

Impact of Delayed HIV Diagnosis and Treatment on Dementia Risk in Later Life

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Background. Delayed HIV diagnosis and treatment may increase the risk of developing dementia later in life. We evaluated whether low CD4 count (<200 cells/μL) prior to first known use of antiretroviral therapy (ART)—a proxy for delayed HIV diagnosis or treatment—was associated with risk of age-associated dementia.

Methods. We conducted a retrospective cohort study (2000–2023) among U.S. adults with HIV aged ≥50 years, all on ART and dementia-free at baseline. The exposure of interest was low pre-ART CD4 count. Dementia diagnoses were identified via electronic health records. The association of low pre-ART CD4 with incident dementia was evaluated using Fine–Gray subdistribution hazard models, accounting for the competing risk of death and adjusting for sociodemographic and clinical confounders. Sub-analyses examined dementia risk among individuals who had low pre-ART CD4 but demonstrated CD4 recovery to ≥500 cells/μL after ART initiation.

Results. Among 21 354 people with HIV on ART (mean age 54; 87% men; 46% White, 23% Black, 21% Hispanic, 4% Asian), 30% had pre-ART CD4 < 200 cells/μL. Over a mean follow-up of 7 years, 618 were diagnosed with dementia. Low pre-ART CD4 was associated with greater risk of dementia (adjusted hazard ratio [aHR]: 1.33, 95% CI: 1.13–1.57). CD4 recovery with ART attenuated but did not eliminate dementia risk (aHR: 1.17, 95% CI: 0.85–1.60).

Conclusions. Low CD4 count prior to ART—reflecting delayed HIV diagnosis or treatment—was associated with higher dementia risk. Continuing assertive HIV screening and prompt ART initiation in the community will be important to support long-term cognitive health in people with HIV.

Keywords. aging; antiretroviral therapy; CD4 count; dementia; HIV.

As people with HIV live longer due to the success of antiretroviral therapy (ART), age-related cognitive decline has become an increasingly prominent concern in HIV care. Emerging evidence suggests that older adults with HIV are at higher risk for age-associated dementias [1–4]. This elevated risk persists even after accounting for dementia risk factors that are common in this population, such as cardiovascular disease, depression, and substance use [1–4]. One possible explanation is that untreated HIV infection during early stages results in lasting “legacy effects”

on the brain that are not fully reversed by ART [5, 6]. Supporting this hypothesis, neuroimaging studies have shown accelerated brain atrophy and cortical tissue loss in chronic HIV infection, particularly among individuals with low nadir CD4 counts—a marker of delayed HIV diagnosis or treatment initiation [7–10].

These concerns about cognitive aging build on a long-standing recognition that HIV can affect the brain. HIV enters the central nervous system during acute infection and is associated with a spectrum of cognitive impairments collectively known as HIV-associated neurocognitive disorders (HAND) [11]. While ART has substantially reduced the incidence of severe HAND, milder cognitive impairments remain common, even among individuals with well-controlled HIV [5, 6, 12]. These impairments are thought to result from multiple factors, including chronic immune activation, HIV-induced inflammation, comorbid conditions, and suboptimal ART penetration across the blood-brain barrier [6, 13]. In addition, prior studies have identified a distinct contribution of legacy effects—particularly low nadir CD4 counts—to increased risk of HAND [14–19].

However, much less is known about how early HIV-related immunosuppression may influence cognitive outcomes in older age. While some research suggests that cognitive decline in

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the ART era may be more strongly influenced by aging-related factors than by HIV itself [20], the potential contribution of legacy effects remains unclear. Notably, no prior study has examined the impact of pre-ART immunosuppression on risk of age-associated dementia. Therefore, a critical question remains: To what extent does dementia risk among older adults with HIV reflect the enduring impacts of prior immunosuppression versus the influence of aging and comorbidities?

