analysis

We calculated descriptive statistics for all measures and used independent *t* tests (or Mann–Whitney *U*) and χ^2 analyses (or Fisher's exact tests) to investigate between-group differences at baseline and follow-up. We used R version 4.2.2 and RStudio version 2023.03.0 to complete all inferential analyses, with the threshold for statistical significance set at $\alpha=0\cdot05$.

14 outcome variables were derived from the neuropsychological test data. Domain T scores were calculated (mean 50, SD 10) and converted to deficit scores, with global deficit score (GDS) calculated by averaging domain deficit scores. Low cognitive performance was indicated by a GDS of 0·5 or higher. We used linear mixed-effects fit by maximum likelihood when the outcome variable was continuous and Poisson regression models and cluster-robust SEs with a logarithmic link function when the outcome variable was categorical to investigate the effects of switch on cognitive and functional outcomes.

A subanalysis was done to investigate the effects of ART switch on the components of sleep in people with HIV using Wilcoxon matched pairs sign-rank test.

Further detail on statistical analyses is given in the appendix (p 2).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 12, 2019, and Sept 16, 2022, we recruited 178 people with HIV and 95 people without HIV (figure 1; table 1). We controlled for baseline difference in years of education was with regression-based norming processes (appendix p 1). 145 (81%) of 178 people with HIV had follow-up assessment on dolutegravir-based ART. There were no instances of dolutegravir discontinuation due to side-effects.

41 (68%) of 60 people without HIV who were offered follow-up returned for assessment; one person without HIV became HIV-positive and was thus excluded from follow-up analysis. Retention in people without HIV was lower than in people with HIV (p=0·033), as individuals with HIV regularly attended the local HIV clinic. People without HIV who were not followed up were mean 4·8 years older (SD 2·8) than those who were followed up. Further comparison of baseline characteristics of those followed up and not followed up are given in the appendix (p 1). Mean time between baseline and follow-up visits was 358 days (SD 106) in people without HIV and 343 days (100) in people with HIV (p=0·39). There was no change in weight of people with HIV over time (83·2 kg at baseline *vs* 84·0 kg at follow-up; p=0·73).

At baseline, cognitive performance was lower in people with HIV than in people without HIV, but at follow-up there was no significant difference between the groups (table 2; figure 2).

The statistical model for change in global T score over time showed a significant main effect for group and timepoint, and a group×timepoint interaction, indicating that global cognitive performance in people with HIV improved significantly more than in people without HIV over time by an estimated 1·40 points (table 3). The proportion of people with HIV with low cognitive performance as a binary measure (by GDS) decreased by 14%. Models for individual domain T scores are in the appendix (p 5). There was no significant difference between people with HIV and people without HIV in functional measures by PAOFI or CTADL at baseline or follow-up (table 2), and no change over time in statistical models (table 3).

There were nine incident cases of MDD (as assessed by Mini) in people with HIV following switch to dolutegravir, representing 6·2% of this group, a significant increase over time, although the 95% CI is wide (table 3). Depressive symptoms and diagnoses of MDD at baseline were more frequent in people with than in people without HIV (table 2). Our COVID-19 questionnaire found an association between lower CES-D scores and the subjective overall emotional impact of the pandemic (appendix p 6).

Anxiety scores (STAI-Trait) in people with HIV were similar to people without HIV (table 2) and did not change significantly over time (table 3). Rates of GAD, panic disorder, and PTSD on Mini were low. Rates of suicidality were similar between groups and did not change over time (table 2).

	Participants with HIV (N=178)	Participants without HIV (N=95)	p value
(Continued from previous page)			
Biometrics			
BMI, kg/m²			0·93*
Mean (SD)	31·78 (8·58)	31·69 (8·56)	
Median (IQR)	30·83 (25·62–36·13)	30·30 (25·34–36·84)	
Systolic blood pressure, mm Hg			0·22*
Mean (SD)	125·81 (14·76)	130·61 (21·01)	
Median (IQR)	125·00 (116·00–134·00)	127·00 (114·00–140·75)	
Diastolic blood pressure, mm Hg			0·20*
Mean (SD)	81·61 (10·56)	84·83 (13·87)	
Median (IQR)	81·00 (75·00–88·00)	83·00 (75·25–90·00)	

Data are n (%) or n/N (%), unless otherwise indicated. WHO clinical stage data available for 69 people with HIV. Most recent CD4 count data available for 87 people with HIV. BMI data for 174 people with HIV and 93 people without HIV. Blood pressure data for 177 participants with HIV and 90 people without HIV. *Mann–Whitney *U* test instead of *t* test. †Fisher's exact test instead of χ^2 test.

