HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2024 April 10.

Published in final edited form as:

AIDS. 2022 May 01; 36(6): 815–827. doi:10.1097/QAD.0000000000003171.

Aging, trends in CD4+/CD8+ cell ratio, and clinical outcomes with persistent HIV suppression in a dynamic cohort of ambulatory HIV patients

Richard M. Novak[a], **Carl Armon**[b], **Linda Battalora**[b,c], **Kate Buchacz**[d], **Jun Li**[d], **Douglas Ward**[e], **Kimberly Carlson**[b], **Frank J. Palella Jr**[f],
HIV Outpatient Study (HOPS) Investigators

[a]University of Illinois College of Medicine, Chicago, Illinois

[b]Cerner Corporation, Kansas City, Missouri

[c]Colorado School of Mines, Golden, Colorado

[d]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

[e]Dupont Circle Physicians Group, Washington, DC

[f]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.

Abstract

Background: Age blunts $CD4^+$ lymphocyte cell count/μl ($CD4^+$) improvements observed with antiretroviral therapy (ART)-induced viral suppression among people with HIV (PWH). Prolonged viral suppression reduces immune dysregulation, reflected by rising $CD4^+/CD8^+$ ratios ($CD4^+/CD8^+$). We studied $CD4^+/CD8^+$ over time to determine whether it predicts risk for select comorbidities and mortality among aging PWH with viral suppression.

Methods: We studied HIV Outpatient Study (HOPS) participants prescribed ART during 2000–2018 who achieved a viral load less than 200copies/ml on or after 1 January 2000, and remained virally suppressed at least 1 year thereafter. We modeled associations of $CD4^+/CD8^+$ with select incident comorbidities and all-cause mortality using Cox regression and controlling for demographic and clinical factors.

Results: Of 2480 eligible participants, 1145 (46%) were aged less than 40 years, 835 (34%) 40–49 years, and 500 (20%) ≥ 50 years. At baseline, median $CD4^+/CD8^+$ was 0.53 (interquartile range: 0.30–0.84) and similar among all age groups ($P = 0.18$). $CD4^+/CD8^+$ values and percentage of participants with $CD4^+/CD8^+$ at least 0.70 increased within each age group ($P < 0.001$ for all). $CD4^+/CD8^+$ increase was greatest for PWH aged less than 40 years at baseline. In adjusted

Correspondence to Richard M. Novak, Division of Infectious Diseases, University of Illinois College of Medicine, 808 S. Wood Street, Suite 888 (MC 735), Chicago, IL 60612, USA. rmnovak@uic.edu.

Conflicts of interest

F.J.P. has been a consultant and/or on the Speakers' Bureau for Gilead Sciences, Janssen Pharmaceuticals, Merck and Co., and ViiV. R.M.N. is a consultant to ViiV and Gilead Sciences.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

models, most recent $CD4^+/CD8^+$less than 1.00 and less than 0.70 were independently associated with higher risk of non-AIDS cancer and mortality, respectively.

Conclusion: Pretreatment immune dysregulation may persist as indicated by$CD4^+/CD8^+$ less than 0.70. Persistent viral suppression can improve immune dysregulation over time, reducing comorbidity, and mortality risk. Monitoring $CD4^+/CD8^+$ among ART-treated PWH with lower values provide a means to assess for mortality and comorbidity risk.

Keywords

cancer; $CD4^+/CD8^+$ ratio; HIV; mortality; viral suppression

Introduction

With aging, the thymus gland progressively atrophies and the generation of new naive T cells declines [1]. Data addressing the natural senescence of T-cell phenotypes suggest a decline in naive $CD4^+$ lymphocyte cells ($CD4^+$), a decline in naive and memory $CD8^+$ lymphocyte cells ($CD8^+$) but stable $CD4^+$ memory T-cell numbers with aging [2]. Thymic volume is associated with the degree of $CD4^+$ recovery after initiation of antiretroviral therapy (ART) [3]. Research studies profiling the effects of aging on T-cell phenotypes among people with HIV (PWH) have documented that age influences the degree of improvement in $CD4^+$ cell counts with ART-induced sustained viral suppression among PWH in care, particularly in the first 3–5 years of viral suppression, during which time, a new plateau $CD4^+$ cell count is achieved, influenced by both age and nadir $CD4^+$ [4–6]. However, PWH who are stably virally suppressed may not experience a decline in T-cell subsets with age [7,8]. The effect of HIV disease duration or immune injury on T-cell recovery among aging, virally suppressed PWH, or the disease effect on clinical outcomes warrants further study. We sought to investigate the trends in $CD4^+/CD8^+$ ratio ($CD4^+/CD8^+$) by age group over time, and the associations between $CD4^+/CD8^+$ and select comorbid outcomes and mortality.

Methods

The HIV Outpatient Study

The HIV Outpatient Study (HOPS) is an ongoing, open, prospective cohort study of over 10 000 PWH (aged 18 years and older) seen in HIV-specialty clinics since 1993 [9]. The 10 clinics included in the present analyses are located in six cities in the United States: Tampa, Florida (two sites); Washington, DC; Denver, Colorado (three sites); Chicago, Illinois (two sites); Stony Brook, New York; and Philadelphia, Pennsylvania. All HOPS clinicians have extensive experience treating PWH. Information was abstracted from outpatient charts and/or electronic medical records at each visit, entered electronically by trained staff, compiled centrally, reviewed, and cleaned before being analyzed. Abstracted information included: demographic characteristics, HIV transmission risk activities, clinical diagnoses, prescribed medications, laboratory values (including $CD4^+$ and plasma HIV RNA levels), viral load, mortality, and hospitalization records (primarily from discharge summaries).

Study population

For this analysis, we selected HOPS participants with at least two clinical encounters, who were seen any time during 2000–2018 and had a complete ART history. Included HOPS participants had a viral load less than 200copies/ml on or after 1 January 2000, and remained virally suppressed during the first year after baseline. We defined baseline date as the date of first viral load test result less than 200 copies/ml on or after 1 January 2000. Analyses were restricted to participants prescribed ART at baseline date, with a pre-ART $CD4^+$ available, and at least 1 year of follow-up with at least one $CD4^+$ and $CD8^+$ value recorded during observation. The present analysis is based on HOPS data current up to 30 June 2019. Observation was discontinued at the earliest of death, last HOPS contact, inactive status date (no participant encounters within the last 18 months, or terminating care at the site, or loss to follow-up), or 31 December 2018.

Ethics

Since its inception, the HOPS protocol has been reviewed and approved annually by CDC (Atlanta, Georgia, USA), Cerner Corporation (Kansas City, Missouri, USA) and each local site's institutional review board. All participants provided written informed consent. The study protocol conforms to the guidelines of the US Department of Health and Human Services for the protection of human participants in research.

Outcome measures

We evaluated five incident clinical outcomes as well as all-cause mortality: dyslipidemia, cardiovascular disease, renal disease, diabetes, and non-AIDS cancer (excluding non-AIDS skin cancers) (Appendix A, http://links.lww.com/QAD/C438). Comorbidities were defined based on diagnoses, laboratory measurements, and treatments documented in the patient medical records [10]. Participants with evidence of such outcomes from at least one of the three data sources were classified as having that outcome, except for cardiovascular disease, diabetes, and dyslipidemia, for which evidence was required from at least two of the three sources. If a comorbidity was documented at any time while under HOPS observation, it was considered to be ongoing at the time of last observation.

Independent (predictor) variables

Demographic and disease factors including $CD4^+/CD8^+$ over the course of observation were the independent variables in this analysis. Baseline age was treated as a categorical variable: less than 40, 40 to 49, and at least 50 years, whereas $CD4^+/CD8^+$ was treated as a categorical (<0.50, 0.50 to < 0.70, 0.70 to < 1.00,and ≥ 1.00), binary (< 0.70 versus ≥ 0.70) or continuous variable, with the higher values reflecting less immune dysregulation. Baseline $CD4^+$ cell count values were those closest to baseline date, selecting values recorded up to the baseline date plus 7days.

Statistical analyses

The goal of the analysis was to describe the effect of patient and disease factors including $CD4^+/CD8^+$ at first virologic suppression on subsequent $CD4^+/CD8^+$ trends over time, and to describe associations between $CD4^+/ CD8^+$ over time with select incident

clinical outcomes of interest. We used Jonckheere–Terpstra test of trend for continuous variables, and Cochran–Armitage test of trend for categorical variables to compare patient characteristics by baseline age category. The Yates-corrected chi-square test was used to compare proportion of incident clinical outcomes including cancers and deaths among a quartile distribution of $CD4^+/CD8^+$ values. We performed Cox proportional hazards analyses to assess for associations of patient and disease factors including $CD4^+/CD8^+$ values during observation with these outcomes, sample size permitting. The multivariable models included factors with P less than 0.2 in univariate analyses, and the final multivariable models used backwards selection, where the factors with the highest *P* values were excluded, in order, from each model. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Among 11 179 HOPS participants in the HOPS database as of 30 June 2019, we identified 6368 with at least two HOPS encounters and complete ART history, 5033 under observation during 2000–2018, 4425 with a viral load test result less than 200 copies/ml during observation, 3115 with no viral load test result at least 200copies/ml during first year of observation. We further limited our analysis cohort to 2480 participants with pre-ART $CD4^+$ recorded and with at least 1 year of observation after baseline, during which at least one $CD4^+$ and $CD8^+$ values were recorded (Fig. 1).

