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Neurobehavioral effects of human immunodeficiency virus infection among former plasma donors in rural China

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The human immunodeficiency virus (HIV) epidemic in China has expanded rapidly in recent years, but little is known about the prevalence and features of HIV-associated neurocognitive disorders (HANDs) in this part of the world. We administered a comprehensive Western neuropsychological (NP) test battery to 203 HIV+ and 198 HIV− former plasma donors in the rural area of Anhui province. They found that 26% of the HIV− samples, and 46% of the HIV+ samples, were infected with hepatitis C virus (HCV), which can also have central nervous system (CNS) effects. To classify NP impairment, we developed demographically corrected test norms based upon individuals free of both infections ($N=141$). Using a global summary score, NP impairment was found in 34.2% of the HIV-monoinfected group and 39.7% of the coinfected group, as compared to 12.7% of the uninfected controls ($P<.001$). HIV+ participants with acquired immunodeficiency syndrome (AIDS) were more likely to be impaired (43%) than non-AIDS individuals (29%; $P<.05$). Lastly, when all infection groups were combined, participants with NP impairment reported more cognitive complaints ($P<.01$) and increased dependence in everyday functioning ($P=.01$). In sum, NP impairment in this large rural Chinese sample was associated with both HIV and HCV infections, and the impairment's prevalence, severity, and pattern were

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similar to those reported by Western studies. Clinical significance of NP impairment in this population is suggested by the participants' reports of reduced everyday functioning. These findings indicate that HAND is likely to be an important feature of HIV infection in developing countries, underscoring the need for international efforts to develop CNS-relevant treatments. *Journal of NeuroVirology* (2008) **14,** 536–549.

Keywords: HIV; HCV; neurocognitive disorders; China

Introduction

The human immunodeficiency virus (HIV) epidemic in China is being closely monitored by the Chinese government, together with the World Health Organization (WHO) and UNAIDS. Their most recent reports estimated that 700,000 mainland Chinese people were living with HIV at the end of 2007, and that during that year there were around 50,000 new infections and 20,000 acquired immunodeficiency syndrome (AIDS) deaths (State Council AIDS Working Committee Office and United Nations Theme Group on HIV/AIDS in China, 2007).

In Western countries the initial HIV epidemic tended to be concentrated in urban areas within the gay male population. By contrast, in China the HIV epidemic began in rural areas in association with blood product collection and use, before spreading to urban injection drug users (IDUs), among whom it has reached very high rates of infection in some areas (up to 44%; Zhao *et al,* 2006). The epidemic among Chinese former plasma donors (FPDs), on which this current study is focused, has been centered in agrarian provinces such as Anhui, Hebei, Henan, Hubei, and Shanxi (Cohen, 2004). In these areas prior to the mid 1990s, a large number of poorly regulated commercial plasma collection companies were in operation, some using nonsterile techniques. Residents would supplement their small farming incomes by selling their plasma, in some cases very often, unknowingly placing themselves at risk for exposure to HIV and other blood-borne pathogens. In the mid 1990s, the Chinese government imposed strict regulations to prevent further spread of HIV in this way.

Estimates of future infections are difficult, but UNAIDS and other organizations have predicted that by 2010, there could be a generalized epidemic with between 10 and 20 million HIV-infected Chinese (UNAIDS, 2006). Because China is the most populous country on earth, with 1.3 billion people, the growth of the HIV epidemic there is cause for considerable concern.

It is well documented that HIV enters the central nervous system (CNS) early after infection and can be associated with neurocognitive impairment in up to 50% of individuals with AIDS (Heaton *et al*, 1995; Antinori *et al*, 2007). However, almost all of these data come from studies conducted in the United States, Europe, and Australia. Little is known about the prevalence and nature of neurobehavioral complications of HIV in developing areas of the world, including China.

In the United States, research prior to aviability of highly active antiretroviral therapy (HAART) demonstrated that presence of neuropsychological (NP) impairment in HIV-infected persons conferred an increased risk early mortality, above and beyond what could be predicted from medical indices of disease progression (Mayeux *et al*, 1993; Ellis *et al*, 1997). It is unclear whether NP impairment still produces worse medical outcomes in the context of HAART, but there is considerable evidence that even mild NP impairment is associated with reduced vocational functioning and other difficulties with cognitive aspects of everyday functioning: medication management, driving, and instrumental activities of daily living (IADLs; Carter *et al*, 2003; Heaton *et al*, 2004a; Hinkin *et al*, 2004; Marcotte *et al*, 2006). It is unknown whether any NP deficits that may be observed among HIV-infected Chinese farmers would have the same relevance in their lives, or if such deficits could even be noticed by the patients and others around them.

An even more fundamental question is whether Western NP tests will be valid in developing countries, where the people have very different educational, cultural, and linguistic backgrounds from those in the United States, Europe, and Australia. Previous studies in developing countries have been able to use Western NP tests, but estimates of prevalence of HIV-associated neurocognitive disorders (HANDs) from these studies have varied widely. One impediment to reliable estimates of HAND across studies is the fact that normative data from HIV-uninfected (HIV −) samples matched for age, education, gender, and disease risk factors were not typically available. This means that some of the ''impairment'' interpreted as being due to HIV could reflect variation due to other factors. Other reasons for inconsistent findings include use of more or less conservative definitions of NP impairment, differences in the NP tests themselves, and the degree to which investigators have considered comorbid medical and psychiatric conditions that are common in the various populations being studied (e.g., histories of substance use disorders or significant head trauma, other infectious diseases such as malaria, tuberculosis, syphilis, and hepatitis C virus [HCV]).

So far, the feasibility of cross-cultural NP investigations of HIV effects has been demonstrated best by the WHO Neuropsychiatric AIDS Study Trial (Maj *et al*, 1994a,b). This study examined the NP status of HIV−, HIV+ asymptomatic, and HIV+ symptomatic participants in five countries: Germany, Brazil, Kenya, Zaire, and Thailand. A Western NP test battery covering multiple ability domains was translated and successfully administered in the five relevant languages. An increased prevalence of NP impairment was seen among medically symptomatic HIV+ groups (versus their respective HIV− comparison groups) in all sites, whereas asymptomatic participants showed increased rates of impairment in Brazil and Zaire, and in the lowest educated subgroups in Kenya.

