Antiretroviral therapy CNS penetration and HIV-1–associated CNS disease

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ABSTRACT

Objective: The impact of different antiretroviral agents on the risk of developing or surviving CNS disease remains unknown. The aim of this study was to investigate whether using antiretroviral regimens with higher CNS penetration effectiveness (CPE) scores was associated with reduced incidence of CNS disease and improved survival in the UK Collaborative HIV Cohort (CHIC) Study.

Methods: Adults without previous CNS disease, who commenced combination antiretroviral therapy (cART) between 1996 and 2008, were included ($n = 22,356$). Initial and most recent cART CPE scores were calculated. CNS diseases were HIV encephalopathy (HIVE), progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis (TOXO), and cryptococcal meningitis (CRYPTO). Incidence rates and overall survival were stratified by CPE score. A multivariable Poisson regression model was used to identify independent associations.

Results: The median (interquartile range) CPE score for initial cART regimen increased from 7 (5–8) in 1996–1997 to 9 (8–10) in 2000–2001 and subsequently declined to 6 (7–8) in 2006–2008. Differences in gender, HIV acquisition risk group, and ethnicity existed between CPE score strata. A total of 251 subjects were diagnosed with a CNS disease (HIVE 80; TOXO 59; CRYPTO 56; PML 54). CNS diseases occurred more frequently in subjects prescribed regimens with CPE scores ≤ 4 , and less frequently in those with scores ≥ 10 ; however, these differences were non-significant. Initial and most recent cART CPE scores ≤ 4 were independently associated with increased risk of death.

Conclusion: Clinical status at time of commencing cART influences antiretroviral selection and CPE score. This information should be considered when utilizing CPE scores for retrospective analyses. *Neurology*® 2011;76:693–700

GLOSSARY

cART = combination antiretroviral therapy; **CHIC** = UK Collaborative HIV Cohort; **CPE** = CNS penetration effectiveness; **CRYPTO** = cryptococcal meningitis; **HIVE** = HIV encephalopathy; **IQR** = interquartile range; **PML** = progressive multifocal leukoencephalopathy; **PYFU** = person-years of follow-up; **TOXO** = cerebral toxoplasmosis.

HIV-1–associated CNS diseases including HIV-associated encephalopathy (HIVE) and progressive multifocal leukoencephalopathy (PML) were frequently observed prior to the combination antiretroviral therapy (cART) era.^{1,2} Following the widespread introduction of effective cART, a dramatic reduction in the incidence of such events was observed, as were survival improvements.^{3,4} The impact of different antiretroviral agents on the risk of developing or surviving a CNS disease remains unclear.^{4–6} The CNS penetration effectiveness (CPE) score

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has recently been proposed as a method of estimating the CNS penetration of antiretrovirals.⁷ Based upon pharmacokinetic data, results of clinical studies, and drug properties, antiretrovirals are each assigned a score (with higher scores estimating better penetration). Studies have shown that using regimens with higher CPE scores is associated with an increased probability of achieving undetectable CSF HIV-1 RNA levels,⁸ improved neuropsychological performance,^{8,9} and longer survival.¹⁰ In contrast, worse neurocognitive performance was described in a recent, prospective study in subjects receiving regimens with higher CPE scores.¹¹ Finally, although currently unpublished, data have reported better survival following PML, HIVE, cryptococcal meningitis (CRYPTO), and cerebral toxoplasmosis (TOXO) when antiretroviral regimens with higher CPE scores were used.^{12,13}

The aim of this study was to investigate whether the use of cART with higher CPE scores is associated with reduced incidence of CNS diseases and improved survival within a large UK cohort between 1996 and 2008.

METHODS **Standard protocol approvals, registrations, and patient consents.** The UK Collaborative HIV Cohort (CHIC) Study is an observational cohort study currently involving 12 of the largest UK HIV clinical centers (appendix). Ethical approval was granted via the National Research Ethics Service (West Midlands MREC, UK), reference number MREC/00/7/47. According to UK regulation, individual written consent was not required from patients as only anonymized data routinely collected for other purposes were used.