Table 1: **Baseline characteristics**

Overall sleep quality in people with HIV improved significantly between baseline and follow-up, with a decrease in total PSQI score and a reduced proportion of people with PSQI score of 5 or more (table 3). When the individual components of sleep were analysed, this change was driven by the domain of sleep disturbance, rather than sleep quality, latency, duration, or efficiency (appendix p 7). People with HIV reported significantly more sleep disturbance than people without HIV at baseline (p=0·035), whereas at follow-up there was no difference between the groups (p=0·15). Within the domain of sleep disturbance, the main changes were in questions indicating bad dreams, feeling too hot or cold, and getting up to use the bathroom. At baseline, a higher proportion of people with HIV reported bad dreams disturbing their sleep during the past month compared with at follow-up.

People with HIV reported good adherence to ART at baseline and follow-up, which was supported by pharmacy refill data showing more than 95% of tablets collected in most participants for whom this information was available (table 2).

Lumbar puncture was well tolerated. In 173 procedures there were three cases (2%) of post-lumbar puncture headache, all of which were mild and self-limiting. Other reported adverse events were deemed to be unrelated to study procedures: one case of incidental anaemia, seizure (in one participant who did not undergo lumbar puncture), and one death from COVID-19.

Most plasma and CSF samples showed viral suppression (table 2). At baseline there was one (1%) case of CSF HIV RNA escape, which was at a low level (plasma HIV RNA <50 copies per mL and CSF HIV RNA 150 copies per mL). At follow-up there were three (4%)

	Baseline			Follow-up		
	Participants with HIV (N=178)	Participants without HIV (N=95)	p value	Participants with HIV (N=145)	Participants without HIV (N=40)	p value
Cognition						
Domain T-scores*						
Motor skills	47·86 (42·65–53·99)	50·73 (47·21–54·21)	0·014†	51·70 (45·74-55·71)	53·46 (48·23-64·92)	0·27†
Information processing speed	46·58 (8·15)	49·55 (8·46)	0·0052	50·46 (7·85)	50·87 (9·24)	0·78
Verbal fluency	48·77 (9·20)	50·28 (8·68)	0·19	51·93 (9·45)	52·67 (9·33)	0·66
Attention and working memory	47·93 (10·11)	50·01 (9·95)	0·11	49·77 (10·20)	54·58 (8·80)	0·0073
Audioverbal learning and memory	47·99 (10·52)	49·71 (9·89)	0·19	54·94 (9·29)	53·50 (9·94)	0·39
Visuospatial learning and memory	46·10 (10·24)	50·00 (9·60)	0·0025	51·30 (10·08)	53·83 (11·42)	0·18
Executive functioning	48·07 (8·17)	50·04 (7·59)	0·053	51·46 (7·45)	51·87 (8·09)	0·76
Global cognitive performance (T score)	47·35 (6·22)	49·92 (5·27)	0·0008	51·43 (5·79)	52·73 (6·16)	0·22
Low cognitive performance by Global Deficit Score	53/176 (30%)	11/94 (12%)	0·0007	12 (8%)	3 (8%)	1‡
Functional measures						
PAOFI total score	18·50 (11·25–30·75)	18·00 (12·5–28·0)	0·62†	25·00 (16·00-34·00)	22·00 (11·75-32·50)	0·22†
PAOFI affirmative	52 (29%)	20 (21%)	0·15	47 (32%)	10 (25%)	0·37
CTADL total score	2·00 (1·00–3·00)	2·00 (1·00–2·50)	0·77†	2·00 (2·00-3·00)	2·00 (1·00-2·00)	0·0023†
CTADL affirmative	10 (6%)	2 (2%)	0·23‡	6 (4%)	1 (3%)	1‡
Mental health symptoms						
Depression symptoms (Centre for Epidemiological Studies-Depression score ≥16)	17 (10%)	21 (22%)	0·0043	22 (15%)	6 (15%)	0·98
Trait anxiety (State Trait Anxiety Inventory-Trait total)	37·20 (8·03)	37·55 (9·43)	0·75	36·97 (8·72)	35·85 (9·47)	0·48
Mental health diagnosis (Mini)						
Major depressive disorder	1 (1%)	6 (6%)	0·0080‡	9 (6%)	2 (5%)	1‡
Suicidality			0·89‡			1‡
None	155 (87%)	85 (89%)		127 (88%)	36 (90%)	
Low	19 (11%)	8 (8%)		15 (10%)	4 (10%)	
Moderate	1 (1%)	1 (1%)		2 (1%)	0	
High	3 (2%)	1 (1%)		1 (1%)	0	
Mini—panic disorder	1 (1%)	1 (1%)	1‡	0	0	..
Mini—post-traumatic stress disorder	2 (1%)	1 (1%)	1‡	0	0	..
Mini—general anxiety disorder	1 (1%)	2 (2%)	0·28‡	1 (1%)	1 (3%)	0·39‡
Sleep						
PSQI total	5·79 (3·59)	5·80 (3·94)	0·77†	5·14 (3·76)	6·47 (3·78)	0·032†
PSQI total score ≥5	114 (64%)	60 (63%)	0·89	68 (47%)	25 (63%)	0·081

