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Longitudinal psychomotor speed performance in human immunodeficiency virus–seropositive individuals: impact of age and serostatus

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Older human immunodeficiency virus–seropositive (HIV+) individuals (greater than age 50 years) are twice as likely to develop HIV dementia compared to younger HIV+ individuals. The objective of this study was to examine the impact of both age and serostatus on longitudinal changes in psychomotor speed/executive functioning performance among HIV+ and HIV− individuals. Four hundred and seventy-seven HIV+ and 799 HIV− individuals from the Multicenter AIDS Cohort Study (MACS) were subdivided into three age groups: (1) <40 years, (2) 40–50 years, and (3) >50 years. Psychomotor speed/executive functioning test performance was measured by the Symbol Digit Modalities Test (SDMT) and the Trail Making (TM) Test Parts A and B. Changes in performance were compared among the three age groups for both HIV+ and HIV− individuals. Among HIV+ individuals, on the TM Test Part B the younger group demonstrated improvement in performance over time ($P = .007$). The older and middle age groups demonstrated decline in performance over time ($P = .041$ and .030). The older group had a significantly different trajectory relative to the younger group ($P = .046$). Among the HIV− individuals, there was no effect of age on longitudinal performance. In conclusion, older HIV+ individuals show greater decline over time than younger HIV+ individuals on the TM Test Part B. Our results suggest that both HIV serostatus and age together may impact longitudinal performance on this test. Mild neurocognitive changes over time among older HIV+ individuals are likely to reflect age associated pathophysiological mechanisms including cerebrovascular risk factors. *Journal of NeuroVirology* (2010) **16,** 335–341.

Keywords: age; dementia; HIV; neuropsychological assessment

An increasing proportion of human immunodeficiency virus (HIV)-infected individuals are surviving to age 50 years or older as a result of highly active antiretroviral therapy (HAART) (Goodkin *et al,* 2001). Compared to younger HIV+ individuals, older HIV+ individuals (greater than age 50 years) are twice as likely to develop the most severe form of HIV-associated neurocognitive disorder (HAND) (Valcour *et al,* 2004; Antinori *et al,* 2007), known as HIV dementia. Aging itself can also be associated with several comorbid conditions that by themselves can result in an increased risk of cognitive impairment and slower reaction times (Salthouse, 1996).

Psychomotor speed and executive functioning performance are sensitive indicators of HIV-associated

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cognitive impairment and a predictor of HIV dementia (Sacktor *et al,* 1996). These cognitive domains are also a sensitive indicator of the neurocognitive effects of age or age-associated comorbidities (Birren and Fisher, 1995).

The objective of this study was to examine the combined effects of age and serostatus on longitudinal changes in psychomotor speed and executive functioning test performance among HIV+ and HIV− individuals.

Results

Demographic characteristics

HIV+ individuals as a whole were more likely to be younger (48.9 versus 52.2 years, $P < .001$), non-Caucasian (84.5% versus 91.4%, $P < .001$), college educated (42.1% versus 32.8%, $P < .001$), and were more likely to report depressive symptomatology [Center for Epidemiologic Studies Depression Scale (CES-D) total score] (10.7 versus 8.9, $P = .001$), more likely to report diabetes (15.4% versus 8.1%, $P = .002$), and less likely to report hypercholesterolemia (15.4% versus 21.7%, $P = .005$) compared to HIV− individuals. As expected, CD4 count (cells/mm^3) also was lower for HIV+ individuals (236 versus 718, $P < .001$) compared to HIV− individuals.

Among HIV+ individuals, 35 individuals were in the younger group (age ≤40 years), 242 were in the middle age group (age 40–50 years), and 200 were in the older age group (age >50 years) (Table 1). Older HIV+ individuals were more likely to be Caucasian ($P = .011$) and college educated ($P < .001$), more likely to report hypertension ($P = .006$) and diabetes ($P = .001$), more likely to report a longer duration of HIV infection ($P < .001$) compared to younger HIV+ individuals, and more likely to have a lower plasma HIV RNA level (compared to the middle age group; $P < .001$).