Subject identification. Eligible subjects for this work were HIV-1-infected adults (over 16 years old) who started cART at any date between January 1, 1996, and December 31, 2008, and with at least 1 day of follow-up data after starting cART available for analysis. Data including risk group for HIV acquisition, antiretroviral exposure, laboratory test results, AIDS diagnoses, and deaths were collected. CNS opportunistic diseases (CNS events) included any first report of a clinical diagnosis of HIVE, PML, TOXO, or CRYPTO occurring after commencing cART. Subjects experiencing a CNS event prior to commencing cART were excluded, thus all reported events in this series occurred in subjects who were cART experienced.

cART was defined as any antiretroviral regimen containing a protease inhibitor, non-nucleoside reverse transcriptase inhibitor, abacavir, or an integrase/entry inhibitor, regardless of number of drugs in the combination (thus permitting protease inhibitor monotherapy and some triple nucleoside regimens to be included). cART regimens were then scored using the CPE system and each individual's CPE score was updated each time a drug in the regimen was changed. According to Letendre et al.,¹⁴

each antiretroviral drug was given a CPE score between 1 (low CNS penetration) and 4 (high CNS penetration) and a regimen total calculated.

Statistical analysis. Demographic characteristics and clinical parameters were stratified according to the CPE score of the initial cART regimen (categorized as ≤ 4 , 5–7, 8–9, and ≥ 10). Independent associations between clinical factors and an initial CPE score of ≤ 4 were investigated using multivariable logistic regression analysis, utilizing a backwards selection process. Factors considered for these analyses were gender and mode of HIV transmission (categorized as men having sex with men, female heterosexuals, male heterosexuals, injection drug use, male other/unknown, female other/unknown), ethnicity (white, black African, other/unknown), age, CD4 count, HIV RNA, treatment status (antiretroviral-naïve or experienced), and calendar year at cART initiation.

The incidence of a first CNS event (overall and stratified by CPE score) was calculated by dividing the number of events occurring by the total person-years of follow-up (PYFU) in the cohort. For these analyses, patient follow-up started on the date of cART initiation and ended on the date of the patient's first CNS event. For those who remained free of CNS events at the end of the study period, follow-up was right-censored at the earliest of death, December 31, 2008, or 3 months after the patient's last clinic visit. Poisson regression models were used to describe any association between the CPE score and the development of each event, after adjustment for potential confounding factors. Two sets of analyses were performed: the first considered baseline covariates only (CPE score of initial regimen, sex/mode of transmission, age, ethnicity, CD4 count, HIV RNA, treatment status, and calendar year at cART initiation), whereas the second incorporated changes in several of these covariates over time (latest CPE score, CD4 count, and HIV RNA) through the use of time-dependent covariates—this latter model also incorporated a time-dependent covariate for time since initiation of cART.

Similar analyses were performed for all-cause mortality; for these analyses, patient follow-up started on the date of cART initiation and ended at the earliest of death, December 31, 2008, or 3 months after the patient's last clinic visit. All statistical analyses were performed using SAS v 9.1 software. *p* Values below 0.05 were considered significant.

RESULTS Over the study period, 22,356 subjects with no history of prior CNS events commenced cART. Median (interquartile range [IQR]) duration of follow-up of patients after starting cART was 4.6 (1.9–8.5) years (118,123 PYFU in total), with 89.4% of this follow-up time being spent on cART, 1.1% on non-cART regimens, and 9.5% off treatment. Median (IQR) age at cART initiation was 36 (31–42) years, 16,704 (75%) of subjects were male, and 5,864 (26%) were of black African ethnicity (table 1). At the time of commencing cART, median (IQR) plasma CD4+ lymphocyte count and plasma HIV RNA were 200 (100–300) IU/mL and 4.8 (4.0–5.3) log₁₀ copies/mL, respectively. Over the study period, median (IQR) CPE score for initial cART regimen initially increased from 7 (5–8) in 1996/1997 to 9 (8–10) in 2000/2001 and subse-

Table 1 Baseline characteristics of patients included in the study, overall and stratified by CNS penetration effectiveness (CPE) score of initial combination antiretroviral therapy (cART)

