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## CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy

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### Abstract

**Objective**—Despite immune recovery in individuals on combination antiretroviral therapy (CART), the frequency of HIV-associated neurocognitive disorders (HANDs) remains high. Immune recovery is typically achieved after initiation of ART from the nadir, or the lowest historical CD4. The present study evaluated the probability of neuropsychological impairment (NPI) and HAND as a function of CD4 nadir in an HIV-positive cohort.

**Methods**—One thousand five hundred and twenty-five HIV-positive participants enrolled in CNS HIV Antiretroviral Therapy Effects Research, a multisite, observational study that completed comprehensive neurobehavioral and neuromedical evaluations, including a neurocognitive test battery covering seven cognitive domains. Among impaired individuals, HAND was diagnosed if NPI could not be attributed to comorbidities. CD4 nadir was obtained by self-report or observation. Potential modifiers of the relationship between CD4 nadir and HAND, including demographic and HIV disease characteristics, were assessed in univariate and multivariate analyses.

**Results**—The median CD4 nadir (cells/ $\mu$ l) was 172, and 52% had NPI. Among impaired participants, 603 (75%) had HAND. Higher CD4 nadirs were associated with lower odds of NPI such that for every 5-unit increase in square-root CD4 nadir, the odds of NPI were reduced by 10%. In 589 virally suppressed participants on ART, higher CD4 nadir was associated with lower odds of NPI after adjusting for demographic and clinical factors.

**Conclusion**—As the risk of NPI was lowest in patients whose CD4 cell count was never allowed to fall to low levels before CART initiation, our findings suggest that initiation of CART as early as possible might reduce the risk of developing HAND, the most common source of NPI among HIV-infected individuals.

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#### Conflicts of Interest

The views expressed in this article are those of the authors and do not reflect the official policy or position of the US Government.

## Keywords

CD4 nadir; combination antiretroviral therapy; HIV-associated; neurocognitive disorders; neurocognitive impairment

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## Introduction

Antiretroviral therapy (ART) often leads to substantial immune recovery in HIV-infected individuals, with the current CD4 cell count being much higher than the historical lowest or CD4 nadir. HIV-associated neurocognitive disorders (HANDs) persist in many patients despite good immune recovery. HAND is associated with unemployment, disability, reduced antiretroviral (ARV) adherence and increased mortality after adjusting for other risks. Recently revised US antiretroviral treatment guidelines recommend combination antiretroviral therapy (CART) initiation for individuals with CD4 cell count less than 350 cells/ $\mu$ l, encourage initiation for those with CD4 cell count between 350 and 500 cells/ $\mu$ l and give providers the option to treat when the CD4 cell count is above 500 cells/ $\mu$ l. Although multiple prior studies have suggested that neurocognitive impairment tracks with nadir, rather than current CD4 cell count, these studies were small and therefore of limited generalizability, or were done in cohorts with limited neurocognitive and medical assessments, such that confounding factors could not be carefully evaluated [1-3]. In the present study, we evaluated the relationship between neurocognitive impairment and CD4 nadir in a large, prospective, multicenter US cohort that incorporated comprehensive neurocognitive and medical assessments and utilized a recently published consensus definition of HAND.

## Methods

### Study design and participants

Participants were one thousand five hundred twenty-five HIV-positive individuals enrolled in CNS HIV Antiretroviral Therapy Effects Research (CHARTER), a multisite, prospective, observational study. Enrollment criteria were inclusive and excluded only those with active opportunistic disease, severe and untreated psychiatric disorders, or who were otherwise unable to complete the comprehensive study evaluations. Written informed consent was obtained from all study participants and the study was approved by Human Subjects Protection Committees at each of the participating institutions.

### Clinical evaluations

The comprehensive neuropsychological evaluation tested seven cognitive domains. More detailed descriptions of the neuropsychological battery can be found in Heaton *et al.* [4]. Neuropsychological impairment (NPI) was defined as impaired performance (at least 1 SD below demographically adjusted normative scores) in two of the seven cognitive domains. Additional assessments included a thorough neuromedical history, structured psychiatric interviews for detecting substance use disorders and affective disorders, physical and neurological examinations, and targeted laboratory evaluations. Assessments were performed by clinicians trained and certified according to a centralized protocol. Comorbid conditions were evaluated by a single experienced neuropsychological rater and HAND was diagnosed by published criteria [5].

