Poster Board: 427

Do antiretroviral combination therapies with greater central nervous system (CNS) penetration prevent the development of CNS opportunistic diseases?

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BACKGROUND

•Combination antiretroviral therapies (cART) with greater central nervous system (CNS) penetration may afford protection against the onset of CNS opportunistic disease events.

•The CNS Penetration Effectiveness (CPE) score has been devised by investigators as a method of estimating the ability of antiretrovirals to penetrate the CNS[1]. Ranking is based upon available pharmacokinetic data, results of clinical studies and theoretical drug properties. Each antiretroviral is assigned a score of 0 (low CNS penetration), 0.5 (moderate CNS penetration) or 1 (high CNS penetration) and a total calculated for the regimen.

•Use of cART regimens with higher CPE scores has been associated with lower CSF HIV RNA levels[1] and detectable CSF viral replication is associated with worse neuropsychological performance[2]. Improved survival in subjects with progressive multifocal leucoencephalopathy (PML) following use of cART regimens with higher CPE scores has been reported[3].

•The aim of our study was to investigate whether the use of cART with higher CPE scores is associated with reduced incidence of CNS events and mortality within a large UK cohort.

METHODS

•The UK CHIC study is an ongoing observational cohort study collecting data from the largest UK HIV treatment centres. Eligible subjects for this analysis were HIV-1 infected adults (18-65 years), without a history of previous CNS events, who commenced cART between 1996 and 2007.

•Data on CNS events (including HIV encephalopathy (HIVe), cerebral toxoplasmosis (TOXO),cryptococcal meningitis (CRYPTO) and PML), demographic and clinical factors were reported annually by collaborating centres. cART was defined as any antiretroviral regimen containing a non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), abacavir or enfuvirtide, irrespective of number of drugs in the combination.

•All (initial and subsequent) cART regimens were scored using the CPE score[1]. Factors associated with the initial CPE score (≥ or <3) were identified using multiple logistic regression. Incidence rates of CNS events and mortality were estimated overall and stratified by the initial and latest cART CPE score. Poisson regression analysis was performed to quantify the associations between the initial (fixed covariate) and latest (time-updated covariate) CPE score and the risk of (i) a new CNS event, and (ii) death, after adjusting for sex; age; mode of HIV infection; ethnicity; pre-cART and latest CD4 count; pre-cART and latest HIV RNA level; calendar year; and treatment status (naïve, non-naïve) at start of cART.

•Statistical analyses were performed using SAS *v.9.1* software. *P*-values below 0.05 were considered statistically significant.

RESULTS

•Over the study period 19,828 subjects commenced cART (see Table 1). Median (IQR) duration of follow up was 4.5 (1.9, 8.2) years providing 94,511 person years of follow up (PYFU) data for analysis.

Table 1: Baseline characteristics of study subjects, overall and stratified by initial cART CPE score

