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Cohort Profile: Recruitment cohorts in the neuropsychological substudy of the Multicenter AIDS Cohort Study

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Abstract

The Multicenter AIDS Cohort Study (MACS) is one of the largest and longest running studies of the natural and treated history of HIV disease. The Neuropsychological (NP) substudy was begun in 1988 following reports of significant adverse neurological consequences of HIV disease, including dementia. The goal was to characterize the neuropsychological deficits among individuals with HIV disease, and track the natural history of the neurological complications over time. There were three distinct MACS recruitment stages that focused on different groups of HIV-infected men, or men at risk for infection. Initially, a subcohort was evaluated semi-annually with NP tests but, beginning in 2005, the entire group of MACS participants have had NP examinations biannually, unless closer follow-up was warranted. The participants complete a battery of NP tests, and are classified as either normal, mildly or severely impaired using the Antinori criteria for HIV-Associated Neurocognitive Disorder (HAND). Additional behavioural data, including mood state and psychoactive substance use, are recorded as part of the main MACS

data collection. The MACS public data set (PDS) has been available since 1994 and includes baseline and 6-monthly follow-up data. Beginning in October 1995, the PDS has been released annually with new releases superseding previous versions.

Key Messages

- There are between-cohort differences in age, education, minority status, HIV-related measures and neuropsychological test performance, as well as critical differences in medication usage and survival times.
- A majority of infected participants are currently on combination antiretroviral therapy (cART), and most of the men in the latest cohort enrolled while on cART; the men from the earlier cohorts underwent 10 years of virtually uncontrolled viral replication.
- There were significant differences in the rate of cognitive test abnormalities as a function of HIV status in the first two cohorts (1984/5, 1987/91); there are no HIV-related differences in cognitive performance in the latest cohort (2001/2003).
- Death or dropout during follow-up resulted in a loss of data that may result in an underestimation of the prevalence of neuropsychological abnormalities.

Why was the cohort set up?

The Multicenter AIDS Cohort Study (MACS) is one of the largest and longest-running studies of the natural and treated history of HIV disease in the world. The study has been evaluating cognitive performance among infected men and men at risk for infection for 25+ years. The MACS was designed to characterize the natural history of the infection causing acquired immunodeficiency syndrome (AIDS), identify risk factors for occurrence and clinical expression of the infection and establish a repository of biological specimens for future study.[1] At baseline, nearly 5000 men volunteered for semi-annual interview, physical examination and laboratory testing in four metropolitan areas. At the time of recruitment, the enzyme-linked immunosorbent assay (ELISA) test was not yet available, and therefore none of the study participants were aware of their serostatus, making the MACS unique among similar cohort studies. By the time of the participants' initial evaluation (April 1984–April 1985), infection with the human immunodeficiency virus (HIV) had occurred in 30–40% of the men. The Neuropsychological (NP) Substudy was begun in 1988 following reports of significant neurocognitive consequences of HIV disease, including dementia.[2–7] At the time, there were no effective therapies for the disease, antibody tests to identify the presence of virus had only recently been introduced and there was no means of measuring viraemia. The NP study goal was to characterize the pattern and severity of neuropsychological deficits among individuals with HIV disease, and track the natural and (subsequently) treated history of the neurocognitive complications over time.

Who is in the cohort?

The MACS has evolved into a study of the natural and treated history of HIV infection among gay/bisexual men. There were three distinct recruitment stages that focused on groups of infected men with different demographic characteristics, or men at risk for infection. Study participants were enrolled at four sites (Los Angeles, Pittsburgh, Chicago, Baltimore/Washington) in three waves: 1984/85, 1987/90 and 2001/03.

The men who enrolled in 1984-85 are Cohort 1 (C1), those who enrolled in 1987–91 are Cohort 2 (C2) and those who enrolled between 2001 and 2003 are Cohort 3 (C3). C1 was the original sample of 4954 men and C2 was a 'new recruit cohort' that focused on enrolling minority and special target groups such as the partners of the men in C1. C3 focused on recruiting racial/ethnic minorities as well as a special target group of uninfected men who had been censored from C1 in 1995.

Due to the high cost of administering NP examinations, only subsets of C1 were recruited in Baltimore, Chicago and Pittsburgh. Each participant was invited to participate in the NP study at the time of his regular semi-annual MACS visit. Volunteers were enrolled without regard to serostatus or symptom status until the target number for that centre was reached. In addition, all of the participants

who had become infected with HIV during the course of the study (i.e. seroconverters) were invited to join the NP study. In total, 328, 239 and 231 individuals were enrolled in the Baltimore, Chicago and Pittsburgh centres, respectively. In Los Angeles, all study participants were asked to complete neuropsychological testing and 922 agreed to participate.

At the first NP study visit for C1, there were no differences in the rate of enrolment as a function of serostatus or symptom status (see Miller *et al*. [8] for details). Recruitment of C2 into the NP substudy followed much the same pattern. However, for C3, we enrolled effectively all recruits and evaluated them at the time of their baseline visit. Thus, 25.6% of the men in C1 and 29.0% of the men in C2 did not enrol in the NP study (either by refusal or because target numbers had been reached), and they represent 96.3% of all of the missing data. Only 3% of the men in C3 did not complete NP testing.