In the current study, we address this question in a large cohort of adults with HIV by evaluating whether delayed HIV diagnosis or delayed ART initiation—as indicated by low pre-ART CD4 counts—is associated with increased dementia risk later in life.

METHODS

Study Design, Setting, and Population

A retrospective cohort study was conducted using electronic health record data from Kaiser Permanente (KP) integrated health systems across three U.S. regions—Northern California (KPNC), Southern California (KPSC), and the Mid-Atlantic States (KPMAS; includes Maryland, Virginia, and Washington D.C.). KP health systems provide comprehensive medical, diagnostic, pharmacy, and HIV care services.

People with HIV were identified using Kaiser Permanente's regional HIV registries, which capture all known cases through laboratory results, pharmacy records, and ICD-coded diagnoses. Of these individuals, those aged ≥ 50 years with at least one year of continuous health plan enrollment between 1 January 2000 and 31 December 2023 (allowing gaps up to 90 days) were eligible for inclusion. Individuals were excluded if they had a pre-existing dementia diagnosis, lacked evidence of ART use (≥ 1 ART prescription fill in the past year), or did not have at least one CD4 count measurement at or before their first documented ART use. Study participants were followed from the date of meeting all study criteria (ie, baseline) until the earliest of incident dementia diagnosis, last day of health plan membership, death, or end of the study on 31 December 2023.

Patient Consent Statement

The study protocol was approved by the KPNC Institutional Review Board with a waiver for informed consent. KPSC and KPMAS ceded to the KPNC Institutional Review Board.

Data Collection

For each participant, the lowest known CD4 count before first documented ART prescription fill was identified. Low CD4 count (ie, < 200 cells/ μ L) was used as a proxy for delayed HIV diagnosis or delayed ART initiation.

Dementia was identified from electronic health records using International Classification of Diseases (ICD) codes that included diagnoses of Alzheimer's disease, vascular dementia, Parkinson's

dementia, dementia with Lewy bodies, frontotemporal dementia, and other/unspecified dementias. This set of ICD codes was confirmed in a prior KP study to have high positive predictive value (93%) in people with HIV [2], and for the current study, was updated to reflect new ICD-10-CM classifications adopted in KP health systems in 2022 [21]. Incident dementia was defined as the first dementia diagnosis occurring at an outpatient, inpatient, or telehealth visit.

Data were also collected on factors associated with dementia, including sociodemographics (age, sex, race/ethnicity, Census-based neighborhood-level education), substance use (history of smoking, substance use disorders including alcohol and other drug use disorders), and comorbidities (cardiovascular disease, hypertension, diabetes mellitus, depression, and hepatitis C infection). Administrative data were collected on health insurance type (private, Medicaid, Medicare, Affordable Care Act, and charitable care) and frequency of healthcare encounters (a proxy measure of healthcare engagement). HIV data included date of first known HIV infection, CD4 cell counts, HIV RNA levels, and ART prescription fills.

Statistical Analysis

Characteristics of participants at baseline and dementia types identified at incident diagnosis were summarized descriptively. The association of low CD4 count with incident dementia was evaluated using Fine–Gray subdistribution hazard models to account for the competing risk of death, with age as the time scale. Adjusted models included terms for sex, race/ethnicity, Census-based neighborhood-level education, ever smoking, substance use disorders, cardiovascular disease, hypertension, diabetes, depression, hepatitis C infection, KP region, and number of healthcare encounters in the year prior to baseline. To reduce potential HIV-related confounding not fully accounted for by restriction of the study cohort to individuals on ART, models were additionally adjusted for baseline HIV RNA level and year of HIV diagnosis. HIV viral suppression and ART use during follow-up were examined descriptively but were not incorporated as time-updated covariates in the models given the bidirectional relationship between HIV control and risk of dementia. In sensitivity analyses, hazard ratios were recalculated, excluding people with detectable HIV RNA (≥ 200 copies/mL) at baseline (ie, time of study entry, after ART initiation), to reduce potential confounding due to ART nonadherence.