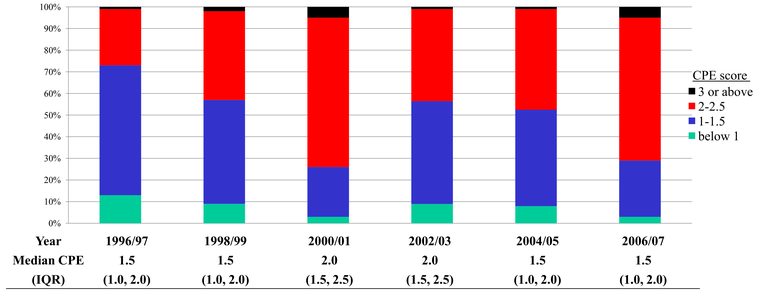
		Total	Initial cART CPE score			
			Below 1	1-1.5	2-2.5	3 or above
Number of patients	***N (%)***	19828 (100)	1560 (7.9)	8444 (42.6)	9386 (47.3)	438 (2.2)
Age (years)	***Median (IQR)***	36 (31, 42)	36 (31, 43)	36 (31, 42)	36 (31, 41)	36 (31, 42)
Female	***N (%)***	4933 (24.9)	276 (17.7)	1791 (21.2)	2779 (29.6)	87 (19.9)
Risk group	***MSM***	10726 (54.1)	982 (63.0)	4937 (58.5)	4541 (48.4)	266 (60.7)
	Heterosexual	6784 (34.2)	368 (23.6)	2444 (28.9)	3836 (40.9)	136 (31.1)
	IDU	762 (3.8)	73 (4.7)	365 (4.3)	310 (3.3)	14 (3.2)
	Other/not known	1556 (7.9)	137 (23.6)	698 (8.3)	699 (7.5)	22 (5.0)
Ethnicity	***White***	11776 (59.4)	1076 (69.0)	5457 (64.6)	4978 (53.0)	265 (60.5)
	Black African	5099 (25.7)	241 (15.5)	1783 (21.1)	2976 (31.7)	99 (22.6)
	Other / not known	2953 (14.9)	243 (15.6)	1204 (14.3)	1432 (15.3)	74 (16.9)
Pre-treatment CD4 (cells/uL)	***Median (IQR)***	190 (91, 290)	178 (80, 288)	190 (87, 293)	195 (103, 290)	172 (61, 300)
Pre-treatment HIV RNA (log_{10} copies/mL)	***Median (IQR)***	4.8 (4.1, 5.3)	4.8 (4.2, 5.2)	4.8 (4.1, 5.3)	4.8 (4.1, 5.3)	5.2 (4.3, 5.7)
Treatment-naive	***N (%)***	15744 (79.4)	1019 (65.3)	6235 (73.8)	8132 (86.6)	358 (81.7)

RESULTS (continued)

•The majority of subjects (89.9%) commenced an initial cART regimen with a CPE score of 1-2.5. Differences in gender, (p=0.0001) HIV-risk group (p=0.0001) and ethnicity (p=0.0001) existed between strata. Highest pre-treatment HIV RNA levels were observed in subjects with a baseline CPE score of 3 or greater. Lowest plasma CD4+ cell counts were seen in subjects with an initial CPE score of <1 or ≥3. The CPE scores of initial cART regimen are shown in Figure 1.

•Factors independently associated with a CPE score ≥3 included the pre-treatment HIV RNA level (p=0.005), commencing cART between 2000 and 2003 (p<0.0001) and commencing NNRTI-containing cART (p<0.0001). Female heterosexual subjects were less likely to be prescribed cART with a CPE score ≥3 than individuals from other HIV risk groups (p<0.0001).

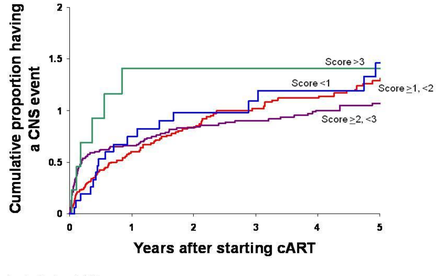
Figure 1: Bar graph to show the CPE score of initial cART regimen between 1996 and 2007



•Of 19828 subjects, 224 experienced a new CNS event during the study period (HIVe:76; TOXO:58; CRYPTO:51; PML:44) giving an overall CNS event rate [95% CI] of 2.4 [2.1, 2.7] per 1000 PYFU.

•When stratified according to initial cART CPE score, CNS event rates were higher in those prescribed regimens with CPE scores of <1 or ≥3 (see Figure 2).

Figure 2: Kaplan-Meier graph illustrating the proportion of subjects diagnosed with a CNS event over time when stratified by initial CPE score



Number of patients under follow-up

<1	1560	1345	1135	935	812	727
≥1, <2	8444	7140	6158	5163	4405	3926
≥2, <3	9386	8042	6941	6097	5187	4132
≥3	438	395	368	343	324	265

RESULTS (continued)

•Shorter time-elapsed since cART initiation, heterosexual HIV-risk group, low baseline or current plasma CD4+ cell count and higher plasma HIV RNA levels were independently associated with a greater risk of CNS events. An initial cART CPE score of 1-1.5 was associated with a reduced event rate in the univariate analysis, however after adjustment, neither initial or latest CPE score remained independently associated with a new CNS event (see Table 2).