Among HIV− individuals, 30 individuals were in the younger group, 315 individuals were in the middle age group, and 454 individuals were in the older group (Table 1). Older HIV− individuals were more likely to be Caucasian ($P < .001$) and college educated ($P = .001$), and more likely to report hypertension ($P = .001$), diabetes ($P = .020$), and hypercholesterolemia ($P = .008$) compared to younger HIV− individuals. There were no significant interactions between HIV serostatus and age group in the demographic characteristics.

In examining longitudinal performance in the era of HAART, 499 HIV-seropositive and 799 HIV-seronegative individuals contributed follow-up data.

Psychomotor speed test results

The initial model demonstrated a significant influence of baseline performance for the Symbol Digit Modalities Test (SDMT) (Table 2). Although those individuals in the oldest group performed worse at baseline compared to those in the youngest group, there was no influence of HIV serostatus or age group on longitudinal progression. This lack of association continued with the inclusion of demographic (interim model) and clinical (final model) characteristics. The lack of significance in the two-way and three-way interactions between HIV serostatus, age, and time indicates that all groups progress at a similar rate over time.

Table 1 Demographic characteristics of the HIV+ and HIV− individuals

	Age groups					
	HIV+			HIV−		
	<40 years (n = 35)	40–50 years (n = 242)	>50 years (n = 200)	<40 years (n = 30)	40–50 years (n = 315)	>50 years (n = 454)
Age [mean (*SD*)]	37.2 (2.3)	45.4 (2.8)	55.1 (4.3)	38.4 (1.5)	45.8 (2.7	57.6 (5.7)
Caucasian (%)	71.4	82.6	89.0	70.0	90.8	93.2
College education (%)	29.4	51.7	70.2	17.2	64.1	72.7
CD4 count [mean (*SD*)]	566 (295)	568 (340)	521 (259)	1025 (343)	968 (311)	974 (333)
CD4 nadir [mean (*SD*)]	235 (157)	239 (171)	233 (152)			
Log plasma HIV RNA [mean (*SD*)]	2.7 (1.4)	2.7 (1.4)	2.4 (1.1)			
Plasma HIV RNA (% undetectable)	42.9	50.4	56.8			
Hypertension (%)	35.3	41.1	56.0	34.5	39.3	55.0
Diabetes (%)	0	10.2	22.5	3.5	2.9	7.4
Hypercholesterolemia (%)	20.0	22.2	21.4	0	12.8	18.3
CES-D ([mean (*SD*)]	10.9 (9.8)	11.0 (10.5)	10.4 (10.7)	7.6 (8.4)	9.5 (9.7)	8.5 (9.5)
Current HAART use (%)	68.6	67.8	74.4			
Previous HAART use (%)	71.4	73.6	78.9			
Duration of HIV infection [mean (*SD*)]	12.2 (4.3)	15.2 (4.2)	16.2 (4.0)			

Note. CES-D = Center for Epidemiological Studies—Depression questionnaire score; HAART = highly active antiretroviral therapy.

Table 2 Symbol Digit Modalities Test (SDMT) results from mixed linear modeling: initial, interim, and final models

