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Short Communication

Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection—The Hawaii Aging with HIV Cohort

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Low CD4 lymphocyte count was a marker for neurological disease in human immunodeficiency virus type 1 (HIV-1); but is now less common among patients with access to highly active antiretroviral therapy. In this study, the authors determine the reliability of self-reported CD4 nadir and its predictive value for neurological status. The authors identify a high degree of reliability ($r = .90$). After adjusting for age, current CD4 count, and duration of HIV-1, CD4 nadir relates to a current diagnosis of HIV-associated dimentia (HAD) (odds ratio [OR]: 1.395 (1.106–1.761), $P = .005$) and distal symmetric polyneuropathy (DSPN) (OR: 1.479 (1.221–1.769, $P < .001$). *Journal of NeuroVirology* (2006) **12,** 387–391.

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Introduction

The relationship between low absolute CD4 lymphocyte count and neurological complications is well established in the era preceding highly active antiretroviral therapy (HAART) (Childs *et al*, 1999). Individuals with CD4 lymphocyte counts below 200 cells/mm^3 were considered highly vulnerable to neurological complications associated with infection, and the risk increased with further reductions in CD4 lymphocyte count (Chiesi *et al*, 1996). The specific neuropathological processes underlying this relationship are not well understood; although immune compromise may facilitate viral entry and damage to the brain (Brew 2004). Markers of immune activation, including monocyte chemoattractant protein (MCP)-1, tumor necrosis factor (TNF)-α, and cell surface markers have consistently related to neurological complications (Kusdra *et al*, 2002; McArthur *et al*, 2005). Immune activation in the central nervous system, as indicated by the presence of encephalopathy at autopsy, persists among demented patients in the HAART era (Masliah *et al*, 2000).

Marked immune compromise, as evidenced by a low CD4 lymphocyte count, is now less frequently encountered among individuals with access to HAART, because most guidelines recommend treatment for individuals with CD4 lymphocyte counts below 200 cells/mm^3 and consideration for starting treatment if the CD4 lymphocyte count is less than 350 cells/mm^3 (AIDSinfo.nih.gov). Unfortunately, the prevalence of human immunodeficiency virus (HIV)-1–associated dementia (HAD)

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has not improved since the introduction of HAART, despite a drop in HAD incidence (Sacktor *et al*, 2002). Furthermore, the CD4 lymphocyte count among patients diagnosed with HAD appears to be higher than that reported in the pre-HAART era (Brew, 2004). This latter finding suggests a change in the relationship between current CD4 lymphocyte count and neurological status, with current CD4 lymphocyte count representing a less useful clinical biomarker of neurological disease status.

It is possible that a period of past severe immune compromise contributes to HIV-1 neuropathogenesis and may partially explain the currently observed stagnant rates of HAD prevalence. The lowest ever CD4 lymphocyte count, the CD4 nadir, may serve as an important marker of such past disease severity. The utility of such a marker will be highly dependent upon the validity of self-report, because many physicians do not have ready access to a comprehensive listing of patients' past laboratory values. There is reason to question the validity of such a report in a population prone to cognitive deficits. However, because the timing of the CD4 nadir may also relate to a memorable medical event, such as the development and treatment of an opportunistic infection or to the initiation of HAART, patients may have reasonable recall of this number.

In this analysis, we first examined the validity of self-reported CD4 nadir in relation to documented medical records. We then determined the risk of HIV-1–related cognitive impairment and neuropathy that is attributable to the lowest CD4 count ever attained.

Results

We completed the analysis on the 266 cases enrolled before July 1, 2005, of which 41 participants (15%) were not able to provide a self-report of CD4 nadir lymphocyte count. Compared to others in the cohort, individuals who did provide these data had a shorter self-reported duration of HIV-1 infection (Table 1).

We then sought to validate the self-reported CD4 nadir by comparing it to that identified in historical records among individuals where at least one historical CD4 lymphocyte count record existed. Because historical reports were often incomplete, we completed this evaluation only among the participants where at least one historical measure of CD4 lymphocyte count existed within plus or minus 1 year from when the participant felt the CD4 nadir had occurred. This resulted in a spearman coefficient of .90 ($n = 53$, $P < .001$) (Figure 1).