To assess the robustness of the relationship between prior low CD4 and risk of dementia, secondary analyses evaluated whether CD4 recovery modified this relationship. Individuals with low pre-ART CD4 and at least one CD4 measurement after ART initiation were stratified based on whether they achieved CD4 recovery, defined as reaching a CD4 count of ≥ 500 cells/ μ L within 2 years of their first documented ART prescription fill. The 2-year period was selected based on prior studies indicating

that the most substantial immune recovery typically occurs within this timeframe [22]. Dementia risk was then assessed separately for people who achieved CD4 recovery and those who did not, using the same reference group as in the primary analysis (people without low pre-ART CD4 counts).

RESULTS

The study included 21 354 people with HIV (mean age 54 years at baseline, 87% men, 46% White, 23% Black, 21% Hispanic, 4% Asian, 6% other, or unknown race/ethnicity; Table 1). All study

Table 1. Characteristics of Study Population at Baseline

Characteristic	N = 21 354 n (%)
Age, mean years (SD)	53.8 (5.6)
Male	18 584 (87.0)
Race/ethnicity	...
White, non-Hispanic	9876 (46.3)
Black, non-Hispanic	4856 (22.7)
Hispanic	4511 (21.1)
Asian, non-Hispanic	861 (4.0)
Other or unknown	1250 (5.9)
Lower neighborhood-level education ^a	3584 (16.8)
Smoking, ever	8726 (40.9)
Substance use disorder ^b	3185 (14.9)
Cardiovascular disease	1 308 (6.1)
Hypertension	7426 (34.8)
Diabetes mellitus	2853 (13.4)
Depression	6133 (28.7)
Hepatitis C infection, ever	2204 (10.3)
Number of healthcare encounters in prior year, mean (SD)	8.9 (10.5)
Year diagnosed with HIV infection	...
Before 2000	9324 (43.7)
2000–2014	10 209 (47.8)
2015 or after	1821 (8.5)
Duration of HIV infection, years (SD)	12.4 (9.0)
CD4 cell count, cells/ μ L ^c	...
≥ 500	11 363 (53.2)
200–499	6887 (32.3)
<200	2351 (11.0)
Unknown	753 (3.5)
Lowest recorded pre-ART CD4 cell count, cells/ μ L	...
≥ 500	5891 (27.6)
200–499	8987 (42.1)
<200	6476 (30.3)
HIV RNA level, copies/mL	...
<200	16 713 (78.3)
200–9999	1537 (7.2)
$\geq 10\,000$	2489 (11.7)
Unknown	615 (2.9)

Abbreviation: SD = standard deviation.

^aLower neighborhood-level education was defined as $\geq 25\%$ of the population in the patient's Census block group having less than a 12th grade level education.

^bIncludes alcohol use disorder and other drug use disorders.

^cBaseline CD4 cell count was defined as the measurement closest to baseline date, selected from all available values within the window of 365 days prior to and up to 30 days after baseline.

participants were on ART (ie, at least one documented ART prescription fill) at the start of follow-up; 41% had a history of smoking, 15% had a substance use disorder diagnosis, 6% had cardiovascular disease, 35% had hypertension, 13% had diabetes, 29% had depression, and 10% had a history of hepatitis C infection. Mean CD4 count was 570 cells/ μ L (SD: 327 cells/ μ L), 78% had undetectable HIV RNA (<200 copies/mL), and the mean duration of HIV infection was 12 years (SD: 9 years); 30% had a pre-ART CD4 count <200 cells/ μ L. The mean duration from HIV diagnosis to ART initiation was 8 years (SD: 9).