More recently, two NP studies of HIV+ groups in sub-Saharan Africa have found very inconsistent results. Robertson *et al* (2007) administered the International HIV Dementia Scale (IHDS) and an NP battery covering five ability areas to 110 HIV+ and 100 HIV− adults in Uganda (see also Sacktor *et al*, 2005, 2006, and Wong *et al*, 2007, for additional findings with these cohorts). Forty-nine (44.5%) of the infected participants had histories of some ART. Although efforts were made to recruit demographically comparable groups, the HIV− participants were younger (mean 27.5 years versus 36.7 for HIV+), more highly educated (mean 12.1 years, versus 9.1 years for HIV+), and contained fewer females (40% versus 70% for HIV+). Using analyses of covariance (ANCOVAs) with education covaried, the HIV+ group did significantly worse on a mean NP *z*-score and on all individual tests except for Timed Gait and Grooved Pegboard. Contrasting results were reported by Clifford *et al* (2007), who administered the IHDS, and Category Fluency (animals), Timed Gait, Grooved Pegboard, and Finger Tapping tests to 73 HIV+ (ART naïve) and 87 HIV− patients in an Ethiopian outpatient clinic. These groups were well matched demographically, and their test performances differed significantly only on Finger Tapping. Clifford and colleagues acknowledged that their test battery was limited, but suggested that their negative results ''may be more reliable than studies from other developing countries'' (p. 70) because their HIV+ and HIV− participants come from the same clinic population, with the same demographic characteristics. Another possibility mentioned by these authors is that the HIV subtype that predominates in Ethiopia (clade C) may have less neurotropism than clade B (predominant in North America, Europe, and Australia) and/or clades more predominant in Uganda (clades A and D). However, there is preliminary evidence of NP and electroencephalographic abnormalities being associated with clade C infection in India (Riedel *et al*, 2006; Sinha and Satishchandra, 2003; Yepthomi *et al*, 2006).

Finally, Cysique *et al*. (2007b) recently reported a small study comparing NP effects of HIV infection (clade B) in China and the United States. An NP test battery that has been used in large multisite studies in the United States was translated and adapted slightly for cultural relevance to the Chinese population, and was administered to 28 HIV+ and 23 demographically similar HIV− controls in China, as well as to 39 HIV+ and 31 HIV− controls in the United States. The test battery was well understood and tolerated by the Chinese participants. Importantly, a comparably robust HIV effect on NP performance was found in the two countries. This served as a pilot study for the current investigation of HIV infection among FPDs in Anhui province. There was no overlap in the samples used in the two studies.

The current study is a first, large-scale attempt at providing estimates of the prevalence and nature of HAND within a major risk group in China (FPDs), and at exploring the possible relevance of such impairments to participants' everyday functioning. All participants (both HIV− and HIV+) were FPDs with no other known risk for HIV infection. In addition to selecting large, demographically comparable samples of HIV+ and HIV− participants from the same population and risk group, our study design involved systematically examining effects of comorbid medical and psychiatric conditions considered relevant to this population. Also, we used data from the uninfected controls to develop demographically corrected, Chinese NP norms, which would enable more accurate classification of acquired NP impairments in individual participants. Our hypotheses were (1) more NP impairment would be seen in the HIV+ group than in the HIV− comparison group; (2) within the HIV+ group, increased NP impairment would be associated with a history of severe immunosuppression (as indexed by the nadir CD4 cell count) and/or AIDS-defining illness; and (3) NP impairment would be associated with reports of decreased functioning in daily life (i.e., more cognitive complaints, lower employment rates, decreased independence in instrumental activities of daily living).

Results

FPD participants' demographic, clinical, and laboratory characteristics

Importantly, 25.6% of the HIV− sample and 46.3% in the HIV+ sample tested positive for HCV ($P < .0001$). Demographic data are therefore presented in Table 1 for the four subject groups: controls, HIV monoinfected; HCV monoinfected, and coinfected samples. The four groups were comparable with respect to age and education, whereas female gender was more prevalent in the HCV-monoinfected group

Table 1 Extended demographic characteristics of controls, HIV-monoinfected, and HCV-monoinfected, and coinfected groups

	Controls ($n=141$)	HIV monoinfected ($n=108$)	HCV monoinfected ($n=51$)	HIV/HCV coinfected ($n=93$)	Comparisons*
Age (years)	40.47 (6.20)	40.88 (6.42)	40.17 (6.70)	39.52 (6.21)	ns
Education (years)	5.80 (2.08)	5.49 (2.24)	5.60 (2.17)	5.43 (2.36)	ns
Gender% Male[a]	63.8%	66.7%	49.0%	53.7%	.07
Speaks Fuyang dialect	100.0%	100.0%	100.0%	100.0%	ns
Speaks Mandarin	12.7%	19.4%	11.7%	7.5%	ns
Han ethnicity	99.3%	99.1%	100%	100%	ns
Grew up in rural area	100%	99.1%	100%	98.9%	ns
Resides in rural area	100%	100%	100%	98.9%	ns
Engaged in farming	91.5%	90.6%	93.9%	86.5%	ns
Number of family members in home	5.1 (1.2)	4.1 (1.4)	5.4 (1.3)	5.2 (1.3)	ns
Currently married[b]	96.5%	86.1%	94.1%	92.4%	.03
Widowed[c]	3.5%	13.9%	5.9%	7.6%	.03
Number of plasma donations[d]	12.3 (24.1)	48.6 (77.9)	16.2 (24.5)	57.3 (113.3)	$<.0001$

*One-way ANOVA or overall chi-square comparison as appropriate. ns, nonsignificant.
[a]HIV monoinfected > HCV+ only ($P=.04$).
[b]HIV monoinfected < controls ($P=.003$).
[c]HIV monoinfected > controls ($P=.003$).
[d]HIV/HCV coinfected > controls ($P<.0001$); HIV monoinfected > controls ($P=.0002$).

when compared to controls. All participants spoke the regional language (Fuyang Chinese dialect) and the proportion of persons fluent in formal Mandarin did not differ between groups. Virtually all participants belong to the Han ethnicity and all grew up and continued to reside in this rural area of Anhui province. The family size in the participants' households did not differ between the groups. All participants were either married or widowed, but the HIV-monoinfected participants were more likely to be widowed when compared to controls. Lastly, we found that HIV-monoinfected and coinfected individuals made on average many more plasma donations compared controls and HCV-monoinfected individuals (see Table 1).