		Initial		Interim		Final	
		Est (*SE*)	*P*	Est (*SE*)	*P*	Est (*SE*)	*P*
Time, years		−.002 (.001)	.080	−.002 (.001)	.086	−.002 (.001)	.088
HIV seropositive		−.002 (.004)	.653	.000 (.004)	.931	.000 (.004)	.953
Age strata	40–50	−.010 (.009)	.247	−.017 (.009)	.065	−.016 (.009)	.077
	>50	**−.024 (.009)**	**.008**	**−.033 (.009)**	**<.001**	**−.030 (.009)**	**.002**
SDMT, baseline		**.665 (.019)**	**<.001**	**.647 (.020)**	**<.001**	**.649 (.020)**	**<.001**
Practice effect		.005 (.005)	.221	.006 (.005)	.196	.006 (.005)	.204
Caucasian race				**.016 (.006)**	**.011**	**.014 (.006)**	**.036**
College educated				**.009 (.004)**	**.036**	.008 (.004)	.056
CES-D				**−.004 (.002)**	**.034**	**−.004 (.002)**	**.035**
Diabetes						−.013 (.008)	.109
Hypertension						−.007 (.004)	.080
Hypercholesterolemia						.008 (.005)	.130
HIV × age	40–50			.006 (.027)	.806	.008 (.027)	.785
	>50			.019 (.027)	.479	.023 (.027)	.405
HIV × time				.004 (.008)	.629	.004 (.008)	.625
Age × time	40–50			.001 (.006)	.933	.001 (.006)	.932
	>50			.001 (.006)	.867	.001 (.006)	.867
HIV × age × time	40–50			−.002 (.008)	.786	−.002 (.008)	.779
	>50			−.005 (.009)	.519	−.005 (.009)	.519

Note. Positive = improvement. **Bold** indicates statistical significance ($P < .05$).

Baseline performance on the Trail Making Test Part A was a significant predictor of long-term performance (Table 3). Individuals with college education demonstrated better performance (interim and final model). Those individuals that reported presence of diabetes demonstrated worse performance (final model). Baseline performance was worse among those in the older group compared to those in the younger group, regardless of HIV serostatus. There was no influence of HIV serostatus and age on longitudinal performance. The lack of significant two- and three-way interaction terms between these main effects in the final model indicated that the groups demonstrated similar changes over time.

Performance on Trail Making Test Part B was influenced by baseline performance (Table 4). Those of Caucasian race and those with a college education demonstrated better performance (interim and final models). Progression over time was reported in $\log_{10}$ seconds per year. Among the HIV− participants,

Table 3 Trail Making Test Part A (TM A) results from mixed linear modeling: initial, interim, and final models

		Initial		Interim		Final	
		Est (*SE*)	*P*	Est (*SE*)	*P*	Est (*SE*)	*P*
Time, years		−.001 (.001)	.098	−.001 (.001)	.156	−.001 (.001)	.152
HIV seropositive		−.002 (.005)	.647	−.005 (.005)	.271	−.006 (.005)	.223
Age strata	40–50	.015 (.010)	.0153	.020 (.010)	.072	.018 (.011)	.095
	>50	**.033 (.011)**	**.002**	**.040 (.011)**	**<.001**	**.036 (.011)**	**.002**
TM A, baseline		**.677 (.015)**	**<.001**	**.667 (.016)**	**<.001**	**.664 (.016)**	**<.001**
Practice effect		−.003 (.003)	.322	−.003 (.016)	.373	−.003 (.003)	.391
Caucasian race				**−.016 (.007)**	**.030**	−.012 (.007)	.111
College educated				**−.014 (.005)**	**.007**	**−.012 (.005)**	**.014**
CES-D				.004 (.002)	.067	.004 (.002)	.068
Diabetes						**.028 (.010)**	**.004**
Hypertension						.009 (.004)	.064
Hypercholesterolemia						−.011 (.006)	.064
HIV × age	40–50	.022 (.026)	.385	.015 (.027)	.579	.012 (.026)	.654
	>50	.003 (.026)	.901	−.004 (.027)	.881	−.010 (.027)	.694
HIV × time		−.003 (.006)	.643	−.001 (.006)	.849	−.001 (.006)	.845
Age × time	40–50	.002 (.004)	.563	.003 (.005)	.480	.001 (.005)	.481
	>50	.002 (.004)	.578	.003 (.005)	.586	. 002 (.005)	.584
HIV × age × time	40–50	.005 (.006)	.403	.004 (.006)	.552	.004 (.006)	.546
	>50	.006 (.006)	.287	.006 (.006)	.336	.006 (.006)	.335

Note. Negative = improvement. **Bold** indicates statistical significance ($P < .05$).