	Total	CPE score of initial cART			
		≤4	5–7	8–9	≥10
No. (%)	22,356 (100.0)	1,248 (5.6)	9,918 (44.4)	7,906 (35.4)	3,284 (14.7)
Sex/mode of transmission					
MSM	11,873 (53.1)	671 (53.8)	5,748 (58.0)	4,021 (50.9)	1,433 (43.6)
Male heterosexual	2,932 (13.1)	191 (15.3)	1,142 (11.5)	1,198 (15.2)	401 (12.2)
Female heterosexual	4,688 (21.0)	221 (17.7)	1,673 (16.9)	1,704 (21.6)	1,090 (33.2)
IDU	790 (3.5)	44 (3.5)	355 (3.6)	281 (3.6)	110 (3.4)
Male other/unknown	1,371 (6.1)	88 (7.1)	696 (7.0)	448 (5.7)	139 (4.2)
Female other/unknown	702 (3.1)	33 (2.6)	304 (3.1)	254 (3.2)	111 (3.4)
Ethnicity					
White	12,853 (57.5)	726 (58.2)	6,185 (62.4)	4,384 (55.5)	1,558 (47.4)
Black African	5,864 (26.2)	285 (22.8)	2,076 (20.9)	2,316 (29.3)	1,187 (36.1)
Other/unknown	3,639 (16.3)	237 (19.0)	1,657 (16.7)	1,206 (15.3)	539 (16.4)
Age, y, median (IQR)	36 (31–42)	37 (32–44)	36 (31–42)	36 (31–42)	34 (30–40)
Pretreatment CD4 (cells/ μ L), median (IQR)	200 (100–300)	170 (75–299)	200 (94–300)	200 (102–297)	202 (114–307)
Pretreatment plasma HIV RNA ($\log_{10}$ copies/mL), median (IQR)	4.8 (4.0–5.3)	4.7 (4.0–5.2)	4.8 (4.1–5.3)	4.8 (4.1–5.3)	4.7 (3.9–5.2)
Treatment-naïve, n (%)	18,204 (81.4)	889 (71.2)	7,819 (78.8)	6,796 (86.0)	2,700 (82.2)
Follow-up, y, median (IQR)	4.6 (1.9–8.5)	3.4 (1.6–9.5)	3.6 (1.3–8.9)	5.1 (2.3–8.0)	6.6 (3.9–8.8)
Calendar year					
1996/1997	3,751 (16.8)	355 (28.5)	2,126 (21.4)	904 (11.4)	366 (11.1)
1998/1999	3,531 (15.8)	146 (11.7)	1,418 (14.3)	1,254 (15.9)	714 (21.7)
2000/2001	2,877 (12.9)	59 (4.7)	598 (6.0)	1,330 (16.8)	890 (27.1)
2002/2003	3,193 (14.3)	61 (4.9)	761 (7.7)	1,599 (20.2)	772 (23.5)
2004/2005	3,496 (15.6)	205 (16.4)	1,737 (17.5)	1,186 (15.0)	368 (11.2)
2006–2008	5,508 (24.6)	422 (33.8)	3,278 (33.1)	1,634 (20.7)	174 (5.3)
Initial regimen					
PI-based	8,396 (37.6)	871 (69.8)	5,363 (54.1)	1,925 (24.4)	237 (7.2)
NNRTI-based	12,783 (57.2)	332 (26.6)	4,273 (43.1)	5,286 (66.9)	2,892 (88.1)
PI- + NNRTI-based	470 (2.1)	6 (0.5)	175 (1.8)	145 (1.8)	144 (4.4)
Other cART	707 (3.2)	39 (3.1)	107 (1.1)	550 (7.0)	11 (0.3)

Abbreviations: IDU = injection drug use; IQR = interquartile range; MSM = men having sex with men; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

quently declined to 6 (7–8) in 2006/2008. The majority of subjects (79.8%) were commenced on an initial cART regimen with a CPE score of 5–9. Differences in gender, HIV risk group, and ethnicity existed between CPE score strata. For instance, subjects with a baseline CPE score of ≤ 4 tended to be older, had lower plasma CD4+ cell counts, and were less likely to be treatment-naïve than those with higher baseline CPE scores.

Multivariable logistic regression analyses revealed that subjects who initiated cART while antiretroviral-naïve and those with a higher CD4 count were less likely to be prescribed an initial regimen with a low CPE score, whereas those of other or unknown ethnici-

ties, older subjects, and those who initiated cART from 1996 to 1999 or from 2004 onwards were more likely to be prescribed an initial regimen with a low CPE score (table 2).