Of the 2480 participants, median duration of follow-up from baseline date to last HOPS encounter was 7.4 years (interquartile range [IQR] = 4.1 – 12.2years). During the first 4 years of observation, 95, 91, and 86% of participants remained virally suppressed through the second, third, and fourth years, respectively. Similarly, 96, 92, 88, and 86% did not have a recorded treatment interruption (when there is a delay between stopping and restarting ART regimens) of 14 or more days during the first, second, third, and fourth years of observation (data not shown).

Among the 2480 participants, 46% were less than 40 years, 34% were 40–49 years, and 20% were at least 50 years old (Table 1). Overall, median baseline age was 41 years; 82% were men; 52% non-Hispanic/Latino (NHL) white, 32% NHL black, and 13% Hispanic/Latino. Sixty percent were on their first ART regimen and 21% on their at least fourth regimen. Fourteen percent had baseline $CD4^+$ cell count less than 200 cells/μl. Across the three age groups, the participants differed in their characteristics, including by race/ethnicity, HIV transmission risk activity, years elapsed since recorded HIV date and calendar year range when ART was started, education level, insurance type, current/prior smoking status, number of ART regimens taken, ART regimen type taken at baseline, baseline $CD4^+$ cell count range, and $CD4^+/CD8^+$ range ($P < 0.05$ for all), see Table 1. Additionally, there were significant differences in the percentage with prevalent cardiovascular disease, nonAIDS cancer, renal disease, dyslipidemia, and diabetes by baseline age group. Furthermore, the number and percentage of participants in each age stratum with incident outcomes during follow-up of non-AIDS cancer, renal disease, cardiovascular disease, dyslipidemia, diabetes and mortality were assessed; because of the small number of outcomes observed for most

conditions, subsequent regression analyses were performed only for non-AIDS cancer and mortality (Table 1).

Baseline $CD4^+/CD8^+$ and the percentage of participants with $CD4^+/CD8^+$ at least 0.70 were similar among the three age groups. At baseline, the median $CD4^+/ CD8^+$ (IQR) was 0.55 (0.31–0.88), 0.52 (0.31–0.81), and 0.49 (0.29–0.81) in the less than 40, 40–49 and, at least 50-year age groups, respectively (P = 0.18, Fig. 2a). At year 4, the median $CD4^+/CD8^+$ (IQR) was 0.80 (0.52–1.15), 0.73 (0.49–1.06), and 0.70 (0.45–1.00) across the three age groups. The percentages of participants with $CD4^+/CD8^+$ ratios at least 0.70 were 36, 32.1, and 33.4% in the less than 40, 40–49, and at least 50-year age groups, respectively (P = 0.18, Fig.2b) at baseline, and they were 58.8, 52.4, and 50% at year 4. The $CD4^+/CD8^+$ and percentage of participants with $CD4^+/CD8^+$ at least 0.70 increased significantly within each age group during observation ($P < 0.001$ for all age groups). However, differences across the age groups in both the median $CD4^+/CD8^+$ and the percentage of participants with $CD4^+/CD8^+$ at least 0.70 ($P < 0.05$ for both measures) persisted at 1 through 4 years after baseline (Fig. 2a and b). Figure 2c provides the inverse image of Fig. 2b, illustrating the percentage of participants with $CD4^+/CD8^+$ less than 0.70 over time, by age group at baseline.

In the analyses stratified by the four baseline $CD4^+/CD8^+$ categories, although $CD4^+/CD8^+$ increased during follow-up in each group by baseline $CD4^+/CD8^+$ stratum ($P < 0.05$), median values remained different between strata from baseline through year 4 (all $P < 0.001$, Fig. 3a). The percentage with $CD4^+/CD8^+$ at least 0.70 during years 1 through 4 decreased for those with $CD4^+/CD8^+$ at least 0.70 at baseline (all $P < 0.001$) but did increase for those with $CD4^+/CD8^+$ less than 0.70 at baseline (all $P < 0.001$, Fig. 3b).

Of the 153 cases of incident non-AIDS cancer, 146 had precancer $CD4^+/CD8^+$ data and were included in the regression modeling analysis. Participants with prevalent cancer were excluded from this analysis, leaving 2424 participants for analysis. In univariate Cox proportional hazards regression, age at least 50 years and having $CD4^+/CD8^+$ less than 0.7 were associated with the outcome of non-AIDS cancer. In the final multivariable analysis using backwards selection, age less than 40 years and age 40–49 years were each inversely associated with the nonAIDS cancer outcome [adjusted hazard ratio (aHR) 0.16, 95% confidence interval (CI) 0.10–0.24, and aHR 0.41, CI 0.28–0.58, respectively] compared with age at least 50 years. Having less than seven alcoholic drinks per week (compared with none) was associated with the outcome (aHR 1.62, 95% CI 1.14–2.30), as was most recent $CD4^+/CD8^+$ ofless than 0.5, 0.5 to less than 0.7, and 0.7 to less than 1.0 (aHR 2.82, 95% CI 1.80–4.42, aHR 1.98, 95% CI 1.21–3.24, and aHR 1.81, 95% CI 1.13–2.89, respectively) compared with $CD4^+/CD8^+$ at least 1.0 (Table 2).

There were 124 decedents. In univariate regression modeling analyses, factors associated with all-cause mortality were age at least 50 years, male sex, non-Hispanic/Latino black race/ethnicity, being a person who injects drugs (PWID), public insurance, being seen at a public clinic, current or prior smoking, third or greater ART regimen, receiving ART containing a protease inhibitor, and having $CD4^+/CD8^+$ less than 0.70. Having Less than seven alcoholic drinks per week or having baseline $CD4^+$ cell count of 350–499 cells/μl had

an inverse association with the outcome. In the final multivariable analysis using backwards selection, age less than 40 or 40–49years (aHR 0.24, 95% CI 0.14–0.41 and aHR 0.65, 95% CI 0.44–0.96, respectively, compared with ≥50 years) and female sex (aHR 0.52, 95% CI 0.28–0.98, compared with male sex) were each inversely associated with mortality, while being a PWID (aHR 2.47, 95% CI 1.54–3.96 compared with MSM), current or prior smoking (aHR 1.88, 95% CI 1.26–2.81, compared with those nota current or prior smoker), receiving third or greater ART regimen (aHR 2.18, 95% CI 1.26–3.78 for third and aHR 1.72, 95% CI 1.12–2.65 for fourth, respectively compared with first regimen), having baseline $CD4^+$ cell count of 350–499 cells/μl (aHR 0.50, 95% CI 0.27–0.96, compared with baseline $CD4^+$ cell count at least 500 cells/μl) and having most recent $CD4^+/CD8^+$ less than 0.50 or 0.50 to less than 0.70 (aHR 4.82, 95% CI 2.67–8.70 and aHR 2.46, 95% CI 1.31–4.62, respectively, compared with 1.00) were positively associated with mortality (Table 2).

Discussion

In our large multicenter, longitudinally followed, prospectively observed cohort of PWH, we found that immune dysregulation (defined as having $CD4^+/CD8^+ < 0.70$) was common and largely persisted among participants virally suppressed on ART. After adjusting for baseline immune dysregulation, lower $CD4^+/CD8^+$ was associated with greater mortality and non-AIDS nonskin cancer risk. $CD4^+/CD8^+$ values and the proportion of participants with $CD4^+/CD8^+$ at least 0.70 increased within each age group over time, indicating some reduction in immune dysregulation over time. In addition, age at the start of observation influenced degree of recovery of the $CD4^+/CD8^+$, with people younger than age 40 at baseline having a more pronounced recovery compared with older PWH. After controlling for age, smoking status and sex, baseline immune dysregulation was positively associated with mortality and non-AIDS nonskin cancer. Not only did people with a $CD4^+/CD8^+$ of less than 0.70 have greater risk of these outcomes but also the frequency of events decreased with higher $CD4^+/CD8^+$ quartiles.

Suppression of $CD4^+/CD8^+$ has been observed as an aspect of HIV-associated immune suppression since the early days of the HIV pandemic [11], and greater rate of decline has been associated with progression to an AIDS diagnosis [12]. HIV infection is associated with accelerated involution of the thymus [1], the degree of which has been negatively correlated with $CD4^+$ cell recovery after the initiation of antiretroviral therapy [3,13,14]. A low $CD4^+/CD8^+$ has been associated with persistent T-cell dysregulation and markers of immune senescence despite normalization of the absolute $CD4^+$ cell count with prolonged ART-induced viral suppression [15,16].