HIV infection was diagnosed by immunoassay with western blot confirmation. Current CD4 T lymphocyte counts (cells/ $\mu$ l) were determined by flow cytometry, Rapid plasma reagin and hepatitis C virus antibody status were assessed at each site by a medical center

laboratory certified by Clinical Laboratory Improvement Amendments (CLIA), or CLIA equivalent. HIV RNA levels were measured centrally in plasma by reverse transcriptase PCR (Roche Amplicor, v. 1.5, lower limit of quantitation 50 copies/ml). CD4 nadir was obtained by self-report, with confirmation by documented prior measurements in a subset of individuals. Date of nadir and date of first exposure to ART were also obtained by self-report.

### Statistical analyses

Univariate and multivariate associations between predictors and NPI were assessed by logistic regression. CD4 nadir was square-root transformed to normalize its distribution for analysis. Chi-squared tests were used to assess group differences for categorical variables. The *t*-tests were used to assess group differences for continuous variables. Nonparametric tests were used for nonnormally distributed variables.

### Results

Seven hundred and ninety-nine patients (52%) met the criteria for global NPI, and 603 of these (75%, or 39% of the total) were diagnostically classified as having NPI due to HIV (HAND). Overall, 39% of the cohort was diagnosed with HAND. As shown in Table 1, neuropsychological impaired patients had significantly lower CD4 nadir (median 155 vs. 187,  $P = 0.002$ ) and were more likely to be taking CART compared with unimpaired individuals (75 vs. 67%,  $P = 0.0007$ ). The impaired and unimpaired groups were similar on all other variables, including demographics, current plasma viral load and CD4 cell count, and hepatitis C serostatus. Figure 1 shows that the probability of NPI decreased linearly in relation to the square root of CD4 nadir; for every 5-unit increase in square-root CD4 nadir, the odds of NPI were reduced by 10%. This relationship was monotonic across the range of nadirs, with no suggestion of an informative threshold. In a multivariate regression adjusting for demographic factors, virologic control, comorbidity classification and duration of infection, higher CD4 nadir remained significantly associated with a lower probability of NPI. There was no significant difference in rates of ACTG 4-day adherence to ART between the impaired and unimpaired groups. Among those diagnosed with HAND ( $n = 603$ ), 428 (71%) had ANI, 148 (25%) had MND and 27 (4%) had HAD. Individuals with no NPI ( $n = 726$ ) had significantly higher median CD4 nadir than those with HAD [187 (interquartile range [IQR] 58–324) vs. 77 (IQR 18–167), respectively;  $P = 0.01$ ]. Median CD4 nadir for those with ANI [161 (IQR 37–282)] and MND [163 (IQR 52–285)] were not significantly different from those with no NPI, or from each other.

Because self-reported CD4 nadir is subject to bias, and is most clinically relevant when plasma virologic suppression has been achieved, we conducted follow-up analyses to test the robustness of our findings in selected sub-groups. These included individuals whose self-reported nadir was verified by documented laboratory measurements, those who had achieved virologic suppression in plasma and those whose nadir could be confirmed as occurring prior to ART initiation.

To validate self-reported CD4 nadir, we examined a subset of individuals who were followed longitudinally and who began the study reporting a nadir at least as high as the measured CD4 cell count at their first study visit. We then compared the nadir reported at the most recent visit with the CD4 cell count measured previously. In this subset, the difference between self-reported nadir and actual nadir was small (mean difference 28.6, SD 21.7) and not statistically significant (paired *t*-test;  $P = 0.20$ ). Among the 1080 patients on CART, 589 (55%) had successful virologic suppression, defined as undetectable plasma viral load. In this subset, higher CD4 nadir was significantly associated with lower rates of NPI. Of these 589, 185 reported a nadir date that preceded their first exposure to CART,

with the remainder reporting either a nadir date after CART initiation, or an uncertain date of initiation or CD4 nadir. In the subgroup of 185, the relationship between CD4 nadir and prevalence of NPI trended toward significance [odds ratio (OR)= 0.96, 95% confidence interval (CI) 0.91–1.01;  $P = 0.09$ ].