A total of 5470 men (78.5%) completed at least one NP test battery. The 1502 men who did not complete any testing were, on average, younger, less well-educated, more likely to use some recreational drugs, more likely to be Caucasian and, among the HIV-infected men, were more likely to develop AIDS and subsequently die, and to have lower CD4+ cell counts at their baseline visit (see Table E-1, available as Supplementary data at *IJE* online).

Recruitment cohort differences

There were differences in the racial characteristics between cohorts: C1 was predominantly White, whereas C2 and C3 were predominantly African American (or other race) (see Table 1). There was a difference between cohorts in years of education; C1 had more education than C2, which had more education than C3. The men in C3 were older than those in C1 or C2. There was a difference between the cohorts in the number/severity of the symptoms of depression they endorsed on the Center for Epidemiological Studies Depression scale (CES-D),[9,10] with C3 participants endorsing more symptoms than those in C1 or C2.

Among the men with HIV infection at baseline, plasma viral load was significantly lower in C3 than in CI/C2, as well as a difference in the distribution of CDC CD4+ cell count classification (i.e. CDC 1, 2 or 3) in the direction of greater numbers of CD4+ T-lymphocytes.[11]

The time between the baseline visit and the first visit at which a participant completed the full NP test battery differed as a function of cohort. There were more than 4 years intervening between baseline and the first NP test battery for C1, approximately 2.5 years for C2 and, on average, the first NP visit was the baseline visit for C3 (see Table E-2, available as Supplementary data at *IJE* online). Between the baseline visit and the first visit that included NP testing, 11% (269/2414) of the seronegative men in C1 became HIV-infected, as did 7.8% (19/176) of the men in C2. None of the men in C3 seroconverted in the interval. Between the first and last NP visits, 157 of the seronegative men in C1 (7.3%), 7 of the men in C2 (3.7%) and 43 of the men in C3 (6.9%) became HIV infected.

Estimated intelligence quotient (IQ) differed as a function of HIV status and cohort at the first NP visit with C1>C2>C3 (see Figure 1). A similar pattern was seen in measures of psychomotor speed (Trail Making Test, Part A), verbal memory (RAVLT, Delayed Recall), non-verbal memory (Rey-Osterrieth Figure Delayed Recall) and fine motor speed/coordination (Grooved Pegboard, nondominant hand).

How often have they been followed up?

From the beginning of the substudy, the participants were evaluated semi-annually. In some cases, when neuropsychological testing was abnormal, a neurological examination was then scheduled. In 2005, the NP protocol changed so that all active MACS participants were evaluated biannually, or more frequently if their performance was considered abnormal.

There is a significant difference in the number of years of follow-up as a function of both cohort of entry ($F(2, 4004) = 295.4$, $P < .001$, $\eta^2 = .13$) and HIV serostatus ($F(1, 4004) = 10.5$, $P = .001$, $\eta^2 = .003$). There is also a significant interaction between cohort and serostatus ($F(2, 4004) = 33.2$, $P < .001$, $\eta^2 = .016$) such that whereas there was a significant difference between the time on study as a function of HIV serostatus in C1, there were no differences in C2 or C3 (see Figure 2).

Survivor effects

Of the 5470 individuals who had ever had an NP test, 32% of the men in C1 and C2 and 66% of the men in C3 are still active (v. inactive or dead) (see Table 2). In order to address the question of the 'persistence' of the cohort effects over time, we directly compared subject characteristics at their first and last NP visits as a function of their cohort of entry (see Figure 3 and also Table E-3 which is available as Supplementary data at *IJE* online). There were main effects of cohort for the CES-D, Trail Making Test, the Rey-Osterrieth Figure Recall and the RAVLT Recall (see Table E-3, available as Supplementary data at *IJE* online). There was significant improvement in performance between the first and last visits on the Trail Making Test, the Rey Figure Recall, the RAVLT Recall and the CES-D.

Table 1. Characteristics of study participants at their baseline visit as a function of status and cohort (1–3)