Psychiatric assessments revealed that none of our participants had lifetime histories of substance (other than alcohol) use disorders. Lifetime prevalence for alcohol use disorders differed significantly between controls ($n=5$; 3.5%) and all other groups: HIV-monoinfected group ($n=19$, 17.6%; $P=.0002$), HCV-monoinfected group ($n=6$, 11.7%; $P=.05$), and coinfected group ($n=10$, 10.7%; $P=.03$). A small minority of our participants ($<1\%$) met criteria for an alcohol use disorder in the last 30 days: one HIV-monoinfected participant, one HCV-monoinfected participant, and one coinfected participant (these three participants did not report drinking more than two alcoholic drinks per day over the past 30 days at the screening enrollment, but gave more candid reports during the subsequent diagnostic interview). Only two controls and three HIV-monoinfected individuals and one coinfected individual met criteria for current major depressive disorder (MDD). Seven controls (4.9%) and three HCV-monoinfected individuals (5.8%) met criteria for lifetime MDD, and this was significantly different from 15 HIV-monoinfected (13.9%; $P=.02$) and 13 coinfected (14%; $P=.02$) participants who met this criteria. Also, the HIV-monoinfected group (10.5 ± 10.4; $P=.002$) and the coinfected group (12.1 ± 12.3; $P<.0001$) reported significantly more currently depressed mood on the BDI-II but not the HCV-monoinfected group (8.9 ± 10.8) as compared to controls (5.9 ± 9.2).

Table 2 summarizes the clinical and laboratory characteristics of the HIV-monoinfected and coinfected groups. AIDS was more common in the monoinfected sample as compared to the coinfected sample, but most of these were so classified because of a history of severe immunosuppression (i.e., only 12% had a history of AIDS-defining illness in the HIV-monoinfected group compared to 18.5% in the coinfected group). Sixty percent in the HIV-monoinfected group and 47% in the coinfected group were prescribed antiretroviral treatment by their local clinicians for an average of 97 days. Almost all treated participants reported being strictly adherent to their medication regimens and this did not differ between monoinfected and coinfected individuals.

NP test results

All 401 participants successfully completed the NP battery and the examiners rated their cooperation and effort as adequate in all cases. Table 3 summarizes raw score results on the individual NP test measures, and also indicates effect sizes obtained comparing the infected groups to the uninfected controls. Small to medium effect sizes were obtained for HIV monoinfection and HIV/HCV coinfection on all measures except the Wisconsin Card Sorting Test (WCST). By contrast, HCV monoinfection was associated with small effect sizes on only

Table 2 Clinical and laboratory characteristics in the HIV-monoinfected and coinfected groups

	HIV monoinfected ($n = 108$)	HIV/HCV co-infected ($n = 93$)	P
Current CD4 count	321 (IQR 194–433)	350 (IQR 187–498)	ns
Nadir CD4 count	199 (IQR 150–315)	258 (IQR 164–383)	ns
Plasma HIV viral load in 132 detectable*	4.2 (0.8)	3.9 (0.8)	.03
HIV RNA% detectable	31%	39%	ns
Duration of known HIV seropositivity in months (SD)	152 (24)	132 (55)	.002
% AIDS	65.7%	45.1%	.004
CDC stages%			
A1	4%	11%	—
A2	18%	35%	—
A3	28%	14%	—
B1	1%	0%	—
B2	11%	8.5%	—
B3	26%	13%	—
C2	2%	5.5%	—
C3	10%	13%	—
On ARV drugs (%)	64%	48%	.03
Type of ART regimen among treated[a]			
HAART (≥ 3 drugs)	84%	93%	ns
Dual-therapy	13%	5%	—
Monotherapy	3%	2%	—
ARV treatment duration in months (SD)	97.5 (60.3)	96.9 (53.7)	ns
CNS penetration-effectiveness (CPE) ranks[b]	1.56 (0.46)	1.46 (0.26)	ns
Self-reported adherence as ''always''	98.5%	97%	ns

Note. Eight individuals (6 HIV − and 2HIV+) did not have available blood tests and therefore no HCV status. ns: nonsignificant; ARV: antiretroviral.

*NucliSens EasyQ HIV-1 from bioMerieux Easy Q assay uses real-time NASBA amplification and molecular beacon detection technology and has a range of 50 to 3 million IU (copies)/mL.

[a]Comparisons was conducted for HAART versus non HAART.

[b]See Letendre *et al* (2008) for more details in the computation of the CPE ranks.

11 of the 18 measures. (Because the WCST demonstrated no sensitivity to any type of infection in this study, it was not included in subsequent analyses of summary scores on the NP ability domains and the total test battery.)

Mean T-scores for the total test battery and the seven ability domains all showed significant overall group effects ($P < .001$). Figure 1 displays the effect sizes (Cohen's d) for comparisons of individual infection groups versus controls. On the global mean T-score, the coinfected group and HIV-monoinfected group showed medium to large effect sizes (d = .83 and .72, respectively), whereas the HCV-monoinfected group showed a small to medium difference (d = .45).

Figure 1 and Table 3 may be considered together to explore pattern differences on the seven ability domains. Both HIV-infected groups showed their largest impairments on measures of processing speed, whereas the HCV-monoinfected group showed small and inconsistent deficits on tests within this domain. All three infected groups showed consistent impairments on measures of learning, memory (delayed recall), and motor skills. Suggestive of some additive effects of HIV and HCV, the coinfected group showed more impairment than either monoinfected group on tests of attention/working memory, learning, and verbal fluency.

Finally, using the standard GDS cut-off of 0.50 to classify individual participants' NP impairment status, rates of impairment were 12.7% in controls, 34.2% for the HIV-monoinfected group, 37.2% in the HCV-monoinfected group, and 39.7% in the coinfected group ($\chi^2(df = 3) = 26.8$, $P < .0001$). Most of this impairment was in the mild range (53.7% of impaired individuals in the combined infected groups; GDS = 0.50–0.99). According to recently updated research definitions of HAND (Antinori *et al*, 2007), only nine (4.4%) of HIV-infected participants in this study met NP criteria for diagnosis of HIV-associated dementia (i.e., at least moderate NP impairment involving two or more ability domains); all but one of these had AIDS.