Several studies have investigated the associations between $CD4^+/CD8^+$ and clinical outcomes or comorbidities. Some cohort studies found an association between lower $CD4^+/CD8^+$ with cardiovascular disease risk and mortality, although this has not been a consistent finding, in part, because of different study designs (i.e. retrospective case–control versus prospective), populations (i.e. different racial compositions, age ranges, treatment types) and a priori risk for cardiovascular disease [4,17–22]. Lower $CD4^+/CD8^+$ is associated with greater carotid artery intimal media thickness in people with well controlled HIV [23,24].

There is a relative paucity of longitudinal data evaluating $CD4^+/CD8^+$ over time. One longitudinal observational cohort evaluated aging and long-term virologic control among PWH and found no effect of advancing age on declines in $CD4^+$ cell count, but did not specifically address the $CD4^+/CD8^+$ [7]. Another study investigated $CD4^+/CD8^+$ and found that older age reduced the likelihood of recovery to a ratio of1 or more [25]. This study did not assess associated clinical outcomes. A more recent analysis of a large data set from multiple pooled cohorts, The Antiretroviral Therapy Cohort Collaboration (ART-CC) reported clear associations of nadir $CD4^+$ cell count and age with $CD4^+/CD8^+$ recovery among PWH with prolonged HIV viral suppression but did not evaluate any associated clinical outcomes [26]. An earlier article from the same group did not find an association of $CD4^+/CD8^+$ with non-AIDS mortality [27].

Another recent study focused on predictors of comorbidities in PWH who were persistently virologically suppressed and did not demonstrate an association between $CD4^+/CD8^+$ with any comorbidity except for neurocognitive dysfunction [21]. This study sample was much smaller than the current study and may have lacked adequate power to identify associations that we observed in our cohort.

Our analysis is subject to some limitations. First, routinely collected medical abstraction data involves variability in the timing of participant healthcare contact screenings, including measurements of $CD4^+/CD8^+$, potentially leading to some information bias. A fraction of patients had preexisting comorbidities at the start of observation for this analysis, thus we focused on evaluating the association between baseline $CD4^+/CD8^+$ and incident comorbidities first documented in follow-up, excluding baseline prevalent diagnoses. Also, the overall inferences regarding the association of $CD4^+/CD8^+$ with comorbid outcomes and mortality were generated from observational data during a prolonged calendar time (18 years), when combination antiretroviral therapy (cART) use patterns evolved. Our findings may have been different had we restricted our analysis to participants treated exclusively with newer cART regimens; this latter group is challenging to evaluate because of the decreasing overall number of incident events, including deaths, observed over calendar time. Finally, our findings were based on data from 10 HIV-specialty public and private clinics, where provider-prescribing preferences may vary. Our findings may not be generalizable to patients in other clinical settings or not in HIV care.

Our findings indicate that there are effects consequent to both aging and the degree of baseline immune dysregulation that influence long-term ability to recover immune function, even after years of viral suppression, and appear to have clinical consequences extending to non-HIV comorbidities and mortality. Persistent viral suppression does lead to improvements in immune dysregulation over time, as measured by changes in $CD4^+/CD8^+$, which appear to diminish the risk of comorbidities and mortality. Monitoring $CD4^+/CD8^+$ amongvirally suppressed ART-treated PWH with lower $CD4^+/CD8^+$ provide a means to assess for mortality and comorbidity risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors contributed equally to this work, based on the following criteria: substantial contributions to the conception or design of the work (R.M.N. and C.A.); the acquisition, analysis, or interpretation of data for the work (R.M.N., K.C., J.L., and C.A.), drafting the work or revising it critically for important intellectual content (R.M.N., F.J.P., L.B., K.C., D.W., and K.B), final approval of the version to be published (R.M.N., K.B., and J.L), and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (R.M.N., C.A., and K.B). We also wish to acknowledge the contributions of the HOPS patients, as well as the HOPS Investigators: Kate Buchacz, Marcus D. Durham, Jun Li, Division of HIV/AIDS Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia; Cheryl Akridge, Stacey Purinton, Selom Agbobil-Nuwoaty, Kalliope Chagaris, Kimberly Carlson, Qingjiang Hou, Carl Armon, Linda Battalora, Jonathan Mahnken, Cerner Corporation, Kansas City, Missouri; Frank J. Palella, Conor Daniel Flaherty, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; Cynthia Firnhaber, Barbara Widick, Rosa Franklin, Billie Thomas, Vivent Health, Denver, CO; Douglas J. Ward, Linda Kirkman, DuPont Circle Physicians Group, Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, Jane Esteves, State University of NewYork (SUNY), Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian, Faye Ruley, Dania Beadle, Princess Davenport, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania; Richard M. Novak, Andrea Wendrow, Stockton Mayer, University of Illinois at Chicago, Chicago, Illinois; Cynthia Mayer, Karen Maroney, Mark Waggoner, Kimberly Braden, Anicette Richardson, St.Joseph’s Hospital Comprehensive Research Institute, Tampa, Florida.

Funding:

This work was supported by Centers for Disease Control and Prevention (contract nos. 200-2001-00133, 200-2006-18797, 200-2011-41872, 200-2015-63931 and 75D30120C08752).

References

1. Haynes BF, Markert ML, Sempowski GD, Patel DD, Hale LP. The role of the thymus in immune reconstitution in aging, bone marrow transplantation, and HIV-1 infection. Annu Rev Immunol 2000; 18:529–560. [PubMed: 10837068]
2. Provinciali M, Moresi R, Donnini A, Lisa RM. Reference values for CD4+ and CD8+ T lymphocytes with naïve or memory phenotype and their association with mortality in the elderly. Gerontology 2009; 55:314–321. [PubMed: 19190395]
3. Rosado-Sanchez I, Herrero-Fernandez I, Genebat M, Ruiz-Mateos E, Leal M, Pacheco YM. Thymic function impacts the peripheral CD4/CD8 ratio of HIV-infected subjects. Clin Infect Dis 2017; 64:152–158. [PubMed: 27986677]
4. Serrano-Villar S, Moreno S, Fuentes-Ferrer M, Sánchez-Marcos C, AvilaM Sainz T, et al. The CD4:CD8 ratio is associated with markers of age-associated disease in virally suppressed HIV-infected patients with immunological recovery. HIV Med 2014; 15:40–49. [PubMed: 24007533]
5. Kaufmann GR, Bloch M, Finlayson R, Zaunders J, Smith D, Cooper DA. The extent of HlV-1-related immunodeficiency and age predict the long-term CD4T lymphocyte response to potent antiretroviral therapy. AIDS 2002; 16:359–367. [PubMed: 11834947]
6. Garcia F, de Lazzari E, Plana M, Castro P, Mestre G, Nomdedeu M, et al. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. J Acquir Immune Defic Syndr 2004; 36:702–713. [PubMed: 15167289]
7. Wright ST, Petoumenos K, Boyd M, Carr A, Downing S, O’Connor CC, et al. Ageing and long-term CD4 cell count trends in HIV-positive patients with 5 years or more combination antiretroviral therapy experience. HIV Med 2013; 14:208–216. [PubMed: 23036045]
8. Reynolds SJ, Sempa JB, Kiragga AN, Newell K, Nakigozi G, Galiwango R, et al. Is CD4 monitoring needed among ugandan clients achieving a virologic and immunologic response to treatment? AIDS Patient Care STDS 2014; 28:575–578. [PubMed: 25290988]
9. Moorman AC, Holmberg SD, Marlowe SI, Von Bargen JC, Yangco BG, Palella FJ, et al. Changing conditions and treatments in a dynamic cohort of ambulatory HIV patients: the HIV outpatient study (HOPS). Ann Epidemiol 1999; 9:349–357. [PubMed: 10475534]