Status	HIV−			HIV+			Statistics[a]	
	1	2	3	1	2	3	HIV	Cohort
Number	2414	191	619	1273	283	690	(*d*)	(*f*)
Age[b]	34.15 (8.0)	32.47 (8.2)	36.83 (9.7)	33.04 (6.4)	32.97 (7.7)	38.85 (8.4)	0.03	0.23*
Education years[b]	16.64 (6.5)	15.88 (2.0)	14.36 (4.6)	16.46 (8.8)	15.33 (6.5)	13.42 (2.7)	–0.11*	0.39*
CES-D[b]	9.44 (8.8)	9.41 (8.0)	13.44 (11)	9.97 (8.5)	12.28 (9.9)	14.86 (12)	0.16*	0.20*
Race %White, (number)	59.40 (1434)	31.41 (60)	37.48 (232)	78.24 (996)	49.12 (139)	37.39 (258)	0.07*	0.32*
Marijuana[c]	60.22 (1452)	37.57 (71)	40.89 (249)	80.77 (1269)	57.04 (158)	34.63 (231)	0.09*	0.26*
Cocaine[c]	27.91 (672)	12.23 (23)	26.93 (164)	50.08 (635)	23.19 (64)	25.49 (170)	0.13*	0.12*
IVD[c]	4.11 (96)	0.00 (0)	14.26 (87)	14.66 (179)	2.23(4)	17.31 (116)	0.14*	0.14*
Opiates[c]	1.12 (27)	0.00 (0)	10.45 (63)	1.97 (25)	1.09 (3)	6.93 (46)	0.02	0.18*
CD4+ cell count[b]	942.83 (380)	1057.11 (400)	923.32 (310)	605.07 (270)	600.27 (320)	516.05 (280)	1.08*	0.13*
Log_{10} HIV viral load[b]	2.75 (1.3)	1.95 (0.48)	1.60 (0.00)	4.11 (0.72)	5.12 (0.34)	2.97 (1.3)	0.61*	0.17*
Shipley IQ[b]	109.75 (9.3)	104.93 (9.8)	96.49 (15)	107.89 (9.4)	101.44 (12)	94.30 (15)	–0.32*	0.53*
Convert HIV status between baseline and first visit[b]	11.14 (269)	7.85 (15)	0.00 (0)	N/A	N/A	N/A	N/A	N/A
CDC CD4+1/2/3 % (*n*)[c]	91.43/6.67/1.91 (2207/161/46)	94.76/3.66/1.57 (181/7/3)	93.86/4.04/2.10 (581/25/13)	60.57/35.27/4.16 (771/449/53)	59.72/31.45/8.83 (169/89/25)	44.78/41.01/14.20 (309/283/98)	0.43*	0.15*
Developed AIDS[c]	8.04 (194)	2.62 (5)	0.16 (1)	64.96 (827)	38.16 (108)	9.42 (65)	0.46*	0.23*
Death from AIDS[c]	52.35 (178)	27.27 (3)	0.00 (0)	90.17 (789)	76.25 (106)	41.25 (33)	0.38*	0.34*
Time from baseline to AIDS diagnosis[b]	9.51 (4.4)	8.49 (3.6)	9.40 (N/A)	7.02 (3.9)	5.22 (3.4)	1.93 (3.6)	0.74*	0.34*

Na, not applicable. [a]Cohen's *d* for HIV comparison, and Cohen's *f* for cohort effects.
[b]Mean (± standard deviation).
[c]Per cent (number) 'Yes'. For these variables, phi is reported as the effect size.
*$P < .05$.