HIV disease history and NP impairment

Blood draw could not be obtained for two HIV+ and six HIV − individuals, so analyses of relationships between current laboratory values and NP status excluded them. As noted above, the large majority of our participants with AIDS were prescribed HAART, which would be expected to suppress HIV plasma viral load and improve immunocompetence. We

Table 3 Raw scores and effect sizes on individual NP test measures

	Controls ($n=141$)	HIV monoinfected ($n=108$)	HCV monoinfected ($n=51$)	HIV/HCV coinfected ($n=93$)
Executive function				
Color Trails II (time seconds)	112.75 (30.94)	132.39 (40.48)*b*	128.78 (47.80)[a]	129.43 (49.02)[a]
WCST (preservative errors)	15.95 (8.48)	15.15 (7.69)	16.18 (9.60)	16.33 (9.13)
Category Test (errors)	64.94 (22.84)	72.00 (27.88)[a]	67.42 (28.01)	73.92 (27.77)[a]
Verbal fluency				
Animal fluency (total correct)	13.39 (3.25)	12.37 (3.28)[a]	12.88 (3.64)	11.90 (2.98)[a]
Action fluency (total correct)	7.72 (2.69)	6.91 (2.63)[a]	7.10 (3.54)[a]	6.78 (2.95)[a]
Attention/WM				
PASAT-50 (total correct)	28.26 (9.36)	24.80 (9.37)[a]	26.24 (10.01)[a]	24.32 (9.57)[b]
WMS-III Spatial Span	14.23 (3.39)	13.56 (3.38)[a]	13.67 (3.30)	12.58 (3.19)[b]
Learning				
HVLT-R Learning (total 3 trials)	18.45 (4.45)	17.35 (5.10)[a]	16.57 (5.57)[a]	15.63 (5.17)[b]
BVMT-R Learning (total correct)	16.67 (6.74)	13.27 (6.92)[b]	14.53 (7.70)[a]	13.51 (7.14)[a]
Memory				
HVLT-R Delayed Recall (total correct)	6.48 (2.20)	5.69 (2.43)[a]	5.51 (2.50)[a]	5.47 (2.33)[a]
BVMT-R Delayed Recall (total correct)	7.65 (2.81)	6.05 (3.07)[b]	6.67 (3.41)[a]	5.98 (3.03)[b]
Motor				
Grooved Pegboard DH (time seconds)	77.18 (15.40)	85.01 (21.31)[a]	83.59 (20.59)[a]	84.24 (28.33)[a]
Grooved Pegboard NDH (time seconds)	80.48 (18.64)	89.18 (21.14)[a]	89.39 (26.22)[b]	88.60 (29.37)[a]
SIP				
WAIS-III Digit Symbol (total correct)	41.73 (12.80)	33.44 (11.40)[b]	41.06 (14.95)	37.03 (12.92)[a]
WAIS-III Symbol Search (total correct)	18.30 (7.29)	14.11 (6.28)[b]	17.90 (6.88)	14.38 (7.12)[b]
Trail-Making Test A (time seconds)	59.08 (16.82)	66.96 (18.94)[a]	65.04 (21.00)[a]	66.87 (19.39)[a]
Color Trails I (time seconds)	58.15 (17.43)	68.97 (23.77)[b]	65.98 (21.77)[a]	64.42 (21.49)[a]
Stroop color (total completed in 90s)	45.90 (12.83)	41.35 (13.58)[a]	44.94 (13.84)	38.75 (11.45)[b]

Note. Data are mean (SD). Six HIV − and two HIV+ participants did not give blood samples, so their HCV status is unknown. Thus data are not included here.Three missing values across all the data set (WCST, Category Test for one participant, and Category Test for another participant).
SIP: peed of Information Processing; WM: Working Memory; WCST: Wisconsin Card Sorting Test; HVLT-R: Hopkins Verbal Learning Test—Revised; BVMT-R: Benton Visual Retention Test—Revised).
[a]Small effect size (d = .20–.49).
[b]Medium effect size (d = .50–.79).

therefore anticipated that NP status would be more related to nadir CD4 cell count (part of the CDC definition of AIDS) than to current CD4 count and current plasma viral load. In fact, HIV+ participants who were NP-impaired ($n=74$) had significantly lower nadir CD4 counts than those ($n=125$) who were NP-normal (respective means $=214.4\pm143.9$ versus 274.8 ± 161.1, $t(197)=2.7$, $P=.007$). Also HIV+ persons with AIDS (defined mostly due to a history of severe immunosuppression; see Table 2) had a higher rate of NP impairment than those without AIDS (43.0% versus 29.2%; $\chi^2(df=1)=4.0$, $P<.05$). This difference was not attributable to coinfection with HCV, because there was a higher prevalence of AIDS in the monoinfected HIV+ group (65.7% versus 45.2% for coinfected group) and AIDS was associated with higher rates of impairment in both HIV+ groups. By contrast, NP impairment was not associated with worse *current* CD4 cell counts (334.7 ± 229.8 in NP-impaired subgroup, versus 358.6 ± 184.3 in NP-normal subgroup; $t(199)=0.7$, $P=.44$). Similarly, plasma HIV RNA was detectable in 60.8% of the NP-impaired subgroup, versus 68% in the unimpaired subgroup; for the infected participants with detectable viral load, the mean $\log_{10}$ HIV RNA was comparable for the impaired and unimpaired subgroups (3.9 ± 0.8 versus 4.1 ± 0.8; $t(130)=0.8$, $P=.38$).