10. Palella FJ, Hart R, Armon C, Tedaldi E, Yangco B, Novak R, et al. HIV Outpatient Study (HOPS). Non-AIDS comorbidity burden differs by sex, race, and insurance type in aging adults in HIV care. AIDS 2019; 33:2327–2335. [PubMed: 31764098]
11. Taylor JM, Fahey JL, Detels R, Giorgi JV. CD4 percentage, CD4 number, and cD4:CD8 ratio in HIV infection: which to choose and how to use. J Acquir Immune Defic Syndr 19881989; 2:114–124.
12. Margolick JB, Gange SJ, Detels R, O'Gorman MR, Rinaldo CR Jr, Lai S. Impact of inversion of the CD4/CD8 ratio on the natural history of HIV-1 infection. J Acquir Immune Defic Syndr 2006; 42:620–626. [PubMed: 16868499]
13. Rubio A, Martínez-Moya M, Leal M, Franco JM, Ruiz-Mateos E, Merchante E, et al. Changes in thymus volume in adult HIV-infected patients under HAART: correlation with the T-cell repopulation. Clin Exp Immunol 2002; 130:121–126. [PubMed: 12296862]
14. Kalayjian RC, Spritzler J, Matining RM, Fiscus SA, Gross BH, Francis IR, et al. Older HIV-infected patients on antiretroviral therapy have B-cell expansion and attenuated CD4 cell increases with immune activation reduction. AIDS 2013; 27:1563–1571. [PubMed: 24047762]
15. Serrano-Villar S, Gutierrez C, Vallejo A, Hernández-Novoa B, Díaz L, Abad Fernandez M, et al. The CD4/CD8 ratio in HIV-infected subjects is independently associated with T-cell activation despite long-term viral suppression. J Infect 2013; 66:57–66. [PubMed: 23046968]
16. Serrano-Villar S, Sainz T, Lee SA, Hunt PW, Sinclair E, Shacklett BL, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. PLoS Pathog 2014; 10:e1004078. [PubMed: 24831517]
17. Menozzi M, Zona S, Santoro A, Carli F, Stentarelli C, Mussini C, Guaraldi G. CD4/CD8 ratio is not predictive of multimorbidity prevalence in HIV-infected patients but identify patients with higher CVD risk. J Int AIDS Soc 2014; 17 (4 Suppl 3):19709. [PubMed: 25397456]
18. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. AIDS 2010; 24:243–253. [PubMed: 19996940]
19. Han WM, Apornpong T, Kerr SJ, Hiransuthikul A, Gatechompol S, Do T, et al. CD4/CD8 ratio normalization rates and low ratio as prognostic marker for non-AIDS defining events among long-term virologically suppressed people living with HIV. AIDS Res Ther 2018; 15:13. [PubMed: 30261902]
20. Mussini C, Lorenzini P, Cozzi-Lepri A, Lapadula G, Marchetti G, Nicastri E, et al. Icona Foundation Study Group. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretro-viral therapy: an observational cohort study. Lancet HIV 2015;2:e98–e106. [PubMed: 26424550]
21. Passos DF, Bremm JM, da Silveira LL, Jantsch MH, da SilvaJLG, Disconzi E, et al. CD4/CD8 ratio, comorbidities, and aging in treated HIV infected individuals on viral suppression. J Med Virol 2020 Apr 21. doi: 10.1002/jmv.25911.
22. Castilho JL, Shepherd BE, Koethe J, Turner M, Bebawy S, Logan J, et al. CD4+/CD8+ ratio, age, and risk of serious noncommunicable diseases in HIV-infected adults on antiretroviral therapy. AIDS 2016; 30:899–908. [PubMed: 26959354]
23. Bernal E, Serrano J, Perez A, Valero S, Garcia E, Marin I, et al. The CD4:CD8 ratio is associated with IMT progression in HIV-infected patients on antiretroviral treatment. J Int AIDS Soc 2014; 17 (4 Suppl 3):19723. [PubMed: 25397469]
24. Utama S, Patriawan P, Dewi A. Correlation of CD4/CD8 ratio with carotid intima-media layer thickness in HIV/AIDS patients at Sanglah General Hospital, Bali, Indonesia. Open Access Maced J Med Sci 2019; 7:1803–1807. [PubMed: 31316662]
25. Francis-Morris A, Mackie NE, Eliahoo J, Ramzan F, Fidler S, Pollock KM. Compromised CD4:CD8 ratio recovery in people living with HIV aged over 50 years: an observational study. HIV Med 2020; 21:109–118. [PubMed: 31617962]
26. Gras L, May M, Ryder LP, Trickey A, Helleberg M, Obel N, et al. Antiretroviral Therapy Cohort Collaboration (ART-CC). Determinants of Restoration of CD4 and CD8 Cell Counts and Their

Ratio in HIV-1-Positive Individuals With Sustained Virological Suppression on Antiretroviral Therapy. J Acquir Immune Defic Syndr 2019; 80:292–300. [PubMed: 30531492]

27. Trickey A, May MT, Schommers P, Tate J, Ingle SM, Guest JL, et al. Antiretroviral Therapy Cohort Collaboration (ART-CC). CD4:CD8 ratio and CD8 count as prognostic markers for mortality in human immunodeficiency virus-infected patients on antiretroviral therapy: the Antiretroviral Therapy Cohort Collaboration (ART-CC). Clin Infect Dis 2017; 65:959–966. [PubMed: 28903507]

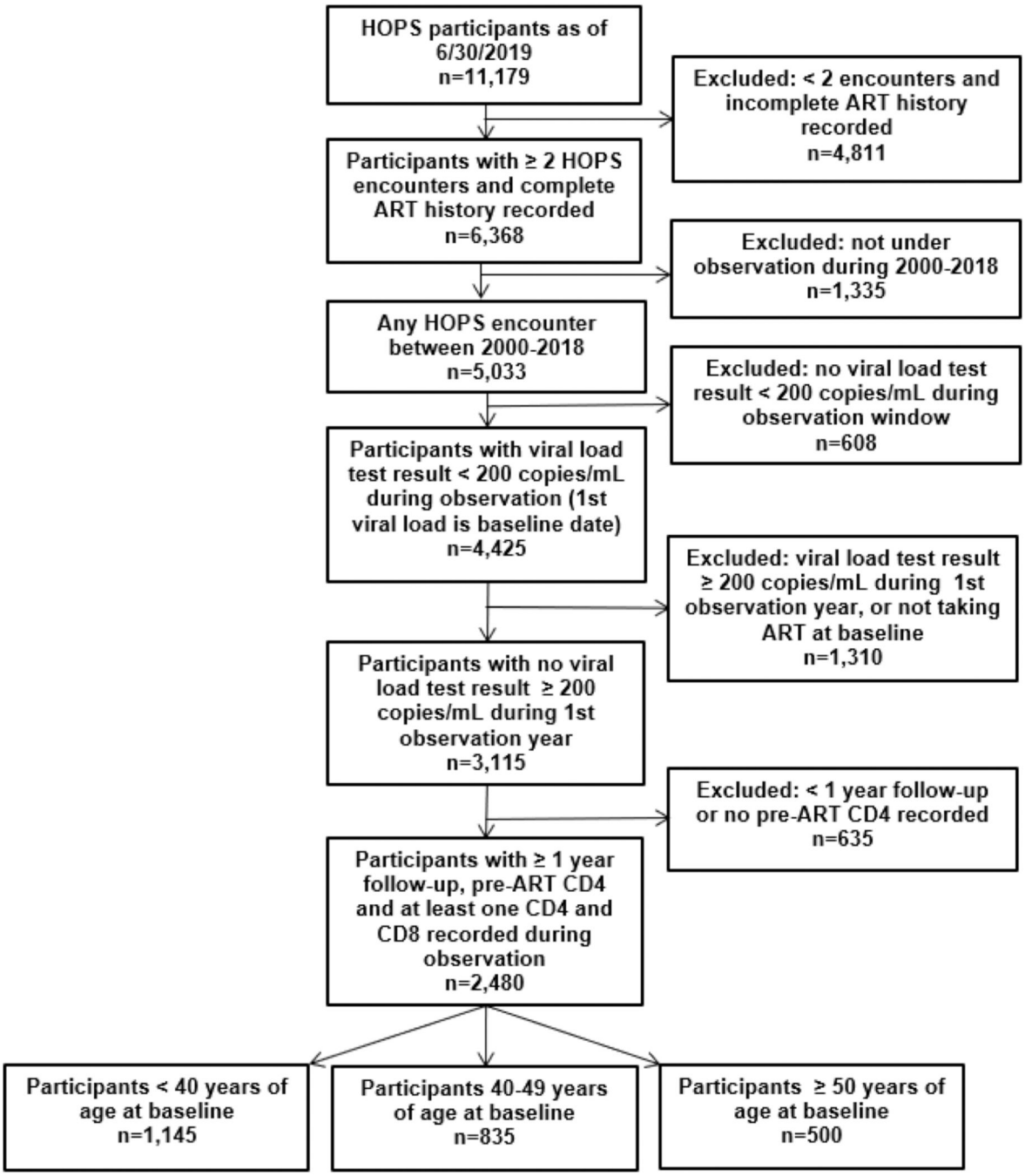
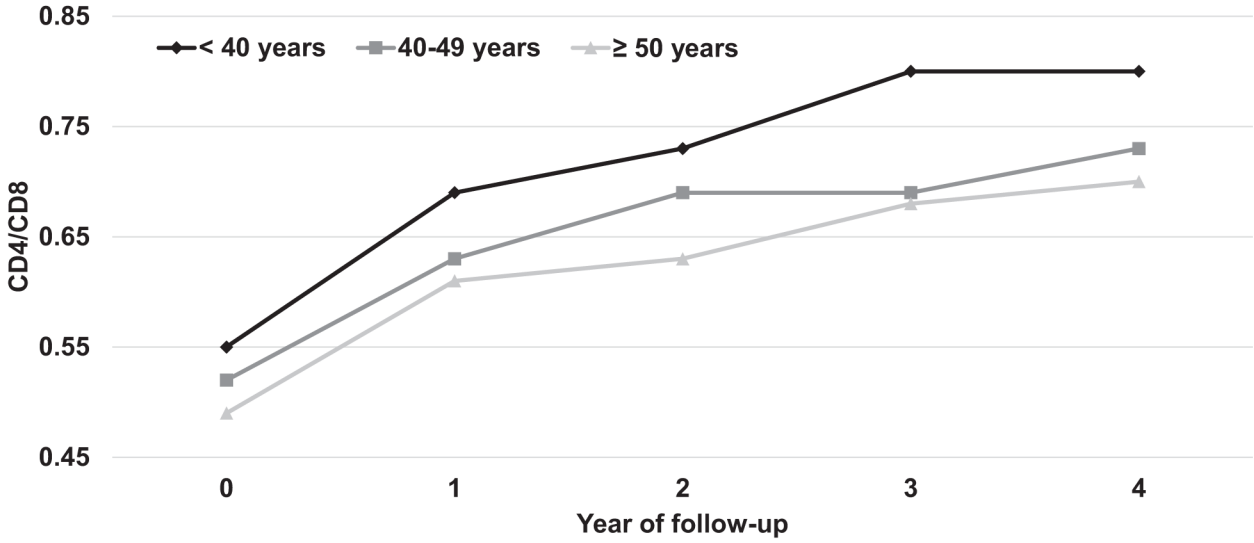


Fig. 1. Selection steps flowchart of patients included in the current analysis, the HIV Outpatient Study 2000–2018, *N* = 2480.