Development of CNS events during study period. In total, 251 subjects experienced a new CNS event during the study period (HIVE: 80; TOXO: 59; CRYPTO: 56; PML: 54) over a total of 113,633 PYFU (censored at first event). Kaplan-Meier estimates of the proportions experiencing a CNS event by 1, 2, 3, 4, and 5 years after initiation of cART were 0.6%, 0.8%, 1.0%, 1.1%, and 1.2%, respectively. The overall CNS event rate after starting

Table 2 Results from multivariable logistic regression analysis of factors associated with a low (≤ 4) baseline CNS penetration score

	Odds ratio	95% Confidence interval	p Value ^a
Ethnicity			
White	1	—	0.008
Black African	0.93	0.78–1.10	
Other/unknown	1.26	1.06–1.50	
Age, per 10 years older	1.14	1.07–1.23	0.0002
Treatment status, antiretroviral-naïve	0.59	0.49–0.71	0.0001
Calendar year			
1996/1997	4.83	3.34–6.99	0.0001
1998/1999	2.28	1.55–3.35	
2000/2001	1	—	
2002/2003	0.96	0.61–1.53	
2004/2005	3.79	2.62–5.47	
2006–2008	5.27	3.72–7.46	
Pretreatment CD4, per 50 cells/ μ L higher	0.98	0.96–0.99	0.0001

^a Global p value derived from comparison of 2 log likelihood values from models that do and do not include the factor of interest.

cART was 2.2 (95% confidence interval 1.9–2.5)/1,000 PYFU. At the time of CNS event, median (IQR) CD4⁺ cell count was 103 (30–240) cells/ μ L, plasma HIV RNA was 4.4 (2.2–5.5) log₁₀ copies/mL. The median (IQR) time since cART initiation was 0.6 (0.1–2.7) years and 40 (17.5%) subjects had discontinued cART. Fifty (22.1%) subjects had an undetectable plasma HIV RNA level at the time of CNS event and their median cART CPE score was 7.

When stratified according to the initial CPE score, CNS event rates were highest in those subjects prescribed regimens with CPE scores of ≤ 4 and were lowest in subjects prescribed regimens with CPE scores of ≥ 10 (figure), although these differences were nonsignificant, both before and after adjust-

ment for potential confounders (table 3). When considering baseline covariates only, predictors of a new CNS event were heterosexual transmission, older age, a lower pretreatment CD4 count or higher plasma HIV RNA, and prior exposure to mono- or dual-NRTI therapy before starting cART. When we considered changes in the CPE score over time, a CPE score of ≤ 4 again appeared to be associated with an increased risk of a new CNS event. However, as with the baseline analysis, this association did not remain significant after adjustment for potential confounders. Similar associations were found between heterosexual transmission, older age, lower CD4 count, and higher plasma HIV RNA and the risk of a new CNS event, as with the baseline analysis. Time since initiation of cART was additionally identified as a strong predictor of a new CNS event in these analyses, with the event rate being particularly high in the first 6 months. After controlling for this covariate, prior NRTI exposure was no longer associated with an increased risk of a new CNS event.

Mortality. During the study period, 1,581 subjects died, giving an overall all-cause mortality rate of 13.8/1,000 PYFU. After stratifying according to the CPE score of the initial regimen, mortality was highest in those who were prescribed regimens with CPE scores ≤ 4 (21.0 deaths/1,000 PYFU) and dropped as the CPE score increased (table 4). Similarly, after stratification by most recent CPE score, rates of death were highest in those with a CPE score ≤ 4 (16.5 deaths/1,000 PYFU) and again dropped as the CPE score increased. A CPE score ≤ 4 , whether based on the initial or latest cART regimen, was strongly associated with an increased mortality risk, although both associations were generally attenuated after adjustment for potential confounders. Of note, patients who had discontinued antiretroviral treatment had the highest mortality risk in time-updated

Figure Rates of new CNS event

Rates of new CNS event (A) stratified by initial and most recent central nervous penetration effectiveness (CPE) scores (B). ART = antiretroviral treatment.