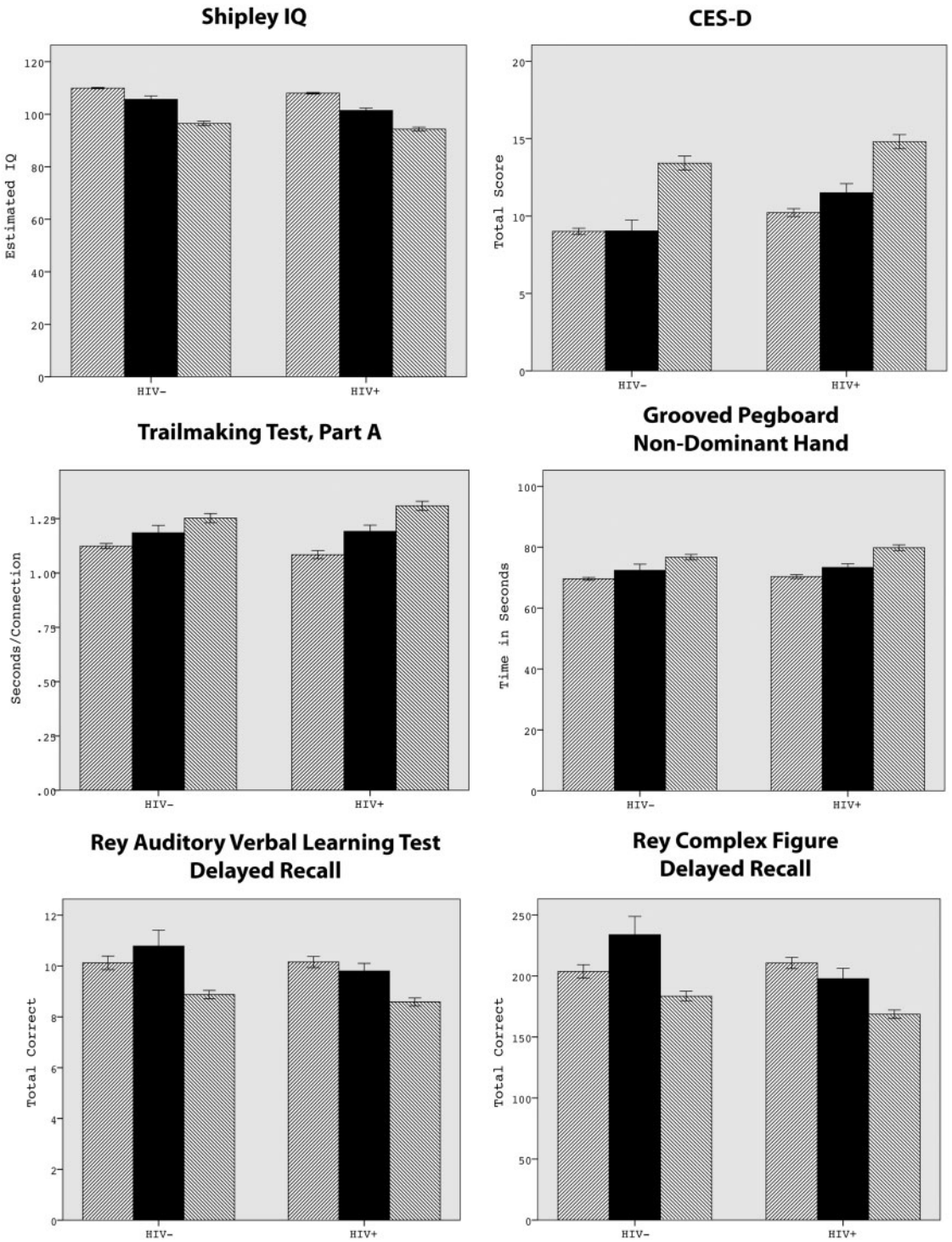

Figure 1. Mean (±1 standard error) IQ measured with the Shipley Institute of Living Scale, Centers for Epidemiological Studies – Depression scale (CES-D), and selected neuropsychological measures as a function of recruitment cohort and HIV serostatus.

There were significant interactions between Cohort and Time for only the Trailmaking Test (both Parts A and B) and the CES-D, but the effects were small (i.e. $\eta^2 < .05$).

A total of 1356 men (592 uninfected and 764 infected) had sufficient neuropsychological testing to be classified as cognitively normal, mildly impaired or severely impaired at each of two study visits. Figure 4 (top) shows the rate of severe abnormality as a function of serostatus and cohort. For the uninfected men, there was no difference in the rate of abnormality between C1/C2 and C3 ($X^2 = 0.93$, df = 1, $P > .05$, Cramer's V = .05) whereas, for the infected men, the rate of abnormality was significantly lower in C3 than

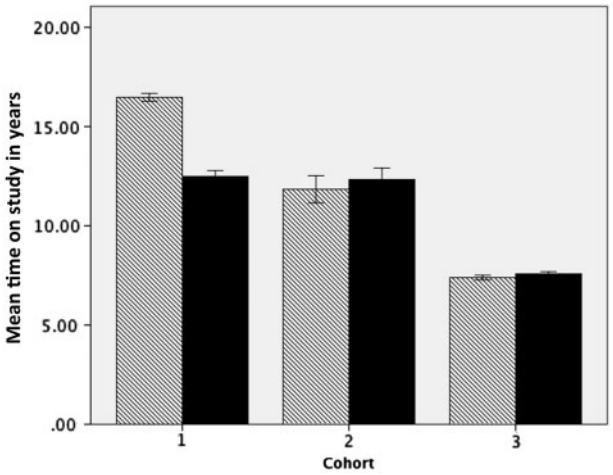

Figure 2. Mean (±1 standard error) time on study as a function of serostatus (HIV-infected are solid black) and recruitment cohort.

in C1/C2 ($X^2 = 26.7$, df = 1, $P < .05$, Cramer's V = .19). For C1/C2, the rate of cognitive abnormality was significantly higher in the HIV-infected men compared with the HIV-negative group ($X^2 = 30.3$, df = 1, $P < .05$, Cramer's V = .24). For C3, there was no HIV-related difference in the rate of cognitive abnormalities ($X^2 = 0.63$, df = 1, $P > .05$, Cramer's V = .03).

The rate of abnormal cognitive performance among the infected men at the first NP visit did not differ as a function of status (active, inactive, dead) in 2012 (see Figure 4, bottom). The men who remained alive and active in the study showed a small increase in the rate of abnormal cognitive performance between the first and last visits (from 6.8% at baseline to 9.2% at their last visit). The rate of severe cognitive abnormality at the last available NP visit was considerably higher among the infected men who were inactive (12.5%) or dead (16.4%) in 2012.

What has been measured?

The overall MACS study design has previously been described;[1,12] participants return every 6 months for an interview, physical examination and collection of blood for laboratory testing. The interview covers physical health, medical treatments and sexual and substance use behaviours. A summary of the data and a list of critical outcomes are shown in Table E-4 (available as Supplementary data at *IJE* online). More information about the MACS study, including data collection instruments, can be found at (http://www.statepi.jhsph.edu/macs/macs.html), and particularly in the MACS dossier (http://www.statepi.jhsph.edu/macs/dossier/MACSdossier.pdf).