Association between NP impairment, alcohol use disorder, and depression

As noted above, although virtually no participants in this study met criteria for current substance use disorders, 14.3% of the HIV+ group versus 5.6% of the HIV − individuals met criteria for an alcohol use disorder in their lifetime. Within the HIV+ group, those with histories of lifetime alcohol use disorders ($n=29$) evidenced a *lower* rate of NP impairment than the large majority who had no history of abuse or dependence (20.6% versus 39.6%; $P=.05$). Also, of the three participants who initially reported minimal current alcohol use but later gave different information that met criteria for alcohol use disorders during the previous 30 days, the two HIV+ individuals were NP-normal whereas the HCV-monoinfected person was NP-impaired. Lastly, the 28 HIV+ participants who met criteria for lifetime MDD had no more NP impairment than their

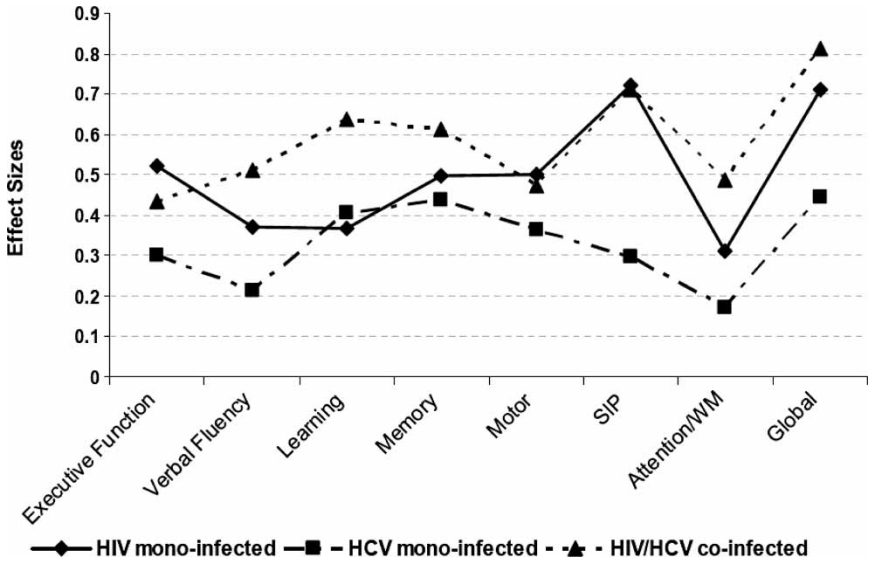

Figure 1 Effect sizes on ability domains (Mean domain T-scores) and the total test battery (Global Mean T-scores) for infected groups as compared to 141 controls.

nondepressed counterparts (32.1% versus 37.7%). Although correlations were statistically significant because of the large sample size, the amounts of shared variance between current depressive symptoms (BDI-II) and NP functioning within the HIV+ group are very small ($R^2 = .03$ for both global mean T-scores and GDS). Finally, 54 (26.6%) of the HIV+ sample reported clinically significant current levels of depressed mood (BDI-II ≥ 17; Beck *et al*, 1996a), but their rate of NP impairment was not significantly greater than that of the non-depressed HIV+ participants (44.4% versus 34.2%; $P = .18$).

Impact of infection and NP impairment on everyday functioning

Table 4 summarizes infection group differences on indicators of impaired (reduced) everyday functioning. Compared to uninfected controls, all three infection groups had more cognitive complaints. Only the HIV/HCV coinfected group reported increased dependence on others in performing IADLs, whereas both HIV-infected groups reported decreased current employment and fewer months worked during past year.

In the combined infection group ($N = 254$), 94 were NP-impaired and 164 were NP-normal. The impaired subgroup reported significantly more cognitive complaints (6.73 ± 6.46 versus 4.33 ± 5.32; $t(252) = -3.0$, $P = .003$), as well as more dependence in IADLs (0.71 ± 1.58 versus 0.30 ± 1.04; $t(252) = -2.3$, $P = .03$). However, NP impairment was not significantly related to employment status (77.7% employed in the NP-impaired versus 85% for NP-normal). The IADLs that were most often impacted among NP-impaired, infected individuals involved financial management, shopping, housekeeping, and cooking.

Discussion

There are three main findings in this study. First, we demonstrated that the NP assessment methods developed and widely used in the United States could be used effectively within the context of rural China, with individuals having very low levels of education compared to U.S. standards. Secondly, we found that increased rates of NP impairment in this large rural Chinese sample of former plasma donors were associated with both HIV and HCV infections. Both HIV-associated and HCV-associated NP impairment showed robust effect sizes, comparable to what has been observed in U.S. cohorts. Thirdly, clinical significance of NP impairment in this population is suggested by the participants' reports of reduced everyday functioning.

All 401 Chinese participants were able to understand and follow the NP test instructions, and obtained what appeared to be valid results. It should be noted that careful translation and piloting of test instruments and the thorough training of the examiners were both important steps in the adaptation and deployment of our NP battery (see Methods and Cysique *et al,* 2007b, for more details). As expected from prior results with Western HIV+ and HIV− cohorts, we found that almost all individual tests in this battery showed some sensitivity to HIV effects in the Chinese FPDs. The single exception was the WCST, which showed no sensitivity to HIV and/or HCV infections in this population. The reason for this is unclear, but it could be that the cultural

Table 4 Cognitive complaints, IADL dependence, and employment in controls, HIV-monoinfected, HCV-monoinfected, and coinfected groups

	Controls ($n=141$)	HIV monoinfected ($n=108$)	HCV monoinfected ($n=51$)	HIV/HCV coinfected ($n=93$)	P
Cognitive complaints (PAOFI)[a]	2.9 (3.9)	4.4 (4.7)	5.0 (5.7)	6.2 (7.0)	<.0001
Decrease IADL dependence[b]	0.08 (0.6)	0.23 (0.83)	0.3 (1.1)	0.76 (1.7)	<.0001
Currently unemployed (%)[c]	4.96%	24.07%	1.96%	18.28%	<.0001
Months worked in the last year[c]	7.3 (2.9)	4.6 (3.3)	8.0 (3.2)	5.7 (3.5)	<.0001

Note. Data are mean (SD). Mean comparisons with Dunnett's method, control group as a reference.
[a]Coinfected different from controls ($P<.0001$); HCV-monoinfected and HIV-monoinfected show trends from controls ($P=.05$; $P=.07$).
[b]Coinfected different from controls ($P<.0001$).
[c]HIV monoinfected different from controls ($P<.0001$); coinfected different from controls ($P=.001$).

and/or educational backgrounds of our participants gave them insufficient familiarity with the WCST's stimuli, categorization rules, or the need to repeatedly change rules of responding throughout the test. Regardless of the reason, it appears that this particular test has little or no value in assessing rural Chinese people such as those in the current study.