To determine the predictive capacity of CD4 nadir for neurological diagnoses upon entry into the cohort, we performed logistic regression analyses. CD4 nadir count was significantly related to all neurological diagnostic outcomes (Table 2). Specifically, a decrease of 100 cells/mm^3 results in an increased risk for HAD with an odds ratio of 1.395 (1.106–1.761, $P = .005$). In a multivariate logistic regression analysis, age, educational attainment, current CD4 lymphocyte count, and the self-reported duration of HIV-1 infection did not contribute to the HAD model. Similarly, when determining the predictive capacity of CD4 nadir for MCMD, and excluding individuals with HAD, age, educational attainment, current CD4 lymphocyte count, and the self-reported duration of HIV-1 infection did not contribute to the model. The unadjusted odds ratio for minor cognitive motor disorder (MCMD) was 1.273 (1.090–1.488, $P = .0023$).

Table 1 Demographic and medical parameters by ability to provide self-reported data regarding CD4 nadir

Characteristics	*Participants without self-reports*	*Participants with self-reports*	P
Sample size	41	225	
Mean age (years) (SD)	44.6 (12.5)	46.0 (10.9)	0.504
Mean education (years) (SD)	13.8 (2.2)	14.0 (2.3)	0.565
% Female	17%	15%	0.692
Ethnicity			0.064
% API	37%	28%	
% Caucasian	44%	60%	
% Hispanic	17%	5%	
% in older group	57%	54%	0.702
HIV infection parameters			
On HAART at entry	63%	74%	0.268
Mean entry CD4 count (SD)	504 (279)	448 (241)	0.235
% undetectable viral load	51%	48%	0.666
Mean years infected (SD)	7.0 (5.5)	10.2 (5.9)	0.001
% meeting HAD criteria	16%	19%	0.579
% with DSPN	39%	54%	0.0964
% with Symptomatic DSPN	21%	30%	0.224

API = Asian Pacific Islander.

For neuropathy outcomes, and considering age, current CD4 lymphocyte count, and duration of HIV-1 infection, only age at entry contributed to the models. The age-adjusted odds ratios for DSPN and symptomatic DSPN were 1.479 (1.221–1.791, $P < .001$) and 1.856 (1.422–2.421, $P < .001$), respectively.

Discussion

The Hawaii Aging with HIV Cohort is a unique longitudinal cohort study enriched with older individuals and aiming to identify relevant risk factors for this population in the era of HAART. In this analysis, we identify CD4 nadir as a risk for HAD and identify odds ratios for a 100 cells/mm^3 decrease in CD4 nadir regarding both cognitive and neurological outcomes. These findings are consistent with published work by Tozzi *et al*, identifying older age and CD4 nadir as risk factors for prevalent neurocognitive impairment in an Italian cohort (Tozzi *et al*, 2005). We had previously published that CD4 nadir is related to neuropathy in our cohort (Watters *et al*, 2004) and herein present