During follow-up (mean 7 years, SD: 5), we observed 618 cases of incident dementia. Among individuals diagnosed with dementia, 117 (18.9%) had detectable HIV RNA at dementia diagnosis despite the vast majority ($n = 595$; 96.3%) having evidence of ongoing ART use (ie, ≥ 1 ART prescription fill within the prior year). At incident diagnosis, unspecified dementia was the most common (46.7% of dementias identified), followed by other specified dementias (37.5%) and vascular dementias (13.4%; Supplementary Table 1). For individuals in the cohort who were not diagnosed with dementia, follow-up ended due to end of the study (47.6%), health plan disenrollment (44.0%), or death (8.4%). Low pre-ART CD4 count (<200 cells/ μ L) was associated with greater risk of developing dementia (hazard ratio [HR]: 1.56, 95% CI: 1.33–1.83), even after adjustment for possible confounders (adjusted hazard ratio [aHR]: 1.33, 95% CI: 1.13–1.57; Figure 1; Supplementary Table 2). Sensitivity analyses which excluded people with detectable HIV RNA at baseline yielded similar results (aHR: 1.32, 95% CI: 1.06–1.63).

Of the 6476 people with low CD4 count at start of follow-up, 6378 (98.5%) had ≥ 1 CD4 measure after ART initiation and were included in analyses of CD4 recovery; 20.6% had CD4 recovery to ≥ 500 cells/ μ L within 2 years of ART initiation. Risk of dementia remained elevated in these individuals (aHR: 1.17, 95% CI: 0.85–1.60) but was no longer statistically significant (Figure 1). Among individuals who did *not* achieve CD4 recovery, risk of dementia remained significantly elevated (aHR: 1.31, 95% CI: 1.10–1.57).

DISCUSSION

This study advances our understanding of the long-term neurocognitive consequences of pre-ART immune compromise in HIV. Among people with HIV aged ≥ 50 years and on ART, those with low pre-ART CD4 counts (<200 cells/ μ L)—a proxy for delayed HIV diagnosis and treatment—had a 33% higher risk of incident dementia diagnosis, even after accounting for attained age, dementia-related comorbidities, and the competing risk of death. Elevated dementia risk was also observed among individuals with well-controlled HIV, as indicated by undetectable HIV RNA at baseline. Importantly, though recovery of CD4 counts to ≥ 500 cells/ μ L within 2 years of ART initiation reduced dementia risk, it did not entirely eliminate it, which further

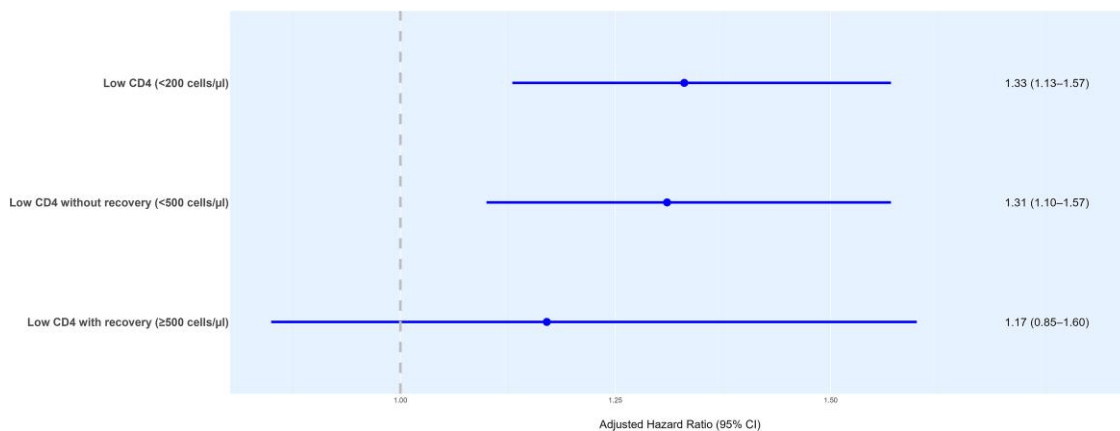


Figure 1. Dementia risk by pre-ART CD4 count and CD4 recovery status. The association of low CD4 count with incident dementia was evaluated using Fine–Gray sub-distribution hazard models, accounting for the competing risk of death and with age as the time scale. Low CD4 was defined as CD4 count <200 cells/μL prior to ART initiation. CD4 recovery was defined as CD4 count ≥500 cells/μL within 2 years of ART initiation. Models were adjusted for age, sex, race/ethnicity, Census-based neighborhood-level education, ever smoking, substance use disorders, cardiovascular disease, hypertension, diabetes mellitus, depression, hepatitis C infection, KP region, year of HIV diagnosis, HIV RNA level at start of follow-up, and health care utilization (number of healthcare encounters in the year before baseline).