(Table 2 continues on next page)

cases of CSF HIV RNA escape. Two of these cases were at a low level (plasma HIV RNA <50 copies per mL and CSF HIV RNA 70 copies per mL and 81 copies per mL). One participant had more marked CSF escape, with plasma HIV RNA 448 copies per mL and CSF HIV RNA 4204 copies per mL. This participant had no symptoms and their cognitive profile was unchanged over time. Their HIV RNA at baseline had been 91 copies per mL in plasma and fewer than 50 copies per mL in CSF. A third lumbar puncture was done in this participant 5 months later, with no change in ART, at which point CSF escape had resolved with plasma HIV RNA of 170 copies per mL and CSF fewer than 50 copies per mL. The participant reported good adherence throughout, supported by pharmacy refill data, with 99% of tablets removed from the pack at baseline and 100% at follow-up.

Discussion

In this study, we found improvements in global cognitive performance and sleep, and a potential increase in depression, following switch from efavirenz-based to dolutegravir-based ART. To our knowledge, these are the first data to show CNS effects of recent programmatic ART switch, and the first to examine these effects in an African population, where this treatment change has been most widely applied. Our cohort was majority female, broadly reflective of the recruiting clinic and the demographic of HIV in South Africa, where almost twice as many women than men are living with HIV.[18] A strength of our study was prospective recruitment of an appropriate control group of people without HIV and the follow-up of these controls. Although improvements in cognition observed in other studies could be explained by practice effects,[19,20]

	Baseline			Follow-up		
	Participants with HIV (N=178)	Participants without HIV (N=95)	p value	Participants with HIV (N=145)	Participants without HIV (N=40)	p value
(Continued from previous page)						
HIV RNA and antiretroviral adherence						
Plasma HIV RNA			..			..
<1000 copies per mL	111/113 (98%)	..		117/122 (96%)	..	
<50 copies per mL	104/113 (92%)	..		103/122 (84%)	..	
CSF HIV RNA			..			..
<1000 copies per mL	93/94 (99%)	..		76/77 (99%)	..	
<50 copies per mL	92/94 (98%)	..		73/77 (95%)	..	
CSF white cell count, cells per µL§	1·40 (0·84–2·37)†	..	..	1·26 (0·49-2·37)†	..	..
Self-reported adherence	6 (1)	..	..	6 (1)	..	..
Pharmacy refill			..			..
0–49%	2 (2%)	..		1 (2%)	..	
50–79%	9 (11%)	..		4 (9%)	..	
80–94%	4 (5%)	..		6 (13%)	..	
95–100%	70 (82%)	..		36 (77%)	..	

