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Individual Differences in CD4/CD8 T-Cell Ratio Trajectories and Associated Risk Profiles Modeled From Acute HIV Infection

Robert Paul, PhD, Kyu Cho, MS, Jacob Bolzenius, PhD, Carlo Sacdalan, MD, Lishomwa C. Ndhlovu, MD, PhD, Lydie Trautmann, PhD, Shelly Krebs, PhD, Somporn Tipsuk, MD, Trevor A. Crowell, MD, PhD, Duanghathai Suttichom, MD, Donn J. Colby, MD, Thomas A. Premeaux, PhD, Nittaya Phanuphak, MD, PhD, Phillip Chan, MBChB, PhD, Eugène Kroon, MD, Sandhya Vasan, MD, Denise Hsu, MBBS, PhD, Adam Carrico, PhD, Victor Valcour, MD, PhD, Jintanat Ananworanich, MD, PhD, Merlin L. Robb, MD, Julie A. Ake, MD, Somchai Sriplienchan, MD, MPH, and Serena Spudich, MD, for the RV254/SEARCH 010 Study Team

ABSTRACT

Objective: We examined individual differences in CD4/CD8 T-cell ratio trajectories and associated risk profiles from acute HIV infection (AHI) through 144 weeks of antiretroviral therapy (ART) using a data-driven approach.

Methods: A total of 483 AHI participants began ART during Fiebig I–V and completed follow-up evaluations for 144 weeks. CD4+, CD8+, and CD4/CD8 T-cell ratio trajectories were defined followed by analyses to identify associated risk variables.

Results: Participants had a median viral load (VL) of 5.88 copies/ml and CD4/CD8 T-cell ratio of 0.71 at enrollment. After 144 weeks of ART, the median CD4/CD8 T-cell ratio was 1.3. Longitudinal models revealed five CD4/CD8 T-cell ratio subgroups: group 1 (3%) exhibited a ratio >1.0 at all visits; groups 2 (18%) and 3 (29%) exhibited inversion at enrollment, with normalization 4 and 12 weeks after ART, respectively; and groups 4 (31%) and 5 (18%) experienced CD4/CD8 T-cell ratio inversion due to slow CD4+ T-cell recovery (group 4) or high CD8+ T-cell count (group 5). Persistent inversion corresponded to ART onset after Fiebig II, higher VL, soluble CD27 and TIM-3, and lower eosinophil count. Individuals with slow CD4+ T-cell recovery exhibited higher VL, lower white blood cell count, lower basophil percent, and treatment with standard ART, as well as worse mental health and cognition, compared with individuals with high CD8+ T-cell count.

Conclusions: Early HIV disease dynamics predict unfavorable CD4/CD8 T-cell ratio outcomes after ART. CD4+ and CD8+ T-cell trajectories contribute to inversion risk and correspond to specific viral, immune, and psychological profiles during AHI. Adjunctive strategies to achieve immune normalization merit consideration.

Key words: HIV, CD4/CD8 T-cell ratio, machine learning, GBTA, trajectories, ART.

INTRODUCTION

The CD4/CD8 T-cell ratio represents an important indicator of HIV disease severity and response to antiretroviral therapy (ART) (1). People with HIV (PWH) with persistent CD4/CD8 T-cell ratio inversion (defined as a ratio <1.0) exhibit elevated biomarkers of T-cell activation, exhaustion, and immunosenescence

AHI = acute HIV infection, **ART** = antiretroviral therapy, **AUC** = area under the curve, **DTG** = dolutegravir, **EIA** = enzyme immunoassay, **GBM** = gradient-boosted multivariate regression, **GBMTA** = group-based multitrajectory analysis, **IgM** = immunoglobin M, **IQR** = interquartile range, **QOL** = quality of life, **PWH** = people with HIV, **VL** = viral load, **WBC** = white blood cell

SDC Supplemental Digital Content

From the Department of Psychological Sciences (Paul) and Missouri Institute of Mental Health (Cho, Bolzenius), University of Missouri, St. Louis, Missouri; SEARCH (Sacdalan, Tipsuk, Suttichom, Phanuphak, Chan, Kroon, Sriplienchan), Institute of HIV Research and Innovation (IHRI), Bangkok, Thailand; Department of Medicine, Division of Infectious Diseases (Ndhlovu, Premeaux), Weill Cornell Medicine, New York City, New York; Vaccine and Gene Therapy Institute (Trautmann), Oregon Health and Science University, Beaverton, Oregon; U.S. Military HIV Research Program (Krebs, Crowell, Colby, Vasan, Hsu, Robb, Ake), Walter Reed Army Institute of Research, Silver Spring; Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (Krebs, Crowell, Colby, Vasan, Hsu, Robb), Inc., Bethesda, Maryland; Department of Neurology (Chan, Spudich), Yale University School of Medicine, New Haven, Connecticut; Department of Public Health Sciences (Carrico), University of Miami Miller School of Medicine, Miami, Florida; Memory and Aging Center, Department of Neurology (Valcour), University of California, San Francisco, California; Department of Global Health, Amsterdam Medical Center (Ananworanich), University of Amsterdam, Amsterdam, the Netherlands.