Table 2: Poisson regression analyses to identify predictors of new CNS event over study period

		Univariate			Multivariable (initial cART CPE score)			Multivariable (latest cART CPE score)		
		RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI	p-value
Baseline CPE score	***Below 1***	1	-		1	-		n/a		
	1-1.5	0.93	(0.58, 1.49)	0.76	1.04	(0.65, 1.67)	0.87			
	2-2.5	0.91	(0.57, 1.45)	0.69	1.05	(0.64, 1.72)	0.86			
	3 or above	1.09	(0.44, 2.70)	0.85	1.14	(0.45, 2.89)	0.79			
Latest CPE score	***Below 1***	1			n/a			1		
	1-1.5	**0.66**	**(0.46, 0.95)**	**0.03**				0.80	(0.55, 1.16)	0.23
	2-2.5	0.76	(0.54, 1.06)	0.11				1.13	(0.79, 1.62)	0.51
	3 or above	0.84	(0.41, 1.71)	0.63				1.23	(0.60, 2.51)	0.57
Time since initiation of cART (months)	***0-6***	**12.93**	**(9.19, 18.19)**	**0.0001**	**17.06**	**(11.96, 24.33)**	**0.0001**	**3.39**	**(2.29, 5.03)**	**0.0001**
	7-12	**2.75**	**(1.65, 4.60)**	**0.0001**	**3.48**	**(2.07, 5.86)**	**0.0001**	**1.36**	**(0.80, 2.31)**	**0.0001**
	13-18	**2.92**	**(1.75, 4.88)**	**0.0001**	**3.56**	**(2.12, 5.98)**	**0.0001**	**1.73**	**(1.02, 2.91)**	**0.0001**
	19-24	**1.93**	**(1.04, 3.56)**	**0.04**	**2.27**	**(1.23, 4.22)**	**0.009**	**1.25**	**(0.67, 2.33)**	**0.009**
	25-30	1.89	(1.00, 3.56)	0.05	**2.16**	**(1.14, 4.08)**	**0.02**	**1.33**	**(0.70, 2.52)**	**0.02**
	31-36	0.67	(0.24, 1.87)	0.45	0.75	(0.27, 2.08)	0.58	0.51	(0.18, 1.42)	0.58
	Over 36	1			1			1		
Female gender		1.12	(0.82, 1.52)	0.47	0.83	(0.57, 1.21)	0.34	0.88	(0.60, 1.28)	0.50
Age group (years)	***<30***	1			1			1		
	31-40	1.39	(0.94, 2.07)	0.10	1.32	(0.89, 1.97)	0.17	1.38	(0.93, 2.06)	0.11
	41-50	1.43	(0.92, 2.22)	0.11	1.37	(0.88, 2.16)	0.17	1.47	(0.93, 2.31)	0.10
	>50	1.59	(0.92, 2.74)	0.10	1.57	(0.90, 2.74)	0.11	1.71	(0.98, 3.00)	0.06
HIV risk group	***MSM***	1			1			1		
	Hetero	**3.45**	**(2.21, 5.36)**	**0.0001**	**3.18**	**(2.00, 5.07)**	**0.0001**	**2.21**	**(1.38, 3.52)**	**0.0009**
	IDU	**1.56**	**(1.17, 2.07)**	**0.003**	1.20	(0.76, 1.88)	0.44	1.10	(0.70, 1.72)	0.69
Ethnicity	***White***	1			1			1		
	Black African	**1.43**	**(1.06, 1.94)**	**0.02**	1.36	(0.85, 2.17)	0.19	1.19	(0.75, 1.89)	0.47
	Other	**1.65**	**(1.10, 2.48)**	**0.02**	**1.64**	**(1.05, 2.55)**	**0.03**	1.53	(0.98, 2.38)	0.06
Baseline CD4	***Below 50***	**6.11**	**(3.86, 9.66)**	**0.0001**	**4.53**	**(2.81, 7.30)**	**0.0001**	n/a		
	50-199	**2.02**	**(1.26, 3.24)**	**0.004**	**1.74**	**(1.08, 2.80)**	**0.02**			
	200-349	1			1					
	350-500	1.16	(0.56, 2.43)	0.69	1.32	(0.63, 2.76)	0.47			
	Above 500	0.99	(0.38, 2.60)	0.99	1.24	(0.47, 3.26)	0.67			
Latest CD4	***Below 50***	**21.40**	**(14.18, 32.32)**	**0.0001**	n/a			**8.80**	**(5.63, 13.77)**	**0.0001**
	50-199	**4.15**	**(2.76, 6.24)**	**0.0001**				**2.75**	**(1.82, 4.17)**	**0.0001**
	200-349	1						1		
	350-500	**0.37**	**(0.19, 0.71)**	**0.003**				0.52	(0.27, 1.01)	0.05
	Above 500	**0.22**	**(0.11, 0.45)**	**0.0001**				**0.41**	**(0.20, 0.83)**	**0.01**
Latest HIV RNA level	***≤50***	1			n/a			1		
	>50, ≤10,000	**5.42**	**(3.46, 8.49)**	**0.0001**				**2.85**	**(1.78, 4.56)**	**0.0001**
	>10,000, ≤100,000	**10.45**	**(6.51, 16.78)**	**0.0001**				**3.88**	**(2.33, 6.47)**	**0.0001**
	>100,000	**26.55**	**(17.19, 41.01)**	**0.0001**				**5.49**	**(3.33, 9.02)**	**0.0001**
Year of starting cART	***1996/97***	0.99	(0.65, 1.49)	0.95	0.76	(0.46, 1.28)	0.30	0.75	(0.46, 1.22)	0.25
	1998/99	1.06	(0.69, 1.62)	0.78	1.25	(0.80, 1.94)	0.32	1.09	(0.70, 1.68)	0.71
	2000/01	1			1			1		
	2002/03	1.28	(0.80, 2.04)	0.30	1.07	(0.67, 1.71)	0.79	1.20	(0.75, 1.93)	0.44
	2004/05	1.00	(0.57, 1.75)	1.00	0.65	(0.36, 1.15)	0.14	0.83	(0.47, 1.47)	0.53
	2006/07	1.47	(0.73, 2.98)	0.28	0.58	(0.28, 1.20)	0.14	0.72	(0.35, 1.48)	0.37
ARV-naive		0.85	(0.64, 1.12)	0.24	**0.62**	**(0.43, 0.89)**	**0.01**	0.90	(0.63, 1.27)	0.54