We use a battery of neuropsychological tests that allows us to classify participants as either normal or mildly or severely impaired, using the Antinori criteria for HIV-Associated Neurocognitive Disorder (HAND)[8,13–16] as well as an estimated IQ.[17] T-scores are calculated for each of the following test domains: executive (Trail Making Part B and Stroop Interference), speed of information processing (Symbol Digit and Stroop Colour-Naming), attention and working memory (CalCAP 1-back procedures), learning (RAVLT (Total of Trials 1-5 and Rey Complex Figure Immediate Recall), memory (RAVLT Delayed Recall and Rey Complex Figure Delayed Recall) and motor (Grooved Pegboard). In order to be classified, an individual needs to have completed at least one test in at least four of the six domains. In accordance with the guidelines,[14] we classified an individual as mildly impaired if he had two or more domains with T-scores less than 40, and severely impaired if he had two or more domains with T-scores less than 30 or one domain score less than 25 and another domain score less than 40. We also obtained an estimated IQ score using the Shipley Institute of Living Scale[17] (at the first NP visit only).

What has been found?

The MACS has been reporting data regarding NP outcomes since 1990. We describe below a subset of critical findings from the early days of the HIV epidemic through to some of our most recent reports on brain imaging and cognition in the era of combination antiretroviral therapy (cART).

Neuropsychological test performance in HIV disease prior to cART[8]

We found significant differences in performance between the HIV- and symptomatic HIV+ subjects on measures of memory, and motor/psychomotor tasks. Asymptomatic seropositive men, on the other hand, did not differ significantly from seronegative subjects on any of the neuropsychological measures. Among asymptomatic seropositive subjects, we found no statistically significant differences as a function of duration of infection or of immune system function.

Cognitive reserve in HIV disease[18]

We found a prevalence of cognitive abnormality of 38% in seropositive individuals with no more than 12 years of education, compared with <17% in the men with more years of education. The interaction between education level and serostatus remained significant after controlling for the possible confounding effects of age, ethnicity, CD4 level, depression, prior drug history and learning disability, suggesting that low education could serve as a marker variable of lower cognitive reserve capacity.[19–21]

Table 2. Characteristics of study participants at most recent NP visit as a function of HIV status and participation

	HIV−			HIV+			Statistics[1]	
Characteristic	Active	Inactive or censored	Dead	Active	Inactive	Dead	HIV	Status
Number	1141	1103	124	1061	252	982	(d)	(f)
Number by cohort (1/2/3)	65.56/3.77/30.67 (748/43/350)	83.50/8.34/8.16 (921/92/90)	87.90/4.84/7.26 (109/6/9)	44.11/9.43/46.47 (468/100/493)	49.21/18.65/32.14 (124/47/81)	84.52/10.18/5.30 (830/100/52)	0.14*	0.35*