Table 4 Trail Making Test Part B (TM B) results from mixed linear modeling: initial, interim, and final models

		Initial		Interim		Final	
		Est (*SE*)	*P*	Est (*SE*)	*P*	Est (*SE*)	*P*
Time, years		−.005 (.008)	.487	−.006 (.008)	.433	.006 (.008)	.466
HIV seropositive		−.000 (.041)	.932	−.000 (.041)	.995	.002 (.046)	.957
Age strata	40–50	.001 (.032)	.966	.020 (.033)	.548	.018 (.036)	.621
	>50	.026 (.032)	.408	.055 (.033)	.098	.050 (.036)	.165
TM B, baseline		**.647 (.016)**	**<.001**	**.623 (.017)**	**<.001**	**.618 (.017)**	**<.001**
Practice effect		−.008 (.006)	.194	−.008 (.006)	.197	−.008 (.006)	.224
Caucasian race				**−.051 (.021)**	**<.001**	**−.046 (.013)**	**<.001**
College educated				**−.039 (.008)**	**<.001**	**−.035 (.009)**	**<.001**
CES-D				.005 (.004)	.249	.005 (.004)	.254
Diabetes						.030 (.016)	.072
Hypertension						.013 (.008)	.097
Hypercholesterolemia						.001 (.010)	.911
HIV × age	40–50	−.022 (.043)	.603	−.035 (.044)	.419	−.037 (.048)	.444
	>50	−.040 (.044)	.350	−.050 (.044)	.254	−.053 (.048)	.270
HIV × time		−.017 (.010)	.094	−.017 (.011)	.122	−.013 (.011)	.238
Age × time	40–50	.001 (.008)	.926	.000 (.008)	.999	.004 (.008)	.617
	>50	.002 (.008)	.828	.003 (.008)	.754	.002 (.008)	.825
HIV × age × time	40–50	**.023 (.011)**	**.039**	**.023 (.011)**	**.042**	**.023 (.011)**	**.038**
	>50	**.028 (.011)**	**.013**	**.026 (.011)**	**.023**	**.026 (.011)**	**.022**

Note. Negative = improvement. **Bold** indicates statistical significance ($P < .05$).

there was no significant effect of age group on longitudinal performance (Figure 1). Performance over time in the younger (mean slope −0.006 [*SE* 0.008]), middle (mean slope 0.012 [*SE* 0.036]), and older (mean slope 0.044 [*SE* 0.036]) HIV− age groups did not demonstrate a significant change in performance over time ($P = .47$, .74, and .22, respectively). Further, when comparing these three HIV− groups, performance over time among those in the middle and older age groups was not significantly different from those in the younger group ($P = .62$ and .17).

Among the HIV+ participants, individuals in the younger age group demonstrated a significant improvement in Trail Making Test Part B performance over time (mean slope −0.019 [*SE* 0.007]; $P = .007$). Individuals in the older (mean slope 0.059 [*SE* 0.024]) and middle (mean slope 0.026 [*SE* 0.014]) age groups demonstrated a significant decline