Clifford *et al*. (2007) has suggested that some of the reported HIV effect on NP functioning in developing countries may have been biased by the use of HIV − comparison groups that differ from the HIV+ groups in important demographic and background features (e.g., different HIV risk groups). However, the HIV+ and HIV − samples in this study are from the same risk group (FPDs) and have virtually identical demographic and background characteristics (Table 1). Nevertheless, we found robust HIV effects on NP function that are similar to those historically seen in Western countries.

To our knowledge, this is the first effort in HIV research within developing countries to use demographically corrected NP norms, based upon results of a large, uninfected group with very similar backgrounds. This permits more accurate classification of acquired HIV-related impairment in individual cases, and arguably provides the best estimates of prevalence of HIV-related impairment. The association of impairment status with biological variables in this study (nadir CD4 and coinfection with HCV) supports the validity of the tests and the norms in this population. On the other hand, generalizability of these norms to populations in other developing countries is uncertain.

The pattern of NP performance in HIV-monoinfected individuals is consistent with what has been observed in U.S. cohorts (Heaton *et al*, 1995), with predominant deficits in processing speed, learning, motor functions, and some aspects of executive functions. Also as observed in the United States, AIDS status was associated with worse overall rates of impairment when compared to non-AIDS participants. The severity of HIV-associated NP impairment observed in this population also is similar to what is seen in Western countries in the era of HAART: almost all (66 of 75) NP-impaired HIV+ participants had GDSs in the mild to moderate range. Only 4% of the total HIV+ group had NP impairment that was severe enough to be consistent with a diagnosis of HIV-associated dementia (Antinori *et al*, 2007).

Although a majority (56.6%) of our HIV+ FPDs met CDC criteria for an AIDS diagnosis, only 15% had any history of an AIDS-defining illness. Most of the AIDS diagnoses occurred because of a prior history of severe immunosuppression (nadir CD4 $\leq$ 200), which then led to their being prescribed modern and effective antiretroviral treatments. This, then, was a relatively healthy HIV+ cohort from the point of view of the proportion of individuals with a history of symptomatic disease. Compared to a large U.S. HIV+ cohort having almost identical rates of AIDS-defining illness (Heaton *et al*, 1995), the current NP methodology (i.e., GDS approach) yielded very similar rates of HIV-associated NP impairment (34.2% in our monoinfected HIV+ group, versus 31.6% in the U.S. group).

As in studies conducted in Western countries (Letendre *et al*, 2004; Cysique *et al*, 2006; Tozzi *et al*, 2007), we found that in a mixed group of untreated and HAART-treated HIV+ participants, nadir CD4 was associated with NP impairment, whereas current CD4 and plasma HIV RNA were not. This cumulative evidence suggests that in the HAART era, brain injury is relatively independent of current immune status and plasma viral load, whereas NP impairment is associated with past histories of more severe immunosuppression. The fact that we were able to replicate this finding in a very different setting from where these results were initially demonstrated gives further weight to the importance of historical (versus current) measures of disease status in predicting NP outcomes in the HAART era.

We were able to detect a modest rate of NP impairment among asymptomatic or mildly symptomatic HIV+ participants, whereas the five country study by Maj *et al* (1994) found impairment mostly in their symptomatic groups. This difference may be due to differences in ascertainment methods (e.g., different definitions of NP impairment; use of

demographically corrected norms). In the United States, a number of studies have found increased rates of NP impairment in asymptomatic HIV+ groups. In a review of the latter studies, White *et al* (1995) reported a median of 31% NP impairment prevalence among medically asymptomatic HIV+ groups; this is consistent with the 29% prevalence rate that we observed in the non-AIDS FPDs in China.

Many published reports from Western cohorts have analyzed NP data in mixed cohorts of treated and untreated volunteers (e.g., Sevigny *et al*, 2004). This mixture of potentially disparate groups may have accounted for the weakening of the associations between NP impairment and other biological indicators, such as HIV RNA levels, that have been observed in ''post-HAART'' cohorts. In addition, we found that treated HIV+ individuals in comparison to untreated HIV+ individuals were more likely to be globally impaired (45% versus 26%, $P < .005$) and, among those who are impaired, have worse performance (mean GDS 1.1 versus 0.82, $P = .02$). The possible explanations for this observation include that treated individuals were also more likely to have AIDS as compared to untreated individuals (75% versus 30%, $P < .001$) and that those treated with neurotoxic dideoxynucleoside reverse transcriptase inhibitors (dNRTIs) tended towards having worse global NP performance when compared to those who did not (mean Global Deficit Score 0.61 versus 0.36, $P = .07$).

In addition, the variability of regimens was restricted compared to HIV+ cohorts in Western studies. Only seven different antiretrovirals were reported, with 103 HIV+ participants reporting use of non-nucleoside reverse transcriptase inhibitors (NNRTIs; efavirenz, nevirapine) and 97 reporting use of dideoxynucleoside reverse transcriptase inhibitors (dNRTIs; stavudine and didanosine). Only four individuals reported use of a protease inhibitor (atazanavir [3], nelfinavir [1]). The most common regimen was stavudine-didanosine-nevirapine, reported by 69 HIV+ participants. Lastly, only 16% of treated individuals were on the most neuroeffective regimen (CPE ≥ 2; see Letendre *et al.*, 2008, for additional details on this cut-off) precluding further analysis.

Our screening for HCV infection in this study found a high prevalence of such infection among FPDs. Unlike the situation with HIV infection, however, being HCV+ was not related to the number of reported former plasma donations (12.3 ± 24.1 for uninfected group versus 16.2 ± 24.5 for HCV-monoinfected group; $P = .33$). The reason for this is unclear. Although we cannot be certain that HCV infection occurred in the same manner as HIV infection (i.e., in the course of plasma donations), two recent surveys in Shanxi province suggest that prior blood donation was a major source of both types of infection (Qian *et al*, 2005, 2006). Specifically, the latter authors found that (1) HCV seroprevalence was 27.7% among FPDs in Shanxi, versus only 2.5% in non-FPDs; and (2) coinfection with HCV was seen in the large majority (85%) of HIV-infected participants.