Time between first and last NP[2]	15.99 (7.4)	5.23 (4.1)	8.17 (6.3)	14.38 (7.2)	7.31 (5.5)	5.24 (4.0)	0.11*	0.81*
Time last NP-death[2]	N/A	N/A	4.69 (5.0)	N/A	N/A	1.81 (2.3)	1.05*	N/A
Age in years[2]	54.10 (11)	44.51 (9.3)	50.79 (11)	51.09 (8.9)	42.03 (9.4)	42.25 (8.3)	0.30*	0.47*
Education, years[2]	16.04 (5.4)	15.84 (2.7)	16.38 (9.4)	15.05 (4.6)	14.69 (2.9)	15.62 (4.7)	0.16*	0.03
CES-D[2]	9.64 (11)	10.13 (10)	11.99 (11)	11.57 (11)	12.41 (12)	14.78 (11)	0.28*	0.15*
Race[3]	78.35 (894)	86.67 (956)	83.06 (103)	63.43 (673)	64.68 (163)	87.88 (863)	0.10*	0.17*
Marijuana[3]	27.47 (309)	27.45 (302)	24.79 (30)	33.17 (344)	47.97 (118)	39.30 (360)	0.11*	0.06*
Cocaine[3]	8.27 (93)	6.82 (75)	6.61 (8)	11.01 (114)	16.67 (41)	9.06 (83)	0.06*	0.02
IVD[3]	0.53 (6)	0.46 (5)	2.50 (3)	2.13 (22)	1.22 (3)	1.65 (15)	0.05*	0.04*
Opiates[3]	1.20 (13)	0.86 (6)	2.50 (2)	1.19 (12)	1.00 (2)	1.05 (5)	0.00	0.01
CD4+ count[2] % (number)	932.07 (310)	981.55 (340)	950.53 (350)	595.38 (290)	504.49 (300)	174.93 (210)	1.64*	0.69*
Standardized viral load[2]	1.59 (0.72)	1.60 (0.00)	1.60 (0.00)	1.76 (1.2)	3.11 (1.4)	4.57 (1.3)	0.62*	0.97*
Shipley IQ[2]	106.68 (13)	107.26 (11)	108.47 (12)	102.16 (14)	104.53 (12)	106.66 (11)	0.23*	0.09*
Trails A[2] (sec/pt.)	0.86 (0.35)	0.94 (0.53)	1.01 (0.41)	0.87 (0.38)	0.97 (0.50)	1.01 (0.46)	0.09*	0.13*
Trails B[2] (sec/pt.)	1.94 (0.99)	2.12 (1.6)	2.46 (1.2)	2.09 (1.2)	2.43 (2.0)	2.36 (1.3)	0.15*	0.10*
RAVLT trial[2] 1-5 total	54.41 (11)	52.94 (9.5)	48.83 (10)	52.80 (11)	47.31 (13)	50.49 (11)	0.21*	0.13*
RAV Delayed Recall	11.11 (3.2)	10.59 (3.0)	9.90 (3.3)	10.45 (3.3)	9.02 (3.7)	10.13 (3.4)	0.20*	0.09*
Stroop Interference[2]	1.77 (0.31)	1.84 (0.32)	1.87 (0.32)	1.77 (0.33)	1.85 (0.39)	1.85 (0.32)	0.03	0.12*
Grooved Pegboard dominant[2]	70.52 (21)	62.17 (14)	70.98 (20)	70.44 (17)	68.14 (28)	69.10 (19)	0.11*	0.13*
Grooved Pegboard non-dominant[2]	78.00 (24)	67.12 (18)	75.64 (16)	76.48 (19)	70.99 (19)	75.28 (23)	0.08	0.16*
Rey Complex Figure Copy[2]	31.87 (4.1)	33.41 (3.5)	32.78 (3.2)	31.42 (4.5)	33.65 (3.3)	33.68 (3.1)	0.04	0.24*
Rey Immediate Recall[2]	22.04 (7.4)	24.17 (7.6)	23.31 (6.5)	31.34 (7.0)	22.86 (7.4)	23.75 (7.1)	0.04	0.14*
Rey Delayed Recall	21.80 (7.3)	23.89 (7.4)	22.31 (6.1)	21.26 (6.9)	22.42 (7.4)	23.58 (6.9)	0.02	0.14*
Developed AIDS[3]	0.00 (0)	0.00 (0)	1.61 (2)	15.27 (162)	15.08 (38)	78.21 (768)	0.52*	0.67*
Died from AIDS[3]	0.00 (0)	0.00 (0)	7.26 (9)	0.00 (0)	0.00 (0)	85.44 (839)	0.58*	0.60*
CD4+ % 1/2/3 (number)[3]	88.87/4.82/6.31 (1014/55/72)	42.52/2.54/54.94 (469/28/606)	63.71/7.26/29.03 (79/9/36)	58.44/33.46/8.11 (620/355/86)	44.05/42.46/13.49 (111/107/34)	8.96/22.00/69.04 (88/216/678)	0.38*	0.56*
Cognitive outcome none/mild/severe % (number)[3]	73.58/16.51/9.91 (312/70/42)	76.60/20.00/3.40 (203/53/9)	65.00/27.50/7.50 (26/11/3)	70.99/20.52/8.49 (301/87/36)	68.57/20.00/11.43 (48/14/8)	61.60/22.61/15.79 (316/116/81)	0.10*	0.14*
cART[3]	0.09 (1)	0.00 (00)	0.00 (0)	89.73 (952)	55.95 (141)	16.29 (160)	0.62*	0.35*