emphasizes the lasting impact of prior immunosuppression. These findings reinforce the importance of assertive HIV screening and prompt ART initiation to optimize immune recovery and potentially reduce long-term dementia risk.

Our results are consistent with studies which have reported that lower CD4 nadir levels are associated with increased risk of other neurocognitive disorders such as HAND [14–19]. However, whereas earlier work used research-based criteria to measure and classify cognitive impairments, often in younger or cross-sectional cohorts, our study captured clinically diagnosed dementia in routine clinical care among a larger and older population with stable access to ART. Notably, the association between pre-ART immune compromise and dementia remained despite adjustments for age and comorbidities, confirming the hypothesis of a “legacy effect” of delayed HIV diagnosis and treatment, and immunosuppression, on later-life neurocognitive health.

There are several clinical implications to these findings. The lasting cognitive impacts of immunosuppression reinforce the importance of prompt ART initiation, in line with current HIV care guidelines [23, 24]. Encouragingly, some recent neuroimaging studies suggest that early initiation of ART may mitigate, or even reverse, certain patterns of brain injury seen in people with HIV [25, 26], potentially through normalization of inflammatory and immune activation biomarkers [27, 28]. These findings offer hope for improved cognitive outcomes in future generations of people with HIV who initiate ART earlier in the disease course. Additionally, newer ART regimens, particularly those based on integrase strand transfer inhibitors (INSTIs) such as dolutegravir and bictegravir, have demonstrated higher CNS penetration, improved tolerability, and reduced neurotoxicity [29]. These pharmacologic advances

may help reduce neurocognitive complications due to HIV [30–32]. However, results across studies have been mixed, potentially due to differences in populations, methodologies, or follow-up duration [26, 32, 33]. Moreover, there is some evidence that certain groups, including women and individuals over 60 years old, may be more susceptible to neuropsychiatric side effects of dolutegravir-based regimens [34]. Longitudinal studies in older and more diverse populations are needed to clarify the long-term cognitive impacts of early ART and evolving treatment strategies.

While CD4 recovery was associated with reduced dementia risk, residual risk remained, potentially reflecting the lasting impact of HIV-related immunosuppression on the brain. Though this association was not statistically significant, it nevertheless highlights the need to identify additional modifiable factors that could buffer against the long-term neurocognitive effects of past immunosuppression. Addressing comorbid conditions associated with dementia—such as cardiovascular disease and diabetes mellitus, which disproportionately affect people with HIV—may support healthier aging [35], although direct evidence linking comorbidity control to reduced dementia risk among people with HIV is lacking. For instance, a prior KP study found that suboptimal hypertension control did not explain the elevated dementia risk in this population [36]. Lifestyle-based strategies—such as regular physical activity, cognitive engagement, and social connections—may also increase cognitive resilience in aging populations with HIV. Notably, while all individuals included in this study were on ART at baseline, 18.9% of those diagnosed with dementia had detectable HIV RNA, underscoring the importance of sustained HIV control as a potential factor in cognitive aging.