Data are median (IQR), mean (SD), n/N (%), or n (%), unless otherwise indicated. CSF=cerebrospinal fluid. CTADL=Charter Instrumental Activities of Daily Living scale. Mini=Mini International Neuropsychiatric Interview. PAOFI=Patients Own Assessment of Functioning Inventory. PSQI=Pittsburgh Sleep Quality Index. *Baseline cognitive data available for 177 people with HIV (except 176 for attention and working memory, global, and low cognitive performance; and 178 for executive functioning) and 94 people without HIV. †Mann–Whitney *U* test instead of *t* test. ‡Fisher's Exact Test instead of χ^2 test. §Data available for 94 people with HIV and 77 people without HIV.

Table 2: **Cognitive, mental health, sleep and virological indices at baseline and follow-up**

to our knowledge, our study is the first to link improvements in cognition to change in ART.

Cognitive performance in people with HIV on dolutegravir-based ART was not significantly different from people without HIV. This finding is in line with other HIV health parameters, which are similar to those of the HIV-negative population when effective modern ART is widespread and side-effects are minimised. This finding contrasts markedly with existing studies reporting that HIV-associated neurocognitive disorders remain common in people with HIV, particularly in sub-Saharan African populations.[21] Our data support international consensus recommendations suggesting that studies of HIV-associated neurocognitive disorders can overestimate prevalence because of control group differences and failure to consider false classification rates (ie, a proportion of participants without cognitive impairment are falsely classified as impaired on the basis of statistical methodology).[22] Our findings should reassure people with HIV and reinforce the widespread health benefits of adherence to modern ART.

We found no evidence that slightly reduced cognitive performance on efavirenz was symptomatic. Our functional measures showed similar rates of symptoms in people with HIV, showing the subjective nature of cognitive symptoms. The relatively small difference in global T scores between people with HIV and people without HIV at baseline led to a large difference in the prevalence of low cognitive performance. This finding underlines the limitations of dichotomising a variable that is largely continuous, for which small variations around a cutoff can alter a binary outcome.[23] To address this issue, we used the term "low cognitive performance" for those falling below this cutoff (rather than cognitive impairment or HIV-associated neurocognitive disorder), as recommended.[22]

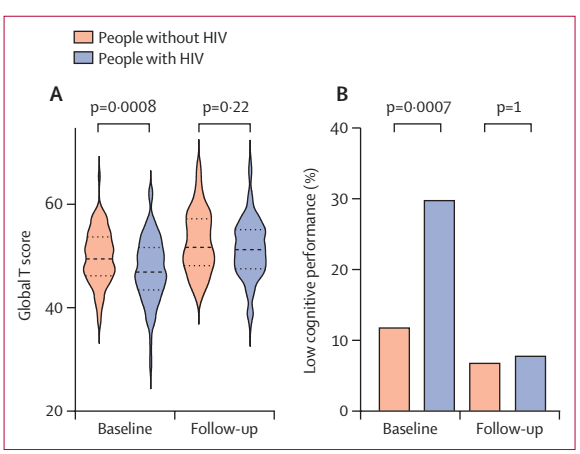

Figure 2: **Cognitive performance at baseline (on efavirenz) and follow-up (on dolutegravir)**
(A) Global T score. (B) Global deficit score.

We propose that the improvement in cognitive performance observed in our study is probably related to efavirenz neurotoxicity at baseline, rather than superior CNS efficacy of dolutegravir at follow-up. A randomised trial of dolutegravir intensification did not find that dolutegravir improved cognitive performance compared with placebo.[7] Our CSF studies did not indicate superior