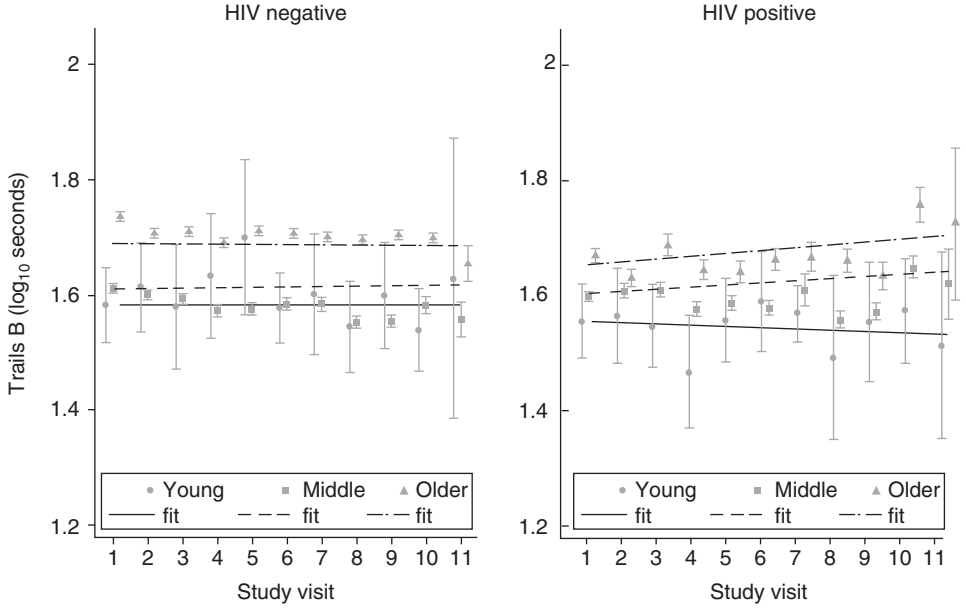

Figure 1 Trail Making Test Part B, performance over time stratified by HIV serostatus and age group. Standard error bar and predicted slope based on mixed model regression. *y*-axis, lower number over time indicates improvement, higher number over time indicates deterioration.

in performance over time ($P = .041$ and 0.30, respectively) (Figure 1). There was a significant interaction between HIV serostatus, age, and time (all models) (Table 4). In comparing longitudinal performance among the three age groups, those in the older and middle age groups had significantly or a marginally significantly different trajectory relative to individuals in the younger age group ($P = .046$ and .063).

Discussion

The results from the current study indicate that among predominantly HAART-experienced HIV+ individuals, there is an interaction between age, serostatus, and time on the TM Test Part B, a commonly used measure of psychomotor speed/executive functioning. Among HIV+ individuals, those in the older and middle age groups demonstrated a significant decline over time, whereas individuals in the younger age group demonstrated a significant improvement in performance over time possibly due to the impact of practice effects in the younger group. This result indicated an effect of aging on performance. This differential performance across age groups was not observed among HIV− individuals. In fact, the model demonstrated relatively stable performance over time for HIV− individuals in all these groups. The TM Test Part B, which includes an additional set-shifting component, evaluates both psychomotor speed (speed of information processing) and executive functioning, whereas the SDMT and TM Test Part A evaluate only speed of information processing. As age itself was not associated with a difference in longitudinal performance over time among the combined group of HIV+ and HIV− individuals, and HIV serostatus itself was not associated with a difference in longitudinal performance over time among individuals from all age groups, our results suggest that both HIV serostatus and age together may impact longitudinal performance specifically in a test sensitive to executive functioning.

During the 5-year period of the study, the change over time in psychomotor speed performance among those HAART-experienced HIV+ individuals was very small. These results are thus consistent with those from a previous study from the MACS demonstrating relatively stable psychomotor speed performance over many years among HIV+ individuals with well-controlled HIV viremia (Cole *et al,* 2007).

Aging is associated with an increased risk of systemic illnesses that could have an effect on cognitive performance. Alzheimer's disease is an important cause of cognitive impairment among older individuals. However, this condition usually occurs in individuals who are greater than 65 years of age. In our study, only 3.0% of the HIV+ and 11.2 % of the HIV− individuals were greater than age 65. In addition, early Alzheimer's disease is not usually associated with motor or psychomotor slowing. A previous study of the neuropsychological test profile of young and old HIV+ individuals suggested that the profile in older HIV+ cases with dementia is not typical of the profile seen in Alzheimer's disease, as there was no difference in verbal recognition memory between the two groups (Sacktor *et al,* 2007). If Alzheimer's disease was the cause of the dementia syndrome in the older HIV+ individuals, then a decrease in verbal recognition memory performance would have been anticipated in the older group.