ART initiation increasingly occurs at higher CD4 counts in more recent years, which may reduce the prognostic value of low pre-ART CD4 in some populations. Indeed, in the neurology sub-study of the Strategic Timing of Antiretroviral Treatment (START) trial, Wright and colleagues observed no significant cognitive benefit among participants who initiated ART at CD4 $\geq$ 500 cells/ μ L [37]. However, low CD4 at ART initiation remains clinically relevant for the neurocognitive health for individuals who are still being diagnosed late and starting treatment in advanced immunosuppression. A deeper understanding of patients treated early, and who maintain stable and optimal immune profiles, may help uncover novel targets to support long-term cognitive health. In addition, research on how age-related changes in immune function (eg, immunosenescence) intersect with neurodegenerative processes could provide further insight. This is especially relevant in light of ongoing research into shared neuropathological features between HAND and aging-related neurodegenerative conditions such as Alzheimer's disease [38], as well as data suggesting that some cognitive domains may be especially vulnerable to aging in the context of HIV [18, 39].

This study had some limitations. First, evolving clinical practices, including changes in timing of ART initiation, may have influenced results. Models were adjusted for calendar year of HIV diagnosis to mitigate some of these effects. Second, though analyses accounted for the competing risk of death, survival bias remains a potential concern. Some individuals with lower CD4 counts or more advanced HIV disease may have died before reaching age 50 and thus would not have been included in the cohort. This could have resulted in a study population that is more resilient to adverse outcomes, thereby underestimating the risk of dementia among people with low pre-ART CD4 counts. Third, while we included a descriptive analysis of ART use and viral suppression, we were unable to account for longitudinal variations in ART history, including regimen-specific differences in CNS penetration or ART adherence patterns, which themselves may be influenced by cognitive status. Evaluating cumulative ART exposures and continuity of ART use over time would be an important direction for future research particularly given growing evidence that long-term ART use may be associated with neurotoxicities that offset its neurocognitive benefits [6, 40]. Additionally, we were unable to assess prior history of HAND at baseline, as there is no standardized ICD-coded definition for HAND in the electronic health record; this limited our ability to assess whether prior HAND may increase vulnerability to later-life dementia. Finally, we did not examine longitudinal CD4 or viral load trajectories. These patterns could provide a more nuanced understanding of how the duration and severity of immunosuppression may impact dementia risk, and whether sustained viral suppression modifies this risk. However, pre-ART CD4 remains a well-established and clinically relevant marker of early immune compromise and a predictor of neurocognitive risk.

Strengths of this study include the large cohort of older adults with HIV on ART, objective ART confirmation using pharmacy records linked to electronic health records, and adjustment for individual-level dementia risk factors and comorbidities. We also leveraged robust HIV-specific data, including pre-ART CD4 and baseline HIV RNA levels, from regional HIV registries. Importantly, by using physician-diagnosed dementia as our outcome, we captured clinically meaningful cognitive impairment, extending the existing body of research largely focused on research-defined HAND. These strengths enhance the applicability of our findings to aging HIV populations most likely seen in clinical care.

CONCLUSIONS

In summary, our findings suggest that significant prior immunosuppression leaves a lasting impact on cognitive health, increasing dementia risk in older individuals with HIV. While CD4 count recovery is associated with reduced risk, some vulnerability persists. This highlights the need to explore additional modifiable factors, such as better management of comorbidities and implementation of lifestyle interventions, to improve long-term neurocognitive outcomes in this population. Ensuring that longer lifespans enabled by ART are accompanied by preserved cognitive abilities and quality of life remains a vital goal—one that will also be supported by continued efforts to promote early HIV diagnosis and timely ART initiation in the community.

Supplementary Data

Supplementary materials are available at [Open Forum Infectious Diseases](https://academic.oup.com/ofid/article/13/1/ofaf791/6431583) online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. J. O. L. conceptualized and designed the study, conducted the data analysis, interpreted results, and drafted the manuscript. C. L., C. E. H., W. J. T., and M. A. H. interpreted results and provided input on the manuscript. D. F. collected and harmonized data and created analytic datasets. H. H. and E. L. collected data. A. L. provided administrative support. M. J. S. contributed to study conceptualization and design, interpreted data, and provided input on the manuscript.

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