	Coefficient or risk ratio (95% CI)	p value
Cognitive outcomes		
Global T score		
Baseline global T score	0·91* (0·88 to 0·94)	<0·0001
Group (HIV-positive *vs* HIV-negative)	–0·23* (–0·78 to 0·31)	0·40
Timepoint (baseline *vs* follow-up)	2·60* (1·80 to 3·39)	<0·0001
Group × timepoint interaction	1·40* (0·48 to 2·32)	0·0028
Low cognitive performance by Global Deficit Score		
Group (HIV-positive *vs* HIV-negative)	1·16† (1·08 to 1·26)	0·0001
Timepoint (baseline *vs* follow-up)	0·96† (0·89 to 1·04)	0·35
Group × timepoint interaction	0·86† (0·78 to 0·96)	0·0045
Functional outcomes		
PAOFI total		
Group (HIV-positive *vs* HIV-negative)	–0·41* (–3·88 to 3·06)	0·82
Timepoint (baseline *vs* follow-up)	3·49* (–0·14 to 7·13)	0·060
Group × timepoint interaction	1·41* (–2·74 to 5·55)	0·51
PAOFI affirmative		
Group (HIV-positive *vs* HIV-negative)	1·07† (0·98 to 1·16)	0·13
Timepoint (baseline *vs* follow-up)	1·03† (0·93 to 1·15)	0·55
Group × timepoint interaction	0·99† (0·88 to 1·12)	0·90
CTADL total		
Group (HIV-positive *vs* HIV-negative)	0·25* (–0·05 to 0·56)	0·10
Timepoint (baseline *vs* follow-up)	–0·03* (–0·44 to 0·38)	0·89
Group × timepoint interaction	0·39* (–0·09 to 0·86)	0·11
CTADL affirmative		
Group (HIV-positive *vs* HIV-negative)	1·03† (0·99 to 1·08)	0·12
Timepoint (baseline *vs* follow-up)	1·00† (0·95 to 1·06)	0·89
Group × timepoint interaction	0·98† (0·92 to 1·05)	0·61
Mental health outcomes (people with HIV only)		
Centre for Epidemiological Studies-Depression score ≥16		
Timepoint (baseline *vs* follow-up)	1·05† (0·99 to 1·11)	0·083
Mini International Neuropsychiatric Interview-major depressive disorder		
Timepoint (baseline *vs* follow-up)	11·05† (1·39 to 87·82)	0·023
State Trait Anxiety Inventory-Trait total		
Timepoint (baseline *vs* follow-up)	–0·07* (–1·37 to 1·23)	0·92
Sleep outcomes (people with HIV only)		
PSQI Total		
Timepoint (baseline *vs* follow-up)	–0·63* (–1·24 to –0·02)	0·042
PSQI total score ≥ 5		
Timepoint (baseline *vs* follow-up)	0·90† (0·84 to 0·95)	0·0002

CTADL=Charter Instrumental Activities of Daily Living scale. PAOFI=Patients Own Assessment of Functioning Inventory. PSQI=Pittsburgh Sleep Quality Index. *Coefficient. †Risk ratio.

Table 3: **Linear mixed-effects and Poisson regression models showing effects of switch on neuropsychiatric outcomes**

virological efficacy of dolutegravir compared with efavirenz. The change in sleep disturbance with dolutegravir indicated that a degree of efavirenz neurotoxicity was present in this cohort. Black South African people have a high prevalence of genotypic slow efavirenz metaboliser status (*CYP2B6*), leading to increased CNS concentrations and an increased risk of efavirenz side-effects.[24] Given the relatively high threshold for second-line ART in South Africa,[17] it is possible that people with HIV in our cohort could have been tolerating high efavirenz CNS concentrations that impaired cognitive performance and disturbed sleep, but were not treatment limiting. Further analysis in this cohort will examine the association of clinical changes with drug exposure and CSF inflammatory biomarkers.

Our data are reassuring in terms of CSF viral control and support that CSF HIV RNA escape is becoming less common with modern ART.[25] Whether low-level CSF escape represents compartmentalised virus, transient fluctuations, or the release of latent virus is unclear.[16] Longitudinal studies have shown that most CSF escape at this level represents a transient asymptomatic blip.[26] Our single case of CSF escape at a higher level was transient and asymptomatic. We did not do phylogenetic analysis; however, it is unlikely that virus was truly compartmentalised as escape was quickly supressed with continuation of the same ART regimen. Although adherence markers in this individual appeared good, we speculate that this episode could have followed a period of poor adherence, with subsequent suppression in CSF occurring at a different rate to plasma.[13]

Rates of MDD worsened after switch. Previous studies have reported depression related to dolutegravir therapy,[4,27,28] and cases of severe depression induced by dolutegravir have been described.[29] The risk of depression on dolutegravir is almost three times higher in women than in men,[4] who represented the majority of our cohort, in contrast to most previous studies, which have been majority men. However, these data should be interpreted with caution. Some randomised comparisons of efavirenz and dolutegravir have found no differences in depression symptoms.[8,9] Our 95% CIs were wide because of small numbers with of events. There were baseline differences, with lower rates of depression in people, potentially related to engagement with health care. The COVID-19 pandemic started shortly after recruitment commenced and our questionnaire showed differences in reported emotional impact in those with depressive symptoms.