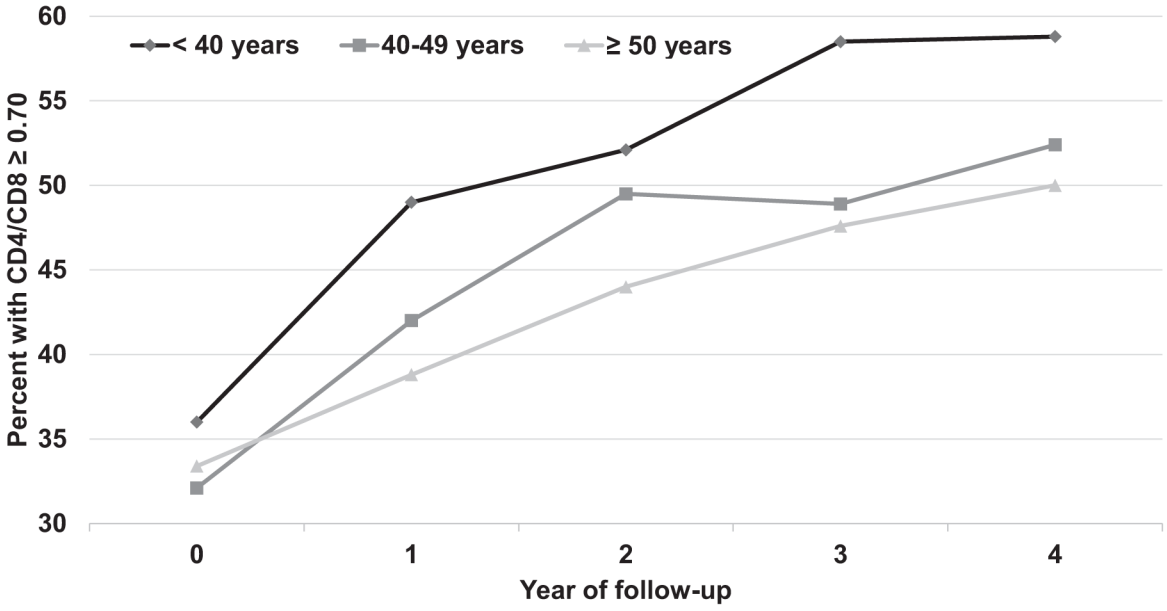
(a)



Baseline age, years	Year 0	Year 1	Year 2	Year 3	Year 4	P-value* across time
< 40	1,145	1,022	943	843	735	< 0.001
CD4/CD8: median (IQR)	0.55 (0.31-0.88)	0.69 (0.44-1.01)	0.73 (0.48-1.07)	0.80 (0.50-1.12)	0.80 (0.52-1.15)	
40-49	835	735	693	605	574	< 0.001
CD4/CD8: median (IQR)	0.52 (0.31-0.81)	0.63 (0.41-0.92)	0.69 (0.46-1.02)	0.69 (0.45-1.03)	0.73 (0.49-1.06)	
≥ 50	500	448	425	370	322	< 0.001
CD4/CD8: median (IQR)	0.49 (0.29-0.81)	0.61 (0.38-0.92)	0.63 (0.40-0.99)	0.68 (0.43-1.06)	0.70 (0.45-1.00)	
P-value* across age groups	0.18	< 0.001	0.003	< 0.001	< 0.001	

* Jonckheere-Terpstra test of trend
Abbreviation: IQR, interquartile range.

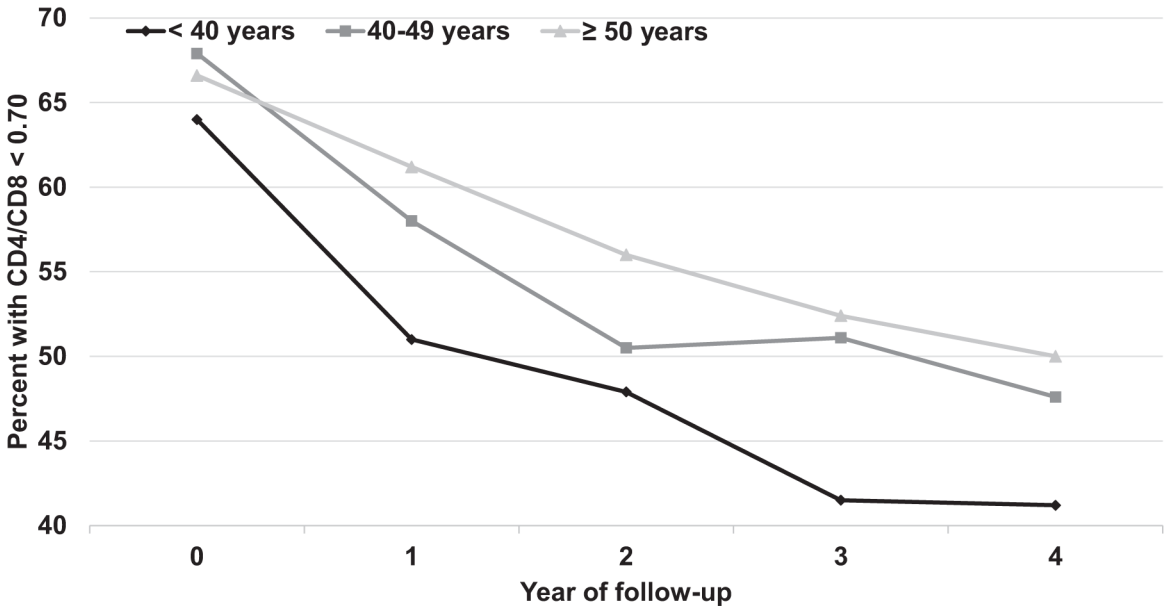
(b)



Baseline age, years	Year 0	Year 1	Year 2	Year 3	Year 4	P-value* across time
< 40	1,145	1,022	943	843	735	< 0.001
≥ 0.70, n (%)	412 (36.0)	501 (49.0)	491 (52.1)	493 (58.5)	432 (58.8)	
40-49	835	735	693	605	574	< 0.001
≥ 0.70, n (%)	268 (32.1)	309 (42.0)	343 (49.5)	296 (48.9)	301 (52.4)	
≥ 50	500	448	425	370	322	< 0.001
≥ 0.70, n (%)	167 (33.4)	174 (38.8)	187 (44.0)	176 (47.6)	161 (50.0)	
P-value* across age groups	0.18	< 0.001	0.007	< 0.001	0.004	

* Cochran-Armitage test of trend.