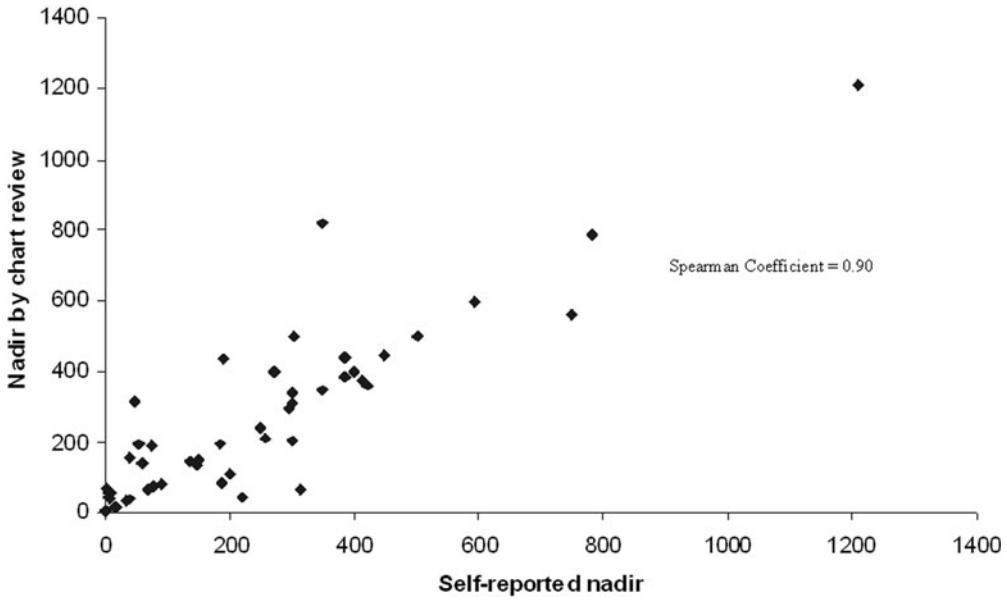

Figure 1 Self-reported CD4 nadir plotted against lowest CD4 count from historical data.

the odds ratios for neuropathy (regardless of symptoms) and symptomatic neuropathy. A relationship between nadir CD4 of less than 50 cells/mm^3 and neuropathy was also identified in the HIV Outpatient Study Cohort (HOPS) (Lichtenstein *et al*, 2005). Furthermore, low CD4 nadir is a risk factor for HIV-1–related lipodystrophy (Mauss *et al*, 2002) and HIV-1 disease progression in general (Miller *et al*, 1999).

We conclude that whereas the relationship between immune function and HIV-1-related neurological disease appears to be absent among individuals with access to HAART, past severity of immune compromise appears to be relevant. Some have speculated that HIV-1 results in irreparable harm to immune function, despite HAART (D'Amico *et al*, 2005). It is plausible that such immune compromise may also have damaged the brain and may now contribute to HAD risk. It is also possible that the immune system remains impaired despite immune reconstitution (elevated CD4 counts), thus increasing risk for neurological damage. Because our analysis was based on entry visits into the cohort, it is also possible that these individuals were cognitively impaired when the CD4 count was low and never recovered their cognitive deficits. Any of these scenarios would contribute to the stagnant prevalence of HAD in the current era. Although this marker's utility may wane over time because fewer patients are anticipated to have very low CD4 nadirs where HAART is available, it is also possible that CD4 nadir will remain an important factor among older individuals who are more likely to present with advanced disease (el-Sadr and Gettler, 1995). Concerns relating to CNS penetration of commonly used regimens (Ellis *et al*, 2002), rates of adherence to antiretrovirals, an aging HIV population, and the potential long-term consequences of HAART may dampen this enthusiasm as well.

Notably, the relationship between past low CD4 count and neurological outcomes did not appear to be due to incomplete immune recovery nor duration of HIV-1 infection as neither contributed to our multivariate models. We are not able to determine if duration of low CD4 count contributed to the effect identified between neurological function and past immunological compromise; although it is reasonable to speculate that this may occur. Interestingly, age did not appear to significantly affect the relationship between CD4 nadir and cognitive outcomes in this cohort.

Table 2 Odds ratios for diagnostic outcomes at entry into the study attributable to CD4 nadir

Diagnostic outcome	*Unadjusted OR per 100 CD4 cells*	P *value*	*Age adjusted OR per 100 CD4 cells*	P *value*
HAD	1.395 (1.106–1.761)	.005	—*	—*
MCMD	1.273 (1.090–1.488)	.002	—*	—*
DSPN	1.482 (1.241–1.769)	<.001	1.479 (1.221–1.791)	<.001
SxDSPN	1.773 (1.393–2.257)	<.001	1.856 (1.422–2.421)	<.001

*Age did not contribute to the HAD and MCMD models; thus, adjusted models for OR are not provided. Duration of infection and CD4 lymphocyte count at study entry did not contribute to any model and are therefore not included in adjustment.

It is reassuring that reliability of self-reported CD4 nadir is high. Few individuals were not able to provide this information. A longer duration of illness predicted those individuals who recalled their CD4 nadirs. Cognitive status did not appear to be a factor in ability to recall this event, although individuals with dementia in this cohort typically had mild disease (Memorial Sloan Ketering [MSK] of 1). We conclude that it is possible to use such self-report in clinical practice with reasonable assurance that it reflects actual historical data.