Table 3 Results from adjusted Poisson regression analyses of factors associated with the development of a new CNS event over follow-up

	Baseline (fixed) covariates only			Latest (time-updated) covariates		
	Relative rate	95% Confidence interval	p Value	Relative rate	95% Confidence interval	p Value
CPE score						
≤4	1	—	0.97	1	—	0.66
5-7	0.95	(0.57-1.60)		0.96	(0.56-1.65)	
8-9	1.02	(0.59-1.74)		1.20	(0.69-2.07)	
≥10	0.95	(0.53-1.72)		1.03	(0.56-1.89)	
Off treatment	NA			1.20	(0.66-2.17)	
Time since initiation of cART, mo						
0-6	NA			3.37	(2.32-4.89)	0.0001
7-12				1.28	(0.77-2.12)	
13-18				1.62	(0.98-2.67)	
19-24				1.13	(0.62-2.08)	
25-30				1.12	(0.58-2.14)	
31-36				1.05	(0.52-2.12)	
>36				1	—	
Sex/mode of transmission						
MSM	1	—	0.006	1	—	0.11
Male heterosexual	2.44	(1.34-4.45)		1.46	(0.80-2.67)	
Female heterosexual	3.18	(1.54-6.57)		1.98	(0.95-4.10)	
IDU	1.32	(0.90-1.94)		1.15	(0.78-1.69)	
Male other/unknown	0.74	(0.35-1.54)		0.54	(0.26-1.12)	
Female other/unknown	1.37	(0.65-2.88)		1.18	(0.56-2.49)	
Age, y						
≤30	—	—	0.30	1	—	0.15
31-40	1.36	(0.94-1.97)		1.42	(0.98-2.07)	
41-50	1.45	(0.95-2.20)		1.57	(1.04-2.39)	
>50	1.40	(0.81-2.43)		1.50	(0.87-2.60)	
Ethnicity						
White	1	—	0.11	1	—	0.06
Black African	1.22	(0.80-1.85)		1.08	(0.71-1.65)	
Other	1.47	(0.97-2.24)		1.44	(0.95-2.20)	
Unknown	0.61	(0.28-1.31)		0.51	(0.24-1.09)	
CD4 count, cells/μL						
0-50	5.75	(3.60-9.18)	0.0001	10.10	(6.55-15.57)	0.0001
50-199	2.02	(1.26-3.23)		3.27	(2.19-4.89)	
200-349	1	—		1	—	
350-499	1.46	(0.71-2.98)		0.48	(0.25-0.94)	
≥500	1.22	(0.46-3.21)		0.41	(0.20-0.81)	
Missing	2.57	(1.48-4.46)		3.39	(1.80-6.36)	
Plasma HIV RNA, copies/mL						
≤50	1	—	0.0001	1	—	0.0001
>50-≤10,000	1.91	(0.25-14.91)		3.03	(1.93-4.77)	
>10,000-≤100,000	4.94	(0.68-36.15)		4.24	(2.60-6.92)	
>100,000	5.74	(0.79-41.84)		5.35	(3.29-8.69)	
Missing	9.18	(1.25-67.36)		6.36	(3.54-11.45)	

—Continued

Table 3 Continued

	Baseline (fixed) covariates only			Latest (time-updated) covariates		
	Relative rate	95% Confidence interval	p Value	Relative rate	95% Confidence interval	p Value
Year of starting cART						
1996/1997	0.71	(0.43–1.17)	0.02	0.79	(0.49–1.26)	0.11
1998/1999	1.23	(0.81–1.89)		1.14	(0.75–1.74)	
2000/2001	1	—		1	—	
2002/2003	1.38	(0.87–2.18)		1.27	(0.80–2.01)	
2004/2005	0.98	(0.56–1.74)		0.73	(0.42–1.29)	
2006–2008	1.81	(1.02–3.22)		0.78	(0.44–1.39)	
Antiretroviral-naïve	0.58	(0.41–0.82)	0.002	0.89	(0.64–1.24)	0.49

Abbreviations: cART = combination antiretroviral therapy; CPE = CNS penetration effectiveness rank; IDU = injection drug use; MSM = men having sex with men; NA = not available.

analyses, supporting the hypothesis that treatment may have been selectively discontinued in those at terminal stages of disease.