(c)



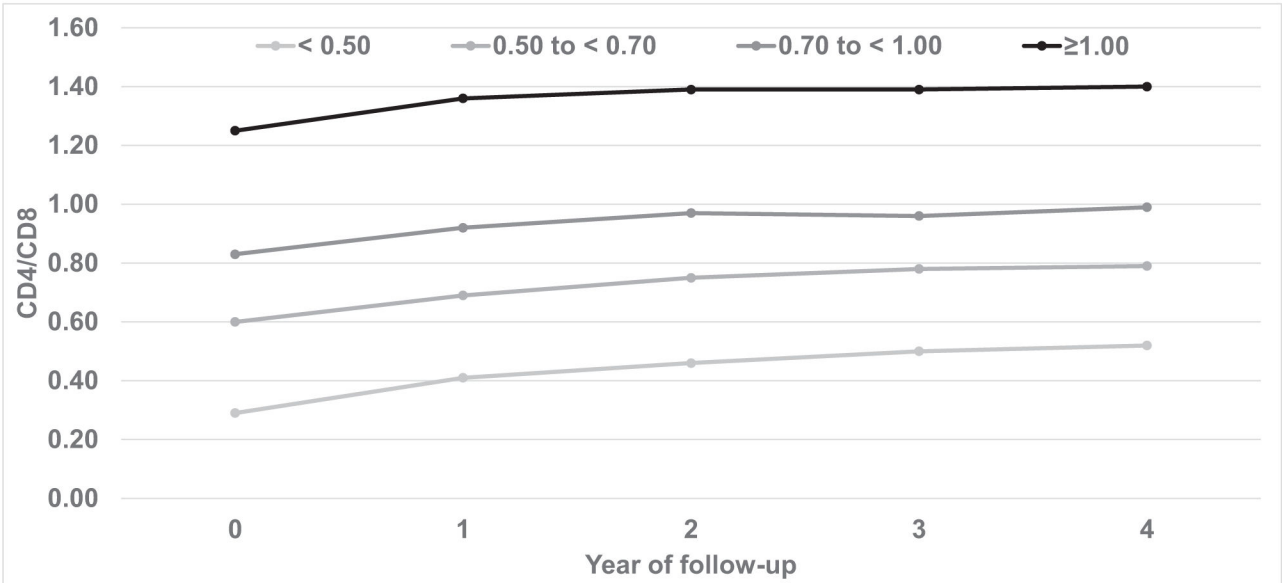
Baseline age, years	Year 0	Year 1	Year 2	Year 3	Year 4	P-value* across time
< 40	1,145	1,022	943	843	735	< 0.001
< 0.70, n (%)	733 (64.0)	521 (51.0)	452 (47.9)	350 (41.5)	303 (41.2)	
40-49	835	735	693	605	574	< 0.001
< 0.70, n (%)	567 (67.9)	426 (58.0)	350 (50.5)	309 (51.1)	273 (47.6)	
≥ 50	500	448	425	370	322	< 0.001
< 0.70, n (%)	333 (66.6)	274 (61.2)	238 (56.0)	194 (52.4)	161 (50.0)	
P-value* across age groups	0.18	< 0.001	0.007	< 0.001	0.004	

* Cochran-Armitage test of trend.

Fig. 2. (a) Median $CD4^+/CD8^+$ by baseline age group and year of follow-up, the HIV Outpatient Study, 2000–2018, *N* = 2480.

*Jonckheere~Terpstra test of trend. IQR, interquartile range. (b) Percentage of participants with $CD4^+/CD8^+$ at least 0.70 by baseline age group and year of follow-up, the HIV Outpatient Study, 2000–2018, N = 2480. *Cochran–Armitage test of trend. (c) Percentage of participants with $CD4^+/CD8^+$ less than 0.70 by baseline age group and year of follow-up, the HIV Outpatient Study, 2000–2018, N = 2480. *Cochran–Armitage test of trend.

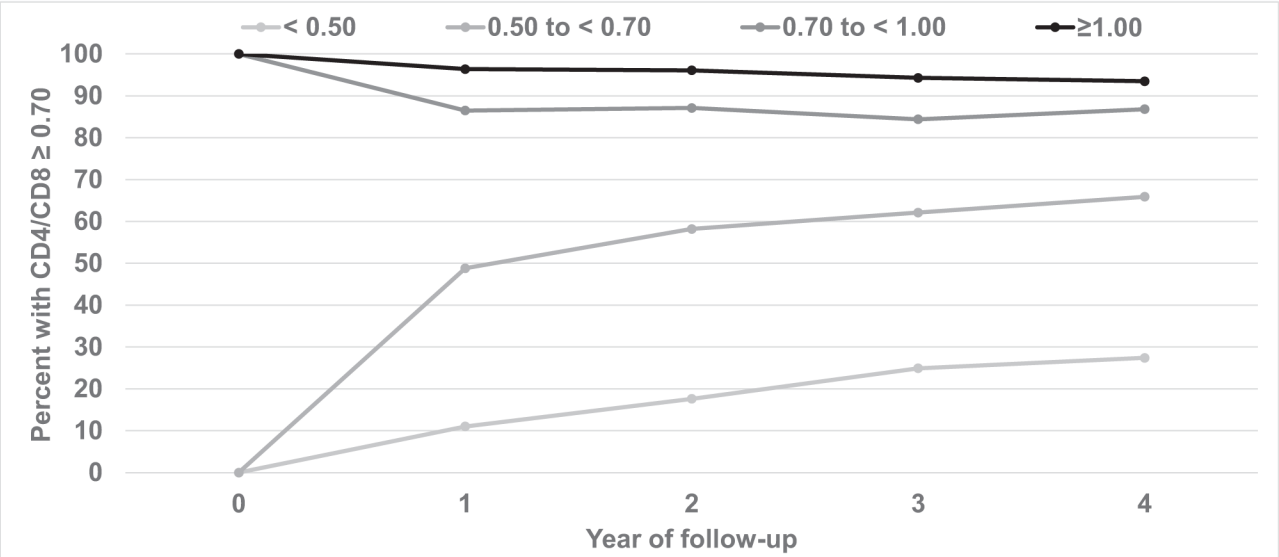
(a)



Baseline CD4/CD8	Year 0	Year 1	Year 2	Year 3	Year 4	P-value* across time
< 0.50	1,172	1,064	994	881	798	
CD4/CD8: median (IQR)	0.29 (0.18-0.39)	0.41 (0.28-0.55	0.46 (0.32-0.62)	0.5 (0.34-0.70)	0.52 (0.36-0.73)	< 0.001
0.50 to < 0.70	461	414	392	335	314	
CD4/CD8: median (IQR)	0.60 (0.55-0.65)	0.69 (0.60-0.84)	0.75 (0.61-0.92)	0.78 (0.62-0.98)	0.79 (0.65-1.00)	< 0.001
0.70 to < 1.00	417	364	340	301	257	
CD4/CD8: median (IQR)	0.83 (0.77-0.90)	0.92 (0.78-1.09)	0.97 (0.82-1.17)	0.96 (0.80-1.23)	0.99 (0.81-1.21)	< 0.001
≥ 1.00	430	363	335	301	262	
CD4/CD8: median (IQR)	1.25 (1.11-1.54)	1.36 (1.10-1.63)	1.39 (1.13-1.66)	1.39 (1.12-1.75)	1.40 (1.12-1.77)	0.049
P-value* across baseline CD4/CD8 ranges	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	

* Jonckheere-Terpstra test of trend
Abbreviation: IQR, interquartile range.

(b)



Baseline CD4/CD8	Year 0	Year 1	Year 2	Year 3	Year 4	P-value* across time
< 0.50	1,172	1,064	994	881	798	< 0.001
≥ 0.7, n (%)	0 (0.0)	117 (11.0)	175 (17.6)	219 (24.9)	219 (27.4)	
0.50 to < 0.70	461	414	392	335	314	< 0.001
≥ 0.7, n (%)	0 (0.0)	202 (48.8)	228 (58.2)	208 (62.1)	207 (65.9)	
0.70 to < 1.00	417	364	340	301	257	< 0.001
≥ 0.7, n (%)	417 (100.0)	315 (86.5)	296 (87.1)	254 (84.4)	223 (86.8)	
≥ 1.00	430	363	335	301	262	< 0.001
≥ 0.7, n (%)	430 (100.0)	350 (96.4)	322 (96.1)	284 (94.4)	245 (93.5)	
P-value* across baseline CD4/CD8 ranges	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	

* Cochran-Armitage test of trend.

Fig. 3. (a) Median $CD4^+/CD8^+$ by baseline $CD4^+/CD8^+$ range and year of follow-up, the HIV Outpatient Study, 2000–2018, N = 2480.

*Jonckheere-Terpstra test of trend. IQR, interquartile range. (b) Percentage of participants with $CD4^+/CD8^+$ at least 0.70 by baseline $CD4^+/CD8^+$ range and year of follow-up, the HIV Outpatient Study, 2000–2018, N = 2480. *Cochran-Armitage test of trend.

Table 1.

Characteristics at baseline of participants by age group, the HIV Outpatient Study, 2000–2018, N U 2480.