We found a small to medium NP effect size among HCV-monoinfected individuals in Anhui. This too is in agreement with the current literature in the United States, which has demonstrated mild neurocognitive impairment in about 30% of HCV+ individuals with mild liver disease, independently of substance use and other comorbid factors such as depression and fatigue (Forton *et al*, 2004). Importantly, in our study the combination of AIDS and HCV was associated with the highest rate of NP impairment (i.e., 50%). This evidence of additive HIV/HCV effects is in accordance with reports in the United States, which have shown worse neurocognitive deficits in coinfected individuals as compared to both HIV and HCV monoinfection individuals (Ryan *et al*, 2004; Cherner *et al*, 2005). However, in the latter U.S. studies, HCV infection was associated with histories of comorbid methamphetamine use disorders, whereas HIV infection was not. The current findings are more clearly interpretable in the absence of drug abuse comorbidity.

In reliably detecting an HCV effect on NP performance, we nevertheless found that the pattern of NP impairment was different in several ways from HAND. Specifically, it appeared that individuals with HCV monoinfection were less likely to show deficits on tests of processing speed, attention/working memory, and verbal fluency. This should be interpreted with caution, however, given the rather small size of the HCV mono-infected group in the current study ($n = 51$). Additional research with larger HCV-monoinfected samples is needed to better establish the prevalence and nature of NP impairments associated with HCV infection among Chinese FPDs. Such research also should examine whether NP impairment is related to active HCV viral replication and/or indices of liver disease, as such findings could have relevance to future clinical care (medical screening, and establishing treatment priorities) within this population.

Our HIV+ cohort in Anhui had lower rates of psychiatric comorbidity than is typically seen in HIV+ groups in Western countries (less current and lifetime substance use disorders and MDD; Atkinson *et al*, 2008; Bing *et al*, 2001). Regarding substance use, lifetime alcohol use disorders were not associated with higher rate of NP impairment. Less than 2% of both the overall cohort met criteria for current MDD. Although a somewhat higher prevalence of prior lifetime MDD was seen among HIV-monoinfected and coinfected participants (14% versus 5.0% for controls), this too was lower than what has been reported in U.S. HIV+ cohorts (about 30%) and was unrelated to NP impairment. Similar to what is seen in Western countries, our Chinese

HIV+ groups had a modest increase in depressed mood (BDI-II). The size of the association between current depressive symptoms and NP functioning, however, was clinically trivial (shared variance of less than 3%). This is consistent with similar cross-sectional and longitudinal findings from the United States (Goggin *et al*, 1997; Carter *et al*, 2003; Cysique *et al*, 2007a), and argues against the possibility that depression occurring in the context of HIV infection is *causing* the NP impairment. Indeed, the opposite may be the case: some increase in depressed mood may occur in response to awareness of reduced neurocognitive functioning.

As expected, we found associations between NP impairment and self reports of cognitive complaints as well as decrease independence in IADLs. This finding is in agreement with what has been reported in U.S. cohorts (Heaton *et al*, 2004a), and demonstrates that NP impairment has negative effects on daily functioning, even in a nonurban context were most individuals are farmers. The increased cognitive complaints in HIV+ individuals may reflect the fact that these individuals were at least partially aware that some cognitive difficulties could be related to their HIV infection. However, it should be noted that individuals with HCV at the time of testing were not aware of their HCV status. With this in mind, we observed that NP-impaired coinfected individuals reported the worst rates of decline in everyday functioning, as well as more cognitive complaints suggesting an additive effect of the illness.

Lastly, although a repeated finding in the United States is that HIV-related NP impairment has been associated with reduced employment (Heaton *et al*, 1994, 2004a), this was not seen in the current Chinese cohort. Despite the fact that the NP-impaired FPDs tended to be aware of having some cognitive difficulties, they remained active in their work duties. Possible explanations for these different employment outcomes between the United States and rural China include (1) cognitive impairment may have less impact on farming activities in China than on urban jobs in the United States; (2) our Chinese participants were mostly self-employed, whereas NP-impaired people in the United States are more likely to be identified by supervisors as having problems; and (3) disability income is more readily available in the United States, whereas in rural China there is a greater need to keep working.

In summary, we find that the prevalence of HAND in a cohort of Chinese participants infected through plasma donation is comparable to prevalence of HAND reported in Western settings. These data underscore that neurocognitive ascertainment methods validated for HIV research in the West can be used in international settings if care is taken to assure their cultural appropriateness, examiners are properly trained, and suitable comparison groups are used. More broadly, the results indicate that HAND is likely to be a substantial problem in the developing world, emphasizing the importance of its early detection and continued efforts to develop treatments that target the CNS effects of HIV.

Methods

This report concerns baseline findings of a 5-year longitudinal project to examine neurobehavioral effects of HIV infection in China. The study was approved by the Institutional Review Boards (IRBs) from the China Center for Disease Control (CDC)/ National Center for AIDS (NCAIDS), as well as the Peking University and the University of California at San Diego (UCSD).

Participants

In December 2005, trained study recruiters in the Fuyang city CDC in Anhui province started the screening of FDPs for the current study. All participants received the HIV Quick Test (OraSure Technologies, Bethlehem, PA) to confirm their HIV status before enrollment. By June 2006, 198 HIV − and 203 HIV+ individuals had been enrolled. Written informed consent was obtained from the participants after the research procedure had been fully explained to them. Participants were reimbursed 80 Chinese Yuan ($10–11) for their time. All participants shared the infection risk of being FDPs and only one participant in the HIV+ group reported homosexual contact as an additional risk factor. Individuals with a known history of non–HIV-related neuromedical factors that might potentially cause impairment of neurocognitive function were excluded from the study. These exclusion criteria consisted of head injury with unconsciousness greater than 30 minutes, and any known, non–HIV-related neurological disorders (e.g., epilepsy, stroke), psychotic disorders (schizophrenia and bipolar disorder), and potentially significant levels of current substance use, defined as more than two alcoholic drinks per day over the past 30 days, or use of any illegal drugs in the past 30 days. Infection with the hepatitis C virus (HCV) was assessed using HCV antibody testing of study blood samples, but was not an exclusion criterion because (a) participants were not aware of their HCV serostatus, and (b) relationship between HCV and NP impairment in China was unknown.