DISCUSSION The relationship between antiretroviral CNS penetration and HIV-related CNS disease is of clinical importance, and may influence future antiretroviral selection in HIV-1-infected subjects. In this large cohort study, we have retrospectively assessed the relationship between CPE score of different cART regimens and the incidence of CNS events and survival. Several interesting observations were made. First, significant changes in the median CPE score of initial cART have occurred between 1996 and 2008. This is likely to reflect changes in prescribing trends (represented in treatment guidelines) as clinical evidence and newly licensed antiretrovirals became available. Interestingly, there has been an overall reduction in CPE score in the most recent years studied. While the majority of individuals achieving full suppression of HIV replication in plasma will achieve similar results in CSF and respond clinically,¹⁵ it is possible that a trend toward

lower CPE scores may, in the future, increase the risk of HIV replication in the CNS compartment, resulting in more cerebral sequelae, including cognitive problems and HIV-associated encephalopathy.

We also observed a significant association between initial cART CPE score and subject demographics (gender, HIV risk group), calendar year of treatment initiation, and clinical parameters (including CD4 cell count and plasma HIV RNA). This novel finding suggests that, according to a subject's clinical status, treatment is tailored or individualized, particularly in those with advanced HIV disease or previous poor adherence. Such individuals in this cohort were more likely to be prescribed regimens with very low (≤ 4) CPE scores. To our knowledge, this association has not previously been reported and may reflect a subgroup of individuals with high levels of comorbidity or opportunistic disease. Such confounders are important considerations when the CPE score is utilized as a research tool in retrospective analyses, as bias in outcome data would be expected.

Table 4 Univariate and multivariable estimates of association between mortality and initial or most recent CPE score

CPE score	Initial CPE score				Most recent CPE score			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	Relative rate (95% confidence interval)	p Value	Relative rate (95% confidence interval)	p Value	Relative rate (95% confidence interval)	p Value	Relative rate (95% confidence interval)	p Value
≤ 4	1	0.0001	1	0.03	1	0.0001	1	0.0001
5–7	0.72 (0.60–0.87)		0.80 (0.66–0.97)		0.71 (0.58–0.87)		0.81 (0.66–0.98)	
8–9	0.60 (0.50–0.73)		0.78 (0.64–0.95)		0.63 (0.50–0.76)		0.80 (0.64–0.98)	
≥ 10	0.50 (0.40–0.62)		0.71 (0.56–0.89)		0.65 (0.51–0.81)		0.83 (0.66–1.04)	
Off treatment	NA				2.21 (1.80–2.72)		1.73 (1.40–2.14)	

Abbreviations: CPE = CNS penetration effectiveness rank; NA = not available; cART = combination antiretroviral therapy; CHIC = UK Collaborative HIV Cohort; CPE = CNS penetration effectiveness; CRYPTO = cryptococcal meningitis; HIVE = HIV encephalopathy; IQR = interquartile range; PML = progressive multifocal leukoencephalopathy; PYFU = person-years of follow-up; TOXO = cerebral toxoplasmosis.

We observed low rates of CNS events overall in this cohort, with low plasma CD4+ cell count, high plasma HIV RNA, and short time elapsed since cART initiation all significantly associated with increased event risk, rather than CPE score. This suggests that strategies to support adherence to effective therapies, particularly in early months of treatment, are more important than selection of neuropenetrative antiretroviral agents. Unfortunately, adherence data are not collected within this cohort study and therefore this important factor could not be further evaluated. Interestingly, however, a proportion of subjects did experience CNS events while plasma HIV RNA was fully suppressed. In these subjects it is possible viral replication within the CNS compartment and modest CPE score of cART (median 7) may have influenced the pathogenesis of these events; however, due to small numbers, it is not possible to draw further conclusions.

In this cohort, we observed an independent association between lower CPE scores (initial and most recent) and higher all-cause mortality, after adjustment for relevant clinical factors. This finding may reflect the process of altering cART due to a subject's clinical parameters (as earlier described) with those deteriorating clinically or with advanced disease being prescribed regimens with lower scores than asymptomatic individuals. Alternatively, it may be hypothesized that an association between low CPE score and poorer survival (despite the absence of relationship with our selected CNS events) is in fact related to cognitive impairment (for which no data were collected) occurring on cART regimens with low neuropenetration. Cognitive impairment has previously been associated with increased mortality in HIV-1-infected adults^{16,17} and improved survival outcomes in perinatally infected adolescents with higher CPE scoring regimens have also been reported.¹⁰ However, without randomized, prospective data, this explanation remains speculative.