In summary, HIV-1–infected individuals appear to provide reliable reports of the lowest CD4 count ever attained. Furthermore, this CD4 nadir is a risk factor for prevalent dementia, MCMD, neuropathy, and symptomatic neuropathy in this cohort that is enriched with older individuals. These effects are independent of current CD4 count and duration of infection.

Methods

Population studied

The Hawaii Aging with HIV Cohort began enrollment in 2001 aiming to understand the fundamental neuroepidemiology of aging with HIV-1 infection. Between October 22, 2001, and July 1, 2005, 141 older (50 or more years old) and 125 younger (less than 40 years old) HIV-1–infected individuals were enrolled and completed at least one cognitive and neurological evaluation within the cohort. All individuals were living in Hawaii at the time of enrollment; although most (64%) grew up on the continental United States. Broad community based recruitment efforts resulted in the constitution of the cohort roughly matching that reported to the Hawaii Department of Health regarding distribution by island, gender, and ethnicity (Hawaii Department of Health, 2005).

Definition of dementia and neuropathy

Clinical characterization of the cohort has been described elsewhere (Valcour *et al*, 2004; Watters *et al*, 2004). Briefly, HIV-1–infected individuals are eligible for enrollment if they speak English as their main language of communication and do not meet major exclusion criteria, including traumatic brain injury, central nervous system opportunistic infection, learning disability, and major neurological or psychiatric illness, such as schizophrenia, bipolar disease, or major stroke. Annual evaluations include an HIV screening neurological examination for cognitive/motor signs and for neuropathy, neuropsychological assessment, and medical histories. All cases are reviewed in a case conference in collaboration with Johns Hopkins University where consensus diagnoses of minor cognitive motor disorder (MCMD) or HAD are assigned using the American Academy of Neurology 1991 criteria (Working Group of the American Academy of Neurology AIDS Task Force, 1991). For the purpose of this analysis, individuals with subtle neuropsychological testing abnormalities that are insufficient to meet MCMD or HAD diagnosis and individuals with larger neuropsychological testing deficits but with an absence of any functional decline were combined with the normal group. We assessed function using self-administered questionnaires to estimate activities of daily living and instrumental activities of daily living, an interview to determine work function, and with the Medical Outcomes Survey. The examining physician further determines functional symptoms and limitations in a structured interview associated with the macroneurological examination.

The neuropathy evaluation encompasses a standard assessment of sensation to cotton, pin, and vibration in the upper and lower extremities in conjunction with an evaluation of ankle reflexes. To meet criteria for neuropathy, individuals must have diminished or absent ankle reflexes, when compared to that at the knees, and a diminution of sensation to cotton, pin, or vibration at the distal portion of bilateral lower extremities. Symptomatic neuropathy (SxDSPN) further requires that the examination findings are accompanied by at least one of the following symptoms: numbness, tingling, burning, pain, or hypersensitivity involving both feet.

CD4 lymphocyte nadir

At the time of entry into the study, individuals are asked to report the date and number of their lowest ever CD4 lymphocyte count. Participants further rate whether they felt the number had good or poor reliability. We then acquired historical laboratory data from primary care physician charts as well as other research protocols within the Hawaii AIDS Clinical Research Program and the Hawaii Seropositivity and Medical Management Program (HSPAMM) of the Hawaii Department of Health. The later dataset has been in operation since 1989 and monitors HIV-1 laboratory parameters, among other factors, every 6 months (Chow *et al*, 2003). It is estimated that nearly 2/3 of Hawaii Aging with HIV Cohort members are also enrolled in the HSPAMM Program. In some cases, no historical data were available.

Statistical analysis and administrative considerations

All patients signed institutional review board (IRB)-approved study consent forms and release of information forms, when indicated, for historical data. Statistical analyses were carried out on SAS 9.1 (SAS Institute, Cary, North Carolina). We estimated the reliability of self-reported nadir as the Spearman correlation between self-reported and chart-review derived nadir values for each member (PROC CORR). We tested the hypothesized association of self-reported nadir to neurological outcomes in logistic regression models (PROC LOGISTIC). Age was treated as a continuous variable even though enrollees were either less than 40 years old or over 49 years old.

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