Procedure

In addition to providing demographic and medical history information, every participant underwent comprehensive neurocognitive and neuromedical evaluations, and a structured psychiatric examination, as well as an assessment of daily functioning. This report focuses on the neurocognitive results and their relation to traditional HIV biomarkers,

HCV seropositivity, depression, lifetime histories of substance use disorders, and self-reports of increased difficulties in everyday functioning.

In order to ensure standardization of all test administration, examiners (physicians and nurses from an Anhui local psychiatric hospital) had 2 weeks of training done by a previously trained and certified Chinese psychiatrist (C.S.) and a team from the United States (R.K.H., H.J., D.F.). There were separate training teams for the neurobehavioral, neuromedical, and psychiatric modules of the battery, with at least one bilingual member on each training team to facilitate discussion. During the 2-week training session in Beijing, each test, examination, or interview was demonstrated, and its purpose and administration nuances were discussed. Several rounds of ''mock testing'' were conducted. Certification sessions subsequently took place using staff or patient volunteers from the hospital as test subjects. All certifications were done in Chinese.

Quality assurance reviews were conducted on test forms on the first 40 visits from Anhui, to ensure that drift had not occurred between training and study start. Copies of the entire battery were sent to the United States and reviewed for administration and scoring accuracy, form completion, and overall quality of data. All queries and data changes were sent to the China team for correction of the raw data as well as correction of the data entry. After the first 40 visits, 15% of all visits were similarly reviewed. As before, all queries and data changes were made to both the raw data and the database.

Details of the NP battery selection and adaptation for use in China are provided in Cysique *et al* (2007b). The NP battery in Mandarin was administered by trained examiners in the local Fuyang dialect, which uses the same written form as the Mandarin, but sometimes is pronounced differently. The NP test battery was composed of 18 individual NP measures, which assessed 7 ability areas that have been found to be affected by HAND in Western countries (see Table 3 for listing). This battery includes tests widely used to study HIV infection in the United States (Carey *et al*, 2004; Woods *et al*, 2004), Europe (Tozzi *et al*, 2007), Australia (Cysique *et al*, 2006), and in multinational studies (Maj *et al*, 1994).

To explore the clinical significance of any NP impairment, we assessed cognitive complaints, degree of independence in activities of daily living, and employment status using Chinese translations of standard English instruments. Subjective neurocognitive complaints were assessed using the patient's assessment of own functioning inventory (PAOFI; Chelune *et al*, 1986). The PAOFI includes 33 items on which participants rate themselves as having or not having neurobehavioral difficulties in their everyday lives, using a 6-point scale: almost never, very infrequently, once in a while, fairly often, very often, and almost always, in domains of memory, language and communication, sensory-perceptual and motor skills, and higher level cognitive functions. The score used is the sum of items on which the participants reported experiencing difficulties as either ''fairly often,'' ''very often,'' or ''almost always'' (Chelune *et al*, 1986). Employment status was derived from the extended demographic interview, which collected information on whether the participant is currently working, as well as type of employment, and income. The modified version of the Lawton and Brody IADL scale was used to assess independence in activities of daily living (Heaton *et al*, 2004a).

In order to assess for major depressive disorder (MDD) and substance use disorders, participants were administered those modules of the Chinese version of the World Mental Health Composite International Diagnostic Interview (WMH-CIDI; Kessler and Ustun, 2004). This lay-administered and fully structured instrument yields diagnoses consistent with those derived by clinician interviewers using the Structured Clinical Interview for DSM-IV (First *et al*, 1996; Kessler *et al*, 2004). Participants also completed the Beck Depression Inventory-II (BDI-II; Beck *et al*, 1996a,b). The BDI-II is a 21-item self-report measure that rates severity of depressive symptoms during the past week, addressing somatic (e.g., weight loss, fatigue) and nonsomatic (e.g., suicidal ideation, feelings of guilt) depressive symptoms—higher scores indicate greater depressive symptomatology.

Data analysis

In order to classify NP impairment in individual participants, we developed demographically corrected norms on the NP tests using data from individuals free of HIV as well as hepatitis C infection ($N = 141$). Preliminary analyses revealed that HCV+ status was associated with NP impairment in this cohort. Statistical methods used to develop demographically corrected norms are detailed in Heaton *et al* (2004b), and include the following steps: First, raw scores on the individual tests were placed on a common metric (normally distributed scaled scores, which have a mean of 10 and a standard deviation of 3 in the Chinese normative group). The scaled scores were then converted into T-scores: the demographic data (age, education, and gender) were used to generate fractional polynomial regression equations to optimally predict the scaled scores. To determine the optimal fractional polynomial equation, the method of Royston and Altman (1994) was employed using the statistical package Stata (StataCorp, 2003). The residuals from optimal regression equations were then converted to T-scores with a mean of 50 and a standard deviation of 10.

In addition to computing mean *T*-scores for each NP test measure, a global mean *T* and mean *T*-scores

for the seven ability domains were computed (see listing in Table 3). Also, the Global Deficit Score (GDS) method was used for classification of overall impairment status on the battery (see Carey *et al*, 2004, and Heaton *et al*, 2004b, for detailed description). Briefly, demographically corrected T-scores were converted to deficit scores according to the following criteria: $T > 39 = 0$ (normal); $39 \geq T \geq 35 = 1$ (mild impairment); $34 \geq T \geq 30 = 2$ (mild to moderate impairment); $29 \geq T \geq 25 = 3$ (moderate impairment); $24 \geq T \geq 20 = 4$ (moderate to severe impairment); $T < 20 = 5$ (severe impairment). Deficit scores were summed across the test battery and then divided by the number of individual measures to compute the GDS. The GDS can be analyzed as a continuous variable indicating number and severity of neurobehavioral deficits across the entire test battery, or as a cut-off of ≥ 0.50 that can be used to classify overall NP impairment (Carey *et al*, 2004; Heaton *et al*, 2004b). Comparisons between groups were made using chi-square tests, Fisher's exact tests, *t* tests, and analyses of variance (ANOVAs) as appropriate. To infer meaningful effects of relevant variables, Cohen's d effect sizes also were computed for group comparisons.

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