Individuals in the 50- to 65-year age range have an increased risk for comorbid medical conditions such as hypertension, diabetes, and hypercholesterolemia, which are all risk factors for subcortical small vessel ischemic disease (den Heijer *et al,* 2005; Dore *et al,* 1999; Jennings *et al,* 2005; Jernigan *et al,* 1993, 2005). These conditions are more likely to be contributing to the mild changes in cognitive performance among both older HIV+ and HIV− individuals in our study (Prins *et al,* 2005). Another study from the MACS recently found that medical factors such as hyperglycemia or increased carotid intima-media thickness were more strongly associated with decreased psychomotor speed performance than HIV disease factors such as CD4 cell count or the presence of detectable plasma HIV RNA (Becker *et al,* 2009). These results suggest that older age may represent a surrogate for the effects of these medical factors with respect to executive functioning performance. Of note, in our study diabetes was associated with worse performance at baseline on the TM Test Part A.

It should be noted that the MACS cohort includes only gay/bisexual men, and additional studies are required to determine if similar results are present in HIV+ women and HIV+ individuals acquiring HIV infection through different risk factors. There may also be a survivorship bias, as some of our older HIV+ individuals have been participants in the MACS cohort for 20 years. These HIV+ individuals may have had differences from those HIV+ individuals who did not survive the complications of HIV infection. Our HIV+ individuals may also be receiving more frequent medical evaluations through their primary providers than either HIV+ or HIV− individuals in the general population.

Further studies are required to examine the potential contribution of each of these cerebrovascular disease risk factors individually towards psychomotor speed and executive functioning performance among both older HIV+ and HIV− individuals. In addition, the impact of age and serostatus in other cognitive domains remains to be determined. The impact of more intensive monitoring and treatment of cerebrovascular disease associated medical conditions on neurocognitive performance also requires further evaluation.

Methods

Research participants
The study was conducted within the Multicenter AIDS Cohort Study (MACS), a prospective study of the natural history of HIV infection among gay/bisexual men (Kaslow *et al,* 1987). Eligibility criteria for the MACS have been described previously (Kaslow *et al,* 1987). Participants undergo an interview and clinical assessment including an evaluation of psychomotor speed performance every 6 months. For the purposes of the analysis, the first study visit in the period of observation was labeled baseline. Participants who were still active in the study between April 2002 (i.e., start of MACS study visit 36) and October 2007 (end of MACS study visit 47) were included in the current study. Four hundred seventy-seven HIV+ and 799 HIV− individuals were studied longitudinally from 2002 to 2007. The median number of visits per participant was 9 (range 3, 12; inter-quartile range 5, 10). HIV+ and HIV− individuals were each stratified by three age groups at baseline: (1) <40 years, (2) 40–50 years, and (3) >50 years (as of April, 2002).

Standard protocol approvals, registrations, and patient consents
An Institutional Review Board (IRB)/ethical standards committee has approved the use of human subjects for this study at each site. Written informed consent was obtained from all subjects participating in the study.

Measures
Psychomotor speed test performance was measured by the Symbol Digit Modalities Test (SDMT) (Smith, 1982) and the Trail Making (TM) Test (Reitan, 1979). The SDMT is a test of speed of visual information processing and attention. The TM Test Part A is a test of attention, motor speed, and visuospatial tracking. The TM Test Part B includes an additional set-shifting component and thus evaluates executive functioning to a greater extent than the SDMT and TM Test Part A. The TM Test is also a sensitive measure of aging effects in the elderly (Ratcliff *et al,* 2003).

Statistical procedures
We compared the baseline demographic and medical characteristics of the HIV-seronegative and -seropositive groups using *t* tests and chi-square tests. Both main effects and interaction between age and HIV serostatus were tested.