Baseline characteristic[a]	N (column %)	Age less than 40 years	Age 40–49 years	Age at least 50 years	*P* value[b]
Overall	2480 (100.0)	1145 (46.2)	835 (33.7)	500 (20.2)	
Sex					0.36
Male	2023 (81.6)	925 (80.8)	686 (82.2)	412 (82.4)	
Female	457 (18.4)	220 (19.2)	149 (17.8)	88 (17.6)	
Race/ethnicity					<0.001
White, non-Hispanic/Latino	1281 (51.6)	541 (47.2)	459 (55.0)	281 (56.2)	
Black, non-Hispanic/Latino	778 (31.4)	375 (32.8)	256 (30.7)	147 (29.4)	
Hispanic/Latino	322 (13.0)	176 (15.4)	91 (10.9)	55 (11.0)	
Other/unknown	99 (4.0)	53 (4.6)	29 (3.5)	17 (3.4)	
HIV transmission risk activity					<0.001
MSM	1561 (62.9)	767 (67.0)	522 (62.5)	272 (54.4)	
Heterosexual	625 (25.2)	275 (24.0)	209 (25.0)	141 (28.2)	
PWID	155 (6.3)	38 (3.3)	65 (7.8)	52 (10.4)	
Other/unknown	139 (5.6)	65 (5.7)	39 (4.7)	35 (7.0)	
Payer					0.013
Private	1486 (59.9)	692 (60.4)	520 (62.3)	274 (54.8)	
Public	772 (31.1)	340 (29.7)	245 (29.3)	187 (37.4)	
No insurance	222 (9.0)	113 (9.9)	70 (8.4)	39 (7.8)	
ART initiation year					<0.001
Started ART before 2000	739 (29.8)	292 (25.5)	296 (35.5)	151 (30.2)	
Started ART during 2001–2007	948 (38.2)	443 (38.7)	315 (37.7)	190 (38.0)	
Started ART during 2008–2012	558 (22.5)	270 (23.6)	172 (20.6)	116 (23.2)	
Started ART during 2013–2017	235 (9.5)	140 (12.2)	52 (6.2)	43 (8.6)	
HIV diagnosis date					<0.001
Before 2000	1147 (46.3)	415 (36.2)	477 (57.1)	255 (51.0)	
During 2001–2007	820 (33.1)	431 (37.6)	231 (27.7)	158 (31.6)	
During 2008–2012	353 (14.2)	204 (17.8)	87 (10.4)	62 (12.4)	
During 2013–2017	160 (6.5)	95 (8.3)	40 (4.8)	25 (5.0)	

Baseline characteristic[a]	N (column %)	Age less than 40 years	Age 40–49 years	Age at least 50 years	*P* value[b]
Years from HIV diagnosis to starting ART, median (IQR)	1.7 (0.2–6.3)	0.9 (0.2–3.9)	2.9 (0.3–8.6)	2.7 (0.2–8.0)	<0.001
Type of HOPS site					0.90
Public clinic	861 (34.7)	408 (35.6)	261 (31.3)	192 (38.4)	
Private clinic	1619 (65.3)	737 (64.4)	574 (68.7)	308 (61.6)	
Smoking status					0.002
Current/prior smoker	1185 (47.8)	505 (44.1)	415 (49.7)	265 (53.0)	
Not a current/prior smoker	1295 (52.2)	640 (55.9)	420 (50.3)	235 (47.0)	
Alcohol use					0.22
No alcohol use	1143 (46.1)	500 (43.7)	409 (49.0)	234 (46.8)	
<7 alcoholic drinks/week	1032 (41.6)	512 (44.7)	323 (38.7)	197 (39.4)	
7–14 alcoholic drinks/week	196 (7.9)	83 (7.3)	63 (7.5)	50 (10.0)	
> 14 alcoholic drinks/week	109 (4.4)	50 (4.4)	40 (4.8)	19 (3.8)	
ART regimen					<0.001
On first regimen	1483 (59.8)	757 (66.1)	446 (53.4)	280 (56.0)	
On second regimen	238 (9.6)	103 (9.0)	81 (9.7)	54 (10.8)	
On third regimen	239 (9.6)	106 (9.3)	85 (10.2)	48 (9.6)	
On fourth or higher regimen	520 (21.0)	179 (15.6)	223 (26.7)	118 (23.6)	
Type of ART regimen					0.002
NNRTI	1012 (40.8)	496 (43.3)	331 (39.6)	185 (37.0)	
PI	994 (40.1)	434 (37.9)	342 (41.0)	218 (43.6)	
INSTI	292 (11.8)	145 (12.7)	91 (10.9)	56 (11.2)	
PI+NNRTI	120 (4.8)	44 (3.8)	51 (6.1)	25 (5.0)	
Other	62 (2.5)	26 (2.3)	20 (2.4)	16 (3.2)	
One pill daily cART regimen	503 (20.3)	263 (23.0)	140 (16.8)	100 (20.0)	0.017
$CD4^+/CD8^+$					0.08
<0.50	1172 (47.3)	520 (45.4)	397 (47.5)	255 (51.0)	
0.50 to <0.70	461 (18.6)	213 (18.6)	170 (20.4)	78 (15.6)	
0.70 to < 1.00	417 (16.8)	210 (18.3)	127 (15.2)	80 (16.0)	
> 1.00	430 (17.3)	202 (17.6)	141 (16.9)	87 (17.4)	
$CD4^+$ cell count (cells/ml)[a]					0.044

Baseline characteristic[a]	N (column %)	Age less than 40 years	Age 40–49 years	Age at least 50 years	*P* value[b]
<200	337 (13.6)	149 (13.0)	123 (14.7)	65 (13.0)	
200–349	545 (22.0)	232 (20.3)	181 (21.7)	132 (26.4)	
350–499	515 (20.8)	249 (21.7)	161 (19.3)	105 (21.0)	
≥500	1083 (43.7)	515 (45.0)	370 (44.3)	198 (39.6)	
Prevalent outcomes (at baseline[a])					
Cardiovascular disease	199 (8.0)	45 (3.9)	72 (8.6)	82 (16.4)	<0.001
Cancer (non-AIDS)	50 (2.0)	12 (1.0)	15 (1.8)	23 (4.6)	<0.001
Renal disease	144 (5.8)	30 (2.6)	50 (6.0)	64 (12.8)	<0.001
Dyslipidemia	678 (27.3)	213 (18.6)	247 (29.6)	218 (43.6)	<0.001
Diabetes	130 (5.2)	26 (2.3)	54 (6.5)	50 (10.0)	<0.001
Incident outcomes during follow-up					
Years follow-up, median (IQR)	7.4 (4.1–12.2)	6.9 (4.0–12.4)	8.3 (4.4–12.3)	7.3 (4.3–11.6)	0.10
Years with viral load < 200 copies/ml [median (IQR)]	7.0 (3.6–11.9)	6.4 (3.4–12.0)	7.9 (3.9–12.0)	6.9 (3.8–11.3)	0.10
Percentage follow-up with viral load <200 copies/ml [median (IQR)]	99 (94–100)	99 (92–100)	99 (95–100)	99 (94–100)	0.044
Died within 6 months of last HOPS contact	124 (5.0)	20 (1.8)	54 (6.5)	50 (10.0)	
Cardiovascular disease	4 (0.2)	3 (0.3)	0 (0.0)	1 (0.2)	
Cancer (non-AIDS)	152 (6.1)	29 (2.5)	53 (6.3)	70 (14.0)	
Renal disease	16 (0.6)	1 (0.1)	6 (0.7)	9 (1.8)	
Dyslipidemia	27 (1.1)	9 (0.8)	14 (1.7)	4 (0.8)	
Diabetes	4 (0.2)	0 (0.0)	2 (0.2)	2 (0.4)	

ART, antiretroviral therapy; cART, combination antiretroviral therapy; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleoside analog reverse transcriptase inhibitor; PI, protease inhibitor; PWID, people who inject drugs.

[a]Baseline is the date of the first viral load test result less than 200copies/ml on or after 1 January 2000.

[b]Jonckheere–Terpstra test of trend.

Table 2.

Cox proportional hazards analyses of factors associated with incident non-AIDS cancer (v = 2425,[a] outcomes = 147) and mortality (v = 2480, outcomes = 124): the HIV Outpatient Study, 2000–2018.

	Outcome: non-AIDS cancer (= 2425[a], outcomes = 147)						Outcome: mortality (N = 2480, outcomes = 124)					
	Univariate		Multivariable		Multivariable, backward selection		Univariate		Multivariable		Multivariable, backward selection	
Participant characteristics	**HR (95% CI)**	***P* value**	**aHR (95% CI)**	***P* value**	**aHR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**aHR (95% CI)**	***P* value**	**aHR (95% CI)**	***P* value**
Age group (years)												
<40	0.15 (0.09–0.23)	<0.001	0.15 (0.10–0.24)	<0.001	0.16 (0.10–0.24)	<0.001	0.16 (0.10–0.28)	<0.001	0.23 (0.13–0.40)	<0.001	0.24 (0.14–0.41)	<0.001
40–49	0.39 (0.27–0.56)	<0.001	0.39 (0.27–0.56)	<0.001	0.41 (0.28–0.58)	<0.001	0.59 (0.40–0.86)	0.007	0.61 (0.41–0.91)	0.017	0.65 (0.44–0.96)	0.032
≥50 years	Referent		Referent		Referent		Referent		Referent		Referent	
Sex												
Male	Referent		Referent				Referent		Referent		Referent	
Female	0.72 (0.46–1.12)	0.15	0.76 (0.47–1.23)	0.26			0.49 (0.28–0.86)	0.013	0.45 (0.23–0.87)	0.017	0.52 (0.28–0.98)	0.041
Race/ethnicity												
White, non- Hispanic/ Latino	Referent		Referent				Referent		Referent			
Black, non-Hispanic/ Latino	1.31 (0.93–1.86)	0.13	1.51 (1.01–2.25)	0.043			1.67 (1.15–2.41)	0.007	1.42 (0.90–2.22)	0.13		
Hispanic/Latino	0.71 (0.39–1.28)	0.25	0.91 (0.49–1.68)	0.75			0.71 (0.36–1.39)	0.32	0.91 (0.44–1.88)	0.79		
Other/unknown	1.01 (0.41–2.49)	0.99	1.45 (0.58–3.61)	0.43			0.54 (0.13–2.20)	0.39	0.87 (0.21–3.63)	0.84		
HIV transmission risk activity												
MSM	Referent						Referent		Referent		Referent	
Heterosexual	0.94 (0.64–1.38)	0.74					0.94 (0.59–1.49)	0.79	0.98 (0.55–1.76)	0.95	1.21 (0.71–2.07)	0.47
PWID	1.36 (0.77–2.39)	0.29					4.05 (2.62–6.27)	<0.001	1.85 (1.05–3.25)	0.033	2.47 (1.54–3.96)	<0.001