IVD, Intravenous Drug Use; sec/pt, Seconds per point connected.

[a]Cohen's d for HIV comparison, and Cohen's f for Status effect.

[b]Mean (± standard deviation)

[c]Percent (number) 'Yes'. For these variables, phi is reported as the effect size.

*$P < .05$.

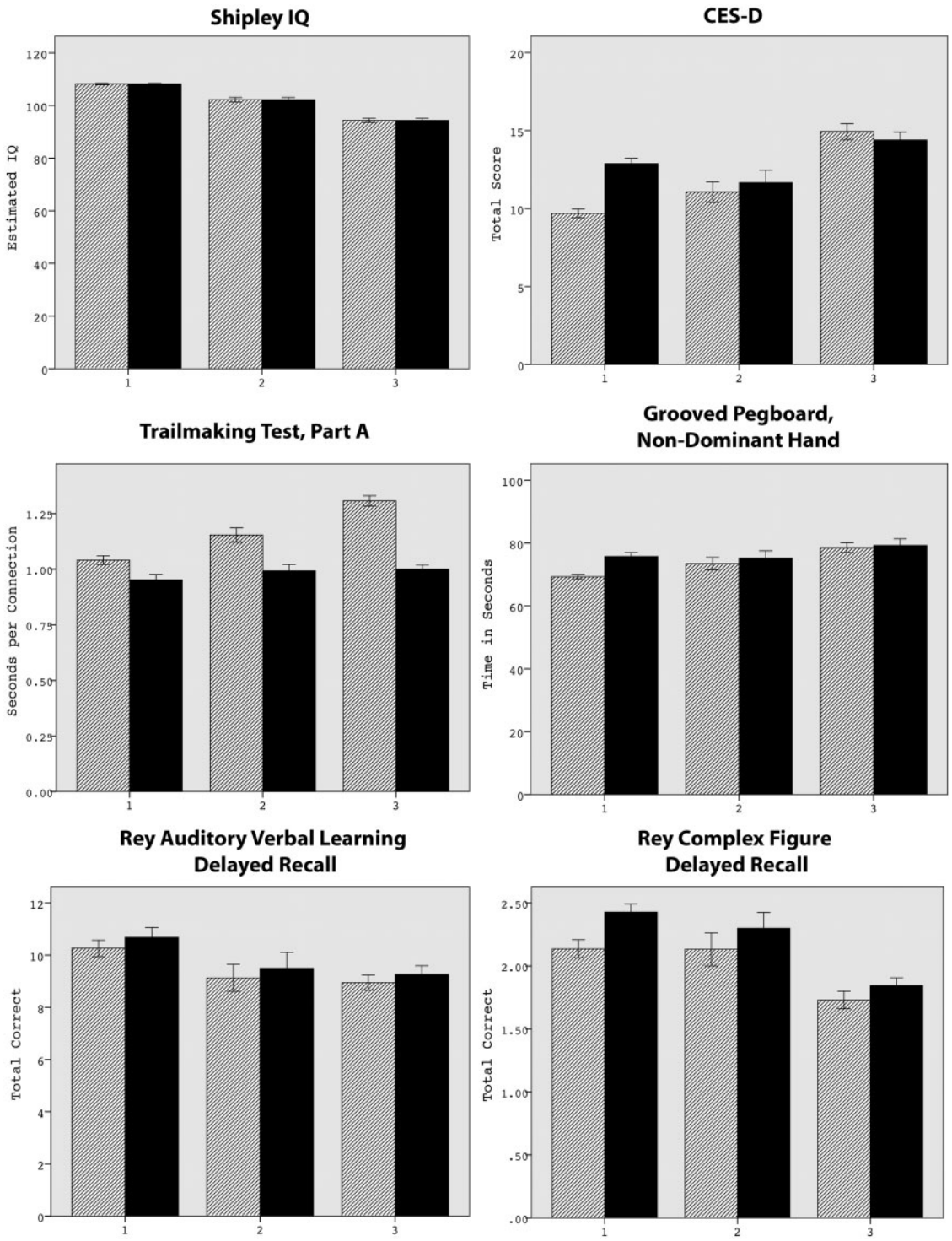

Figure 3. Mean (±1 standard error) IQ measured with the Shipley Institute of Living Scale, Centers for Epidemiological Studies – Depression scale (CES-D), and selected neuropsychological measures as a function of recruitment cohort and time of assessment (first vs last NP visit) among HIV-infected men only.

The incidence and prevalence of HIV-associated dementia prior to cART[22]

During the first 2 years after AIDS, HIV dementia developed at an annual rate of 7%, and 15% (64/492) of the cohort developed dementia prior to death. Pre-AIDS haemoglobin was the most significant predictor of dementia; there were no significant risks associated with demographic characteristics, AIDS-defining illnesses, zidovudine use before AIDS or CD4+ lymphocyte count before AIDS.

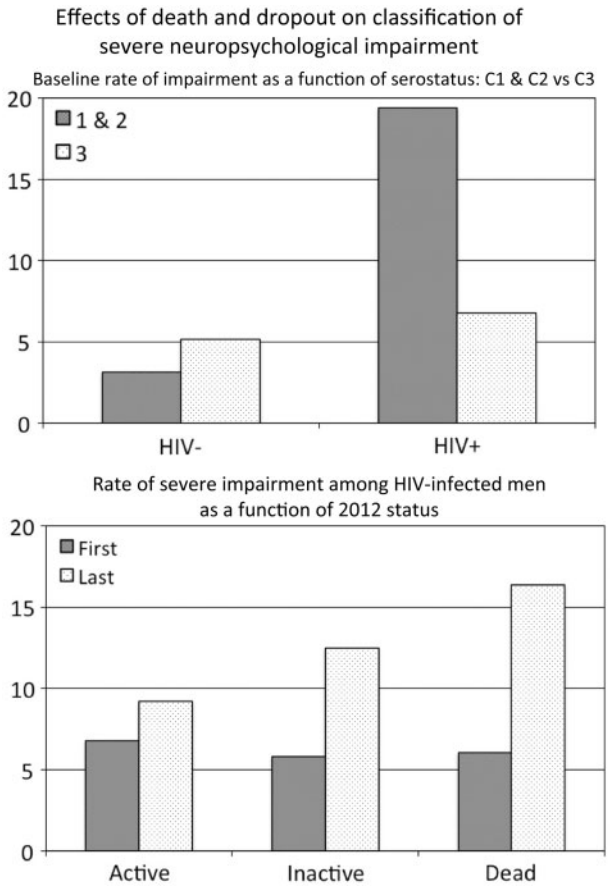

Figure 4. The effects of cohort (C1 and C2 vs C3) on rate of classification of severe cognitive impairment among study participants as a function of HIV serostatus (top); and the proportion of HIV-infected men classified as severely impaired at their first and last NP visits as a function of their status on 31 December 31 2012 (bottom).

Pre-cART incidence of neurological disease[23]

Progressive immunosuppression in the cohort explained all calendar trends of neurological disease except for sensory neuropathy (where an increasing temporal trend remained even after adjusting for CD4+ cell count), and for HIV dementia (where a slight decline was noted). Men receiving didanosine, zalcitabine or stavudine were more likely to develop sensory neuropathy.