The primary data analyses examined within-participant changes in neuropsychological test scores from baseline to the end of the observation period (with neuropsychological assessment at 6-month intervals). This approach allows both improvement and decline relative to a person's baseline performance to be quantified. All analyses were performed using log-transformed raw scores to account for the non-normality of the untransformed scores.

To examine how the changes in neuropsychological test scores over time might be related to participant-specific covariates, we used a separate linear mixed effects model for the log-transformed scores for each test (Diggle *et al,* 2002). The response variable was the individual participant's test scores. The model allowed for a separate random intercept for each participant to account for within-person autocorrelation. To account for a learning effect from baseline to first 6-month assessment, we included an indicator variable to distinguish second and subsequent measurements from the baseline measures. We modeled performance on neuropsychological tests as a function of age stratification, HIV serostatus, time since baseline (years), baseline neuropsychological test performance, and practice effect. This specification served as an initial model of longitudinal performance. Additional covariates believed on the basis of previous research to be relevant for psychomotor performance included race (Caucasian versus otherwise), education (college-educated versus otherwise), and Center for Epidemiologic Studies Depression Scale (CES-D) total score (from the same visit as the neuropsychological test score). This specification served as an interim model of longitudinal performance. The final model included interaction terms between age stratification, HIV serostatus, and time since baseline to test for differential effects on longitudinal performance for these groups. In addition, to adjust for baseline differences in the self-report of diabetes, hypertension, and hypercholesterolemia, these terms were included in the final model.

To test for nonlinearity, we included indicator terms for follow-up at 1 and 3 years post baseline to allow for changes in slope of neuropsychological performance. These indicator terms were not significant and, therefore, not included in the final model.

Appendix

The Multicenter AIDS Cohort Study (MACS) includes the following: Baltimore: The Johns Hopkins University Bloomberg School of Public Health: Joseph B. Margolick (Principal Investigator), Barbara Crain, Adrian Dobs, Homayoon Farzadegan, Joel Gallant, Lisette Johnson-Hill, Shenghan Lai, Ned Sacktor, Ola Selnes, James Shepard, Chloe Thio. Chicago: Howard Brown Health Center, Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services: John P. Phair (Principal Investigator), Steven M. Wolinsky (Co-Principal Investigator), Sheila Badri, Bruce Cohen, Craig Conover, Maurice O'Gorman, David Ostrow, Frank Palella, Ann Ragin, Daina Variakojis. Los Angeles: University of California, UCLA Schools of Public Health and Medicine: Roger Detels (Principal

Investigator), Otoniel Martínez-Maza (Co-Principal Investigator), Aaron Aronow, Robert Bolan, Elizabeth Breen, Anthony Butch, Rita Effros, John Fahey, Beth Jamieson, Eric N. Miller, John Oishi, Harry Vinters, Barbara R. Visscher, Dorothy Wiley, Mallory Witt, Otto Yang, Stephen Young, Zuo Feng Zhang. Pittsburgh: University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (Principal Investigator), Lawrence A. Kingsley (Co-Principal Investigator), James T. Becker, Ross D. Cranston, Jeremy J. Martinson, John W. Mellors, Anthony J. Silvestre, Ronald D. Stall. Data Coordinating Center: The Johns Hopkins University Bloomberg School of Public Health: Lisa P. Jacobson (Principal Investigator), Alvaro Muñoz (Co-Principal Investigator), Alison Abraham, Keri Althoff, Christopher Cox, Gypsyanber D'Souza, Stephen J. Gange, Elizabeth Golub, Janet Schollenberger, Eric C. Seaberg, Sol Su. NIH: National Institute of Allergy and Infectious Diseases: Robin E. Huebner; National Cancer Institute: Geraldina Dominguez. Web site: http://www.statepi.jhsph.edu/macs/macs.html.

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