•During the study period, 1256 of 19,828 subjects (6.3%) died (mortality rate: 13/1000 PYFU). In univariate analysis, initial and latest cART CPE score of <1 or ≥3 were significantly associated with an increased risk of death (p<0.02). After adjustment, only the CPE score of latest cART remained statistically significantly associated with risk of death (see Table 3).

Table 3: Univariate and multivariable estimates of association between mortality and baseline or latest CPE score

	Baseline cART CPE score				Latest cART CPE score			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
CPE Score	***RR (95% CI)***	***p-value***	***RR (95% CI)***	***p-value***	***RR (95% CI)***	***p-value***	***RR (95% CI)***	***p-value***
Below 1	1	-	1	-	1	-	1	-
1–1.5	**0.81 (0.67, 0.96)**	**0.02**	0.89 (0.74, 1.06)	0.20	**0.50 (0.44, 0.57)**	**0.0001**	**0.58 (0.51, 0.67)**	**0.0001**
2-2.5	**0.60 (0.50, 0.72)**	**0.0001**	**0.82 (0.68, 0.99)**	**0.04**	**0.35 (0.30, 0.40)**	**0.0001**	**0.52 (0.44, 0.60)**	**0.0001**
3 or greater	0.80 (0.54, 1.18)	0.26	1.08 (0.73, 1.61)	0.70	**0.77 (0.59, 0.99)**	**0.04**	0.98 (0.75, 1.27)	0.85

CONCLUSION

•The median CPE score of initial cART regimens has changed between 1996 and 2007 in the UK. The CPE score of cART regimens prescribed varies according to clinical parameters. This information should be considered when utilising the CPE score for clinical research.

•Neither the initial CPE score nor the latest CPE score was independently associated with the risk of developing a CNS event over time in this cohort. However individuals with a low (<1) or high (≥3) latest cART CPE score had statistically higher rates of death in the multivariable model. This is likely to be due to the affect of clinical status upon prescribing practice.

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United Kingdom Collaborative HIV Cohort (UK CHIC)

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