The effects of cART on cognition[24]

A total of 411 HIV+ MACS participants were classified into four treatment groups: antiretroviral naive (no antiretroviral medication treatment), monotherapy, cART without protease inhibitors and cART with protease inhibitors. We found that relative to antiretroviral-naïve and monotherapy participants, cART-medicated participants (both with and without protease inhibitors) with abnormal baseline neuropsychological testing showed improved performance compared with antiretroviral-naïve and monotherapy groups.

Virological control and longitudinal change in cogniti on[25]

We compared psychomotor test performance over a 5-year period in three groups of asymptomatic HIV-positive individuals: cART treated with undetectable viral loads ($n = 83$); AIDS-free for more than 15 years without cART ($n = 29$); and absence of clinical AIDS or CD4(+) lymphocyte count below 200 cells/mμl ($n = 233$). We found no evidence of performance differences or performance declines in any of the three long-term asymptomatic groups as compared with HIV-negative controls.

The importance of cardiovascular risk factors for the expression of cognitive impairments in the cART era[26]

In adjusted models, carotid intima-media thickness and glomerular filtration rate were significantly associated with psychomotor speed, whereas intima-media thickness alone was associated with memory test performance. HIV serostatus was not significantly associated with poorer cognitive test performance, although among the HIV-infected individuals, the presence of detectable HIV RNA in plasma was linked to lower memory test performance.

Brain structural abnormalities in the cART era[27]

We found significant atrophy in the HIV-infected men in both the caudate nucleus and the putamen, principally in the anterior regions. The volume of the basal ganglia was inversely associated with the time since first seropositivity, suggesting that either there is a chronic, subclinical process that continues in spite of therapy, or that the extent of the initial insult caused the extent of atrophy.

Cognition following seroconversion in the cART era[28]

We conducted a nested cohort study of 362 HIV-1 seroconverters enrolled in the MACS, comparing neuropsychological test outcomes from 5 years before seroconversion to 2 years after seroconversion. We found no significant changes in the time-dependent score after seroconversion for the majority of the neuropsychological tests. Despite a 50 % decrease in CD4 cell count immediately following infection, HIV-1 does not appear to have a measurable effect on psychomotor or complex cognitive processing for up to 2 years following infection.

What are the main strengths and weaknesses?

There are several strengths to the NP sub study of the MACS. Initial enrolment (at least) was done without regard to serostatus, as the men could not or did not know whether they were infected—recruitment was based on behaviour. The MACS has followed volunteers closely,

which has allowed for the determination of incident infection based on inter-visit changes. The NP substudy has also managed to achieve a balance between frequent screening examinations and infrequent but more detailed assessments. We are now in a position to apply research-level diagnostic criteria to a substantial proportion of the men enrolled and currently active in the MACS. Because of the large amount of data that are required at each study visit, as well as the number of ancillary studies, it is possible to extend the utility of our data beyond their original intent. Plus, it is possible to examine the relationship between cardiovascular risk factors, adiposity, drug use etc. and cognitive test performance or changes in cognitive test performance. Finally, because of the differences among recruitment cohorts, the MACS is (nearly) uniquely positioned to examine changes in HIV-related risk for cognitive impairment as a function of treatment history.

There are, of course, weaknesses. Chief among these is the problem of competing risk. Early in the epidemic, a diagnosis of dementia was closely tied with AIDS-related deaths. As individuals grow older, especially those over the age of 70 years, age-related cognitive problems (and those that may be affected by HIV disease in old age) are themselves associated with death. Both AIDS- and non-AIDS- related mortality affect the ability to detect incident cognitive impairment (i.e. survivor bias). As the cohort ages, and we are no longer able to assume that mortality is only AIDS-related, this problem becomes even more difficult. Finally, in the early phases of the NP study, we did not recruit as many men for evaluation as we in retrospect should have done. This was due in large part to the cost of the assessment in terms of time and money, but also to the very legitimate concern regarding volunteer burden and 'scaring off' study participants who were concerned about their mental health, and their risk for dementia. In 2005 when the NP study was expanded to include all active MACS participants, there was virtually no pushback, because by then the critical importance of understanding the effects of HIV disease (and other conditions) on cognitive functions was increasingly clear to the volunteers.

Can I get hold of the data? Where can I find out more?

The MACS public data set (PDS) has been available since 1994 when the study Executive Committee made the recommendations on the content of the public data. Data are included in the PDS if they were collected by 1 October of the most current year minus 4 years. The data include baseline and 6-month follow-up interview data, including medical history, behaviour, SF36, physical examination data, frailty measurements, neuropsychology tests, concurrent laboratory test results and summary files of HIV status and medical events. The first release of the data was in March 1994 and, beginning October 1995, the PDS has been released annually with new releases superseding previous versions. In order to access the PDS, go to the NTIS website (http://www.ntis.gov/search/index.aspx), enter 'Multicenter AIDS Cohort Study' in the search box and click on 'Run Search' to find the most recent release, pricing and purchasing information.

Any member of the NP Working Group can be contacted regarding possible collaboration (see Acknowledgements). Queries about access to the data can be addressed to any member of the working group, or to the Director of the Center for the Analysis and Management of the MACS Data (CAMACS), Lisa Jacobson (ljacobso@jhsph.edu).

Supplementary Data

Supplementary data are available at *IJE* online.

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