## Discussion

We observed that HIV-infected individuals who never experienced low CD4 cell counts were relatively protected from NPI as compared with those with a history of severe immunosuppression. A regression analysis showed that the relationship between CD4 nadir and probability of impairment was continuous and monotonic across the range of nadirs in the cohort, without the evidence of an informative threshold or cutoff. To evaluate the robustness of the relationship between CD4 nadir and NPI risk, we performed follow-up analyses exploring several potential clinically important modifiers. First, as CD4 nadir is most relevant in the setting of successful ART, wherein sustained CD4 rises are frequently seen, especially when virologic suppression is reached, we analyzed the subset of participants who had achieved undetectable plasma viral load on CART regimens. The CD4 nadir–NPI relationship remained significant in this subset. Second, because non-HIV-related determinants of cognitive performance such as head injury or developmental disability might influence the level of CD4 at which CART was initiated or patients' ability to adhere to their regimens, we performed follow-up analyses including only impaired patients meeting HAND criteria [5], which eliminated such confounding conditions. Again the CD4 nadir–NPI relationship remained significant in this subset. Similarly, the influence of nadir on NPI was significant in analyses adjusting for other covariates, such as ethnicity, sex and hepatitis C coinfection status.

The findings of this study have several limitations. First, we determined CD4 nadir by self-report, which is subject to recall bias. In fact, self-report is the usual method for assessing nadir in clinical practice. Previous studies have established the reliability and validity of self-reported CD4 cell counts in comparison with observed values [6,7]. However, to evaluate potential recall bias, we examined a subset of study participants followed longitudinally in whom the measured CD4 cell count at the baseline visit was in fact lower than their previously reported nadir. At subsequent visits, the nadirs recalled by such participants did not differ significantly, on average, from their actual measured nadirs, suggesting that self-report did not introduce a systematic bias, at least in this subgroup. Second, we were able to verify that the CD4 nadir was measured before the initiation of ART only in a subset of individuals ( $N = 185$ ), with the remainder having either an unknown date or a nadir after the initiation of ART. Third, although no threshold effects were seen over the range of CD4 nadirs in this cohort, the number of individuals on CART with nadirs above 500 cells/ $\mu$ l was small ( $n = 24$ ), yielding wide CIs for the estimation of neuropsychological risk associated with this nadir level. The small number of patients in this nadir range likely reflects previous treatment guidelines, which recommended treatment initiation only when CD4 cell counts fell under 350 cells/ $\mu$ l.

As this was an uncontrolled, observational study, certain factors might have confounded the association between nadir and NPI. For example, older participants or those with longer durations of HIV infection might have had lower nadirs and worse cognitive impairment than those who were younger or had shorter durations of HIV infection. To address this issue, we adjusted our models for age and estimated duration of HIV infection and found that nadir remained a significant predictor of NPI. Additionally, as participants with worse cognitive impairment might demonstrate poor ART adherence or be more likely to develop resistance, such individuals might have systematically lower nadirs. To address this limitation, we repeated our analyses with a subset of participants who demonstrated good

adherence and antiviral efficacy by virtue of having undetectable viral loads on CART. In this subset, CD4 nadir remained a significant predictor of NPI. As this was an observational study, we were not able to exclude other unmeasured differences between the impaired and unimpaired participants. The analysis presented here does not preclude other factors influencing impairment rates, such as the CNS penetration of the specific ARVs used. This issue has been addressed in a prior review based on the CHARTER cohort [8].

Because lower CD4 cell counts are an indication to start ART, but the optimal CD4 cell count for treatment initiation remains a subject of debate, our findings have important clinical implications. The depth of immune suppression reached, as indexed by the CD4 nadir, might represent an important HIV ‘legacy event’ that causes irreversible neural injury, contributing to HAND. If true, then preventing severe or even moderate immunosuppression by initiating ART as soon as possible might reduce subsequent HAND risk. Our data support recent revisions to treatment guidelines that recommend ART use in patients with CD4 cell count higher than 350 cells/ $\mu$ l and raise the question of ART use with CD4 cell count higher than 500 cells/ $\mu$ l. Our findings further emphasize the importance of identifying HIV-seropositive patients early in the course of their illness and encouraging ART use to prevent later complications.