Participant characteristics	Outcome: non-AIDS cancer (= 2425[a], outcomes = 147)						Outcome: mortality (*N* = 2480, outcomes = 124)					
	Univariate		Multivariable		Multivariable, backward selection		Univariate		Multivariable		Multivariable, backward selection	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value	aHR (95% CI)	*P* value	HR (95% CI)	*P* value	aHR (95% CI)	*P* value	aHR (95% CI)	*P* value
Other/unknown	1.00 (0.49–2.06)	1.00					1.29 (0.59–2.81)	0.53	1.22 (0.54–2.78)	0.64	1.30 (0.58–2.88)	0.53
Payer												
Private	Referent		Referent				Referent		Referent			
Public	1.31 (0.93–1.84)	0.13	1.18 (0.80–1.74)	0.40			2.08 (1.45–3.00)	<0.001	1.44 (0.94–2.22)	0.09		
No insurance	0.60 (0.29–1.23)	0.16	0.55 (0.26–1.16)	0.12			0.92 (0.44–1.92)	0.82	0.88 (0.41–1.90)	0.75		
ART initiation date												
Started ART before 2000	0.69 (0.31–1.57)	0.38					2.48 (0.59–10.38)	0.21				
Started ART during 2001 – 2007	0.62 (0.28–1.41)	0.25					1.44 (0.34–6.10)	0.62				
Started ART during 2008–2012	0.63 (0.26–1.51)	0.30					0.81 (0.17–3.86)	0.79				
Started ART during 2013–2017	Referent						Referent					
Years from HIV diagnosis to starting ART	1.02 (0.99–1.06)	0.19					1.05 (1.01–1.08)	0.007	0.99 (0.95–1.03)	0.47		
Type of HOPS site												
Public clinic	0.95 (0.67–1.33)	0.74					1.64 (1.16–2.34)	<0.006	1.05 (0.66–1.68)	0.83		
Private clinic	Referent						Referent		Referent			
Smoking status												
Current/prior smoker	1.05 (0.76–1.46)	0.75					2.50 (1.71–3.67)	<0.001	1.74 (1.14–2.64)	0.010	1.88 (1.26–2.81)	0.002
Not a current/prior smoker	Referent						Referent		Referent		Referent	
Alcohol use												
No alcohol use	Referent		Referent		Referent		Referent		Referent			
<7 alcoholic drinks/week	1.45 (1.02–2.06)	0.037	1.67 (1.16–2.42)	0.006	1.62 (1.14–2.30)	0.008	0.67 (0.45–1.00)	0.047	0.87 (0.56–1.34)	0.52		

Participant characteristics	Outcome: non-AIDS cancer (= 2425[a], outcomes = 147)						Outcome: mortality (*N* = 2480, outcomes = 124)					
	Univariate		Multivariable		Multivariable, backward selection		Univariate		Multivariable		Multivariable, backward selection	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value	aHR (95% CI)	*P* value	HR (95% CI)	*P* value	aHR (95% CI)	*P* value	aHR (95% CI)	*P* value
7–14 alcoholic drinks/ week	1.50 (0.82–2.73)	0.19	1.50 (0.81–2.77)	0.19	1.50 (0.82–2.74)	0.19	1.16 (0.63–2.13)	0.64	1.29 (0.68–2.47)	0.44		
> 14 alcoholic drinks/ week	1.57 (0.75–3.28)	0.23	1.83 (0.86–3.87)	0.12	1.84 (0.88–3.87)	0.11	1.02 (0.44–2.36)	0.96	0.89 (0.37–2.13)	0.79		
ART regimen												
On first regimen	Referent						Referent		Referent		Referent	
On second regimen	0.82 (0.45–1.48)	0.51					1.26 (0.66–2.39)	0.48	1.42 (0.73–2.77)	0.30	1.40 (0.73–2.69)	0.32
On third regimen	1.29 (0.74–2.24)	0.38					2.67 (1.56–4.58)	<0.001	2.22 (1.26–3.93)	0.006	2.18 (1.26–3.78)	0.005
On fourth or higher regimen	1.25 (0.86–1.82)	0.24					2.23 (1.48–3.36)	<0.001	1.77 (1.10–2.86)	0.019	1.72 (1.12–2.65)	0.014
Type of ART regimen, first during observation												
NNRTI	Referent		Referent				Referent		Referent			
PI	1.36 (0.95–1.94)	0.09	1.16 (0.81–1.67)	0.41			1.49 (1.01–2.21)	0.044	0.99 (0.65–1.49)	0.96		
NST1	1.61 (0.81–3.22)	0.18	1.32 (0.66–2.66)	0.43			0.43 (0.10–1.78)	0.24	0.43 (0.10–1.81)	0.25		
P1+NNRT1	0.93 (0.42–2.06)	0.86	0.75 (0.34–1.67)	0.48			2.02 (1.06–3.85)	0.034	1.12 (0.57–2.22)	0.74		
Other	0.77 (0.24–2.48)	0.66	0.84 (0.26–2.72)	0.77			0.67 (0.16–2.76)	0.58	0.59 (0.14–2.49)	0.47		
Baseline $CD4^+$cell count (cells/pl)												
<200	2.16 (1.38–3.37)	<0.001	1.53 (0.87–2.68)	0.14			2.86 (1.80–4.55)	<0.001	1.35 (0.74–2.48)	0.33	1.42 (0.84–2.43)	0.19
200–349	1.44 (0.94–2.21)	0.09	1.00 (0.61–1.64)	1.00			1.95 (1.25–3.05)	0.003	0.97 (0.57–1.67)	0.92	1.04 (0.64–1.69)	0.88
350–499	1.20 (0.76–1.89)	0.44	1.00 (0.62–1.63)	0.99			0.70 (0.37–1.31)	0.26	0.45 (0.23–0.88)	0.019	0.50 (0.27–0.96)	0.036
≥500	Referent		Referent				Referent		Referent		Referent	
$CD4^+/CD8^+$, first during observation												

	Outcome: non-AIDS cancer (= 2425[a], outcomes = 147)						Outcome: mortality (*N* = 2480, outcomes = 124)					
	Univariate		Multivariable		Multivariable, backward selection		Univariate		Multivariable		Multivariable, backward selection	
Participant characteristics	**HR (95% CI)**	***P* value**	**aHR (95% CI)**	***P* value**	**aHR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**aHR (95% CI)**	***P* value**	**aHR (95% CI)**	***P* value**
<0.50	2.24 (1.31–3.85)	0.003	0.88 (0.44–1.77)	0.73			3.42 (1.72–6.84)	<0.001	0.94 (0.40–2.23)	0.89		
0.50 to <0.70	2.20 (1.21–4.02)	0.010	1.31 (0.68–2.55)	0.42			2.50 (1.16–5.41)	0.020	1.46 (0.63–3.40)	0.38		
0.70 to <1.00	1.47 (0.78–2.78)	0.24	1.01 (0.52–1.97)	0.97			1.58 (0.68–3.65)	0.28	1.16 (0.49–2.77)	0.74		
≥1.00	Referent		Referent				Referent		Referent			
$CD4^+/CD8^+$, most recent during observation												
<0.50	3.11 (1.99–4.88)	<0.001	2.64 (1.53–4.58)	<0.001	2.82 (1.80–4.42)	<0.001	7.69 (4.54–13.00)	<0.001	5.21 (2.73–9.96)	<0.001	4.82 (2.67–8.70)	<0.001
0.50 to <0.70	2.29 (1.40–3.75)	<0.001	1.98 (1.15–3.42)	0.015	1.98 (1.21–3.24)	0.007	3.33 (1.81–6.10)	<0.001	2.43 (1.24–4.74)	0.010	2.46 (1.31–4.62)	0.005
0.70 to <1.00	1.88 (1.17–3.00)	0.009	1.77 (1.07–2.94)	0.026	1.81 (1.13–2.89)	0.014	1.78 (0.93–3.39)	0.08	1.58 (0.80–3.11)	0.19	1.57 (0.82–3.01)	0.18
≥1.00	Referent		Referent		Referent		Referent		Referent		Referent	

aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWID, people who inject drugs.

[a]Study population limited to people without prior cancer.