Limitations of our cohort data include the absence of information regarding immune reconstitution syndrome, adherence, and clinic attendance. Furthermore, all CNS events were reports of clinical diagnoses rather than strict protocol-defined criteria, and data regarding cognitive impairment are not collected. Reporting of events may therefore have varied by clinician, center, and over the study period. While the study size is large, CNS events occur relatively infrequently, limiting our power to perform more detailed analyses. Finally, analyses of the changing CPE score over time may be affected by time-varying confounding, in that treatments may be selectively switched in those already showing early signs of CNS problems; thus, it is difficult to assess the causal asso-

ciation between regimens with different CPE scores and the development of these events. While novel statistical methods exist for the evaluation of causal effects (subject to the assumption of no unmeasured confounding), their application requires large study sizes. As such, collaborative efforts are ongoing between several large HIV cohorts to apply these methods to this question, with results anticipated within the next 1–2 years. Nevertheless, this study adds important information to our understanding of the relationship between CPE score, CNS events, and survival. We highlight, in particular, that clinical status at time of commencing cART influences antiretroviral selection and CPE score. This should be considered when utilizing CPE scores for retrospective cohort analyses.

CONTRIBUTORS

David Dunn, Adam Glabay, Abdel Babiker, and Kholoud Porter from the Medical Research Council Clinical Trials Unit (MRC CTU), London, were involved at a coordinating center in arranging funding for the project at local sites, setting up and maintaining local databases, data collection, and data cleaning and validation. Other contributors who were involved in setting up and maintaining local databases, data collection, data cleaning, and validation included Kevin Jones, Rachel Thomas (Barts and The London NHS Trust, London), Nicky Perry, Anthony Pullin, Duncan Churchill (Brighton and Sussex University Hospitals NHS Trust), Steve Bulbeck, Sundhiya Mandalia, Jemima Clarke (Chelsea and Westminster NHS Trust, London), Valerie Delpach (Health Protection Agency Centre for Infections London), Sajid Munshi (Homerton University Hospital NHS Trust, London), Yasar Khan, Paragi Patel, Fatimah Karim, Stephen Duffell (King's College Hospital, London), Shuk-Li Man, Ian Williams (UCL Medical School and The Mortimer Market Centre, London), Debbie Dooley (North Bristol NHS Trust, Bristol), Achim Schwenk (North Middlesex University Hospital NHS Trust, London), Mike Youle, Fiona Lampe, Colette Smith, Helen Grabowska, Clinton Chaloner, Dewi Ismajani Puradiredja (Royal Free NHS Trust and Department of Infection & Population Health, UCL Medical School, London), Nicky Mackie, Jonathan Weber, Christian Kemble, Mark Carder (Imperial College Healthcare NHS Trust, London), Alan Wilson (The Lothian University Hospitals NHS Trust, Edinburgh), and Anne Moore (University Hospitals of Leicester, Leicester).

DISCLOSURE

Dr. Garvey has received speaker honoraria or funding for travel from Abbott, Boehringer Ingelheim, Gilead Sciences, Inc., and Tibotec Therapeutics. Dr. Winston has served on scientific advisory boards for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Inc., GlaxoSmithKline, and Pfizer Inc.; and has received research support from Boehringer Ingelheim, Gilead Sciences, Inc., Janssen, and Pfizer Inc. Dr. Walsh serves on scientific advisory boards for Tibotec Therapeutics, Bristol-Myers Squibb, Gilead Sciences, Inc., and Pfizer Inc.; has received funding for travel from Tibotec Therapeutics, Boehringer Ingelheim, and Gilead Sciences, Inc.; and receives research support from TRXCare Ltd and NHS Westminster. Dr. Post serves on scientific advisory boards for GlaxoSmithKline/ViiV Healthcare, Bristol-Myers Squibb, and Tibotec Therapeutics; has received funding for travel or speaker honoraria from GlaxoSmithKline/ViiV Healthcare, Gilead Sciences, Inc., and Tibotec Therapeutics; serves on speakers' bureaus for GlaxoSmithKline/ViiV Healthcare and Tibotec Therapeutics; and receives research support from GlaxoSmithKline/ViiV Healthcare, Bristol-Myers Squibb and Tibotec Therapeutics. Dr. Porter has received a speaker honorarium from Tibotec Therapeutics; serves as Associate Editor for *BioMed Central Public Health* and on the editorial boards of the *Open AIDS Journal* and *AIDS*; and is an employee of the UK Medical Research Council. Dr. Gazzard serves on

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