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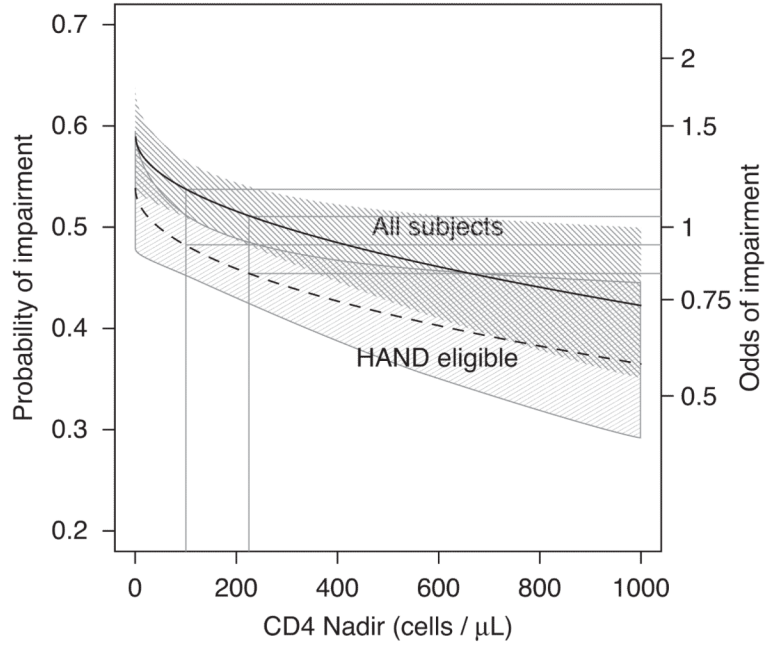
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**Fig. 1. Across the range of values observed in the cohort, higher CD4 nadirs were associated with lower risk of neuropsychological impairment such that for every 5-unit increase in square-root CD4 nadir, the odds of neuropsychological impairment was reduced by 10%**  
This was true for all individuals (solid curve) as well as for HAND-eligible patients (those without major confounding neurocognitive comorbidities; dashed curve) as illustrated by the perpendicular lines showing the odds of impairment at nadirs of 100 and 225 cells/μl for each of these groups. Shaded areas show the 95% confidence interval for the predicted probability/odds of impairment for the two groups. HAND, HIV-associated neurocognitive disorder.



**Table 1**  
**Demographic and clinical characteristics of the study participants**

	Total (n = 1525)	Impaired (n = 799)	Unimpaired (n = 726)	P
Age [years, mean (SD)]	43.2 (8.5)	43.5 (8.2)	42.8 (8.7)	0.11
Education [years, mean (SD)]	12.5 (2.5)	12.5 (2.5)	12.5 (2.6)	0.87
Male [n (%)]	1173 (77)	601 (75)	572 (79)	0.10
White [n (%)]	602 (39)	321 (40)	281 (39)	0.41
Current CD4 cell count [cells/ $\mu$ l, median (IQR)]	420 (262–603)	409 (251–607)	428 (267–602)	0.40
CD4 nadir [cells/ $\mu$ l, median (IQR)]	172 (48–297)	155 (37–277)	187 (58–324)	0.002
Time since CD4 nadir [years, median (IQR)]	2.2 (0.5–6.4)	2.2 (0.6–6.4)	2.3 (0.5–6.4)	0.97
Plasma VL <50copies/ml [n (%)]	895 (59)	460 (58)	435 (61)	0.42
Estimated duration HIV [months, median (IQR)]	120 (53–178)	121 (54–177)	120 (53–178)	0.76
CART status [n (%)]				0.007
Naive	229 (15)	106 (13)	123 (17)	
Past CART	216 (14)	97 (12)	119 (16)	
Current CART	1080 (71)	595 (75)	484 (67)	
HCV-positive	396 (26)	208 (26)	188 (26)	0.95

CART, combination antiretroviral therapy; HCV, hepatitis C virus; IQR, interquartile range; VL, viral load.