Sleep improvements were driven mostly by the domain of disturbed sleep and bad dreams, aligned with the known side-effects of efavirenz. Sleep disturbance was greater in people with HIV than in people without HIV at baseline; however, overall PSQI score was similar in both groups at baseline and improved to be better in people with HIV than in those without at follow-up. We speculate that this result could be because people with HIV have become accustomed to poor sleep on efavirenz and do not report it as subjectively abnormal at baseline. Anecdotally, several of our participants reported at follow-up that they had not realised their sleep had been poor until they switched ART and noticed an improvement.

There are several limitations to our study. A single timepoint for follow-up does not account for evolving or transient symptoms. Recruitment was restricted to those eligible for ART switch, so was not reflective of the broader clinic population with HIV. People on

second-line, with or without non-supressed HIV RNA, might have an increased risk of cognitive impairment; however, such patients are a minority of people with HIV in this setting. Over 90% of people attending our clinic receive WHO first-line ART, 94% have HIV RNA suppression below 1000 copies per mL, and 86% below 50 copies per mL (unpublished clinic data). The majority female population, while applicable to our setting, might not be generalisable to men or populations in other regions. Not all participants were retained at follow-up. Full retention can be challenging in environments where migration between rural and urban settings is common and not every home has a mobile telephone or postal address. Additionally, only the first 60 people without HIV were offered follow-up and loss to follow-up rates were higher than in people with HIV (people with HIV were easier to retain in the study as they routinely attended the local HIV clinic), resulting in a reduced group of people without HIV at follow-up. People without HIV who were not followed up were older than those followed up; however, as age was controlled for in cognitive outcomes using regression-based norming processes, we do not believe this factor would have meaningfully affected our results. There is potential for confounding from baseline differences between people with HIV and people without HIV. History of tuberculosis was more common in people with HIV, although CNS tuberculosis was an exclusion criterion and our previous work found no difference in cognitive outcomes for people with HIV with non-CNS tuberculosis.[30] People with HIV had lower (although not significantly so) blood pressure, prevalence of hyperlipidaemia, and rates of smoking than did people without HIV, which could result from frequent engagement with health care among people with HIV. Differences in comorbid factors might have affected cognitive performance, although these differences were small and not statistically significant. Recruitment was during a global pandemic, with a potential confounding effect on depression scores. The COVID-19 pandemic could also have affected parameters such as sleep and cognition. We could not determine how many participants were exposed to COVID-19 during the study, although reported rates of COVID-19 symptoms were low.

In conclusion, our findings support the WHO recommendations to switch away from the widespread use of efavirenz-based ART to dolutegravir-based ART, due to effects on cognitive performance and sleep, and provide reassurance around low rates of cognitive issues and CSF escape. However, the potential increase in depression warrants further investigation.

Contributors

SN wrote the manuscript. AJD and SN did the statistical analysis and directly accessed and verified the underlying data. KGFT, GvZ, ED, PJWN, CO, PS, AW, SK, and JAJ provided input into the design, analysis, and interpretation of the study, and edited manuscript drafts. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AW reports research grants paid to his institution from ViiV Healthcare, Gilead, and MSD, and lecture honoraria from ViiV Healthcare, Gilead, Janssen, and MSD. PS reports grants paid to her institution from the South African Medical Research Council. SK reports awards for research and drug interactions website paid to their institution from ViiV Healthcare and Merck, an unrestricted grant paid to their institution from Gilead, consulting fees (advisory board) from ViiV Healthcare and Pfizer, lecture honoraria from Pfizer, and receipt of study drug from Merck and GSK. All other authors declare no competing interests.

Data sharing

Data will be made available from the corresponding author on reasonable request.

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