Address correspondence to Robert Paul, PhD, St. Louis Missouri Institute of Mental Health, University of Missouri, 1 University Boulevard, St. Louis, MO 63134. E-mail: paulro@umsl.edu

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(2–6). Relatedly, prior work using a bioinformatic framework (7) suggests that CD4/CD8 T-cell ratio is a robust biomarker of T-cell pathogenesis among PWH. Persistent CD4/CD8 T-cell ratio inversion has been implicated in inflammatory mechanisms involved in the development of non–AIDS-related health comorbidities that emerge in the context of otherwise successful ART (4,5).

Unfortunately, up to 90% of PWH who initiate ART during chronic infection do not achieve CD4/CD8 T-cell ratio normalization after 2 or more years of sustained viral suppression (8,9). A number of studies report that higher viral load (VL), lower CD4+ T-cell count, and lower CD4/CD8 T-cell ratio at treatment onset predict CD4/CD8 T-cell ratio inversion after prolonged use of ART commenced during chronic infection (9–15). However, a few studies indicate that a subset of PWH exhibit persistent CD4/CD8 T-cell ratio inversion due to high CD8+ T-cell counts after ART (5,16,17). Most studies to date have been focused on chronic HIV. Few studies have examined the contribution of CD4+ and CD8+ T-cell perturbations on CD4/CD8 T-cell ratio risk profiles modeled from earlier disease stages.

A recent study of 84 individuals who initiated ART during the first 120 days of infection revealed that the study participants, as a group, achieved a median CD4/CD8 T-cell ratio >1.0 after 12 months of treatment (9). However, this milestone was not achieved universally by all study participants, as 30% of the study sample did not achieve a CD4/CD8 T-cell ratio >1.0 at any study visit. Furthermore, the median CD8+ T-cell count declined after ART initiation, suggesting that persistent inversion resulted from suboptimal CD4+ T-cell recovery. However, the study was not designed to identify the underlying disease mechanisms and associated risk profiles.

We leveraged the unique study design of RV254/SEARCH 010, a prospective investigation of acute HIV infection (AHI) and long-term response to ART (18–20). Novel to the current analysis, we used a recent advance in longitudinal multitrajectory clustering to identify the independent contributions of CD4+ and CD8+ T-cell profiles (before and after ART) on divergent CD4/CD8 T-cell ratio trajectories modeled from the first 30 days of HIV infection through 144 weeks of suppressive ART. Risk profiles and early mechanisms of persistent CD4/CD8 T-cell inversion were examined using a combination of group-based statistics and machine learning methods focused on information acquired at enrollment, before the onset of viral suppression from ART.

METHODS

Study Participants and Procedures

The study design for RV254/SEARCH 010 is described in detail elsewhere (ClinicalTrials.gov identification NCT00796146) (18–20). Briefly, eligibility criteria included the following: a) 18 years of age or older, b) confirmed diagnosis of AHI (Fiebig stages I–V), c) no history of ART, and d) ambulatory outpatient status. Data included in this analysis were acquired between 2009 and 2020. Participants initiated de novo ART and completed extensive clinical phenotyping at enrollment with structured follow-up visits thereafter through week 144. All study visits were completed at a single site in Bangkok, Thailand, with excellent fidelity to the parent protocol. Enrollment was voluntary, and participants provided written informed consent after a thorough explanation of the study procedures. The protocol was approved by the institutional review boards at the Faculty of Medicine, Chulalongkorn University, Yale School of Medicine, University of California, San Francisco, and Walter Reed Army Institute of Research.

Participant Characterization at Enrollment

Potential predictors of CD4/CD8 T-cell ratio trajectories included multidimensional data acquired at the time of enrollment into RV254/SEARCH 010 (i.e., pre-ART; see Table, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A870, for complete list of variables). The number of data observations for each variable is provided hereinafter in parentheses. As noted, a subset of participants underwent cellular immunophenotyping because this procedure was designated as optional in the parent protocol. Methods are summarized hereinafter with more detail available in prior publications (18–23).

Demographics (n = 483): age, sex, gender identity, and educational attainment.

HIV VL (n = 482): absolute and log-transformed VL. HIV-RNA quantification was performed using the COBAS AMPLICOR HIV-1 Monitor Test v1.5 or COBAS Taqman HIV-1 Test v2.0 (Roche Molecular Systems).

Fiebig stage (n = 483): Fiebig stages I–V was determined using a hierarchical algorithm applied to nucleic acid testing, sequential immunoassay, p24 antigen, and Western blot testing (24). The staging included the following: Fiebig I: RNA+, p24 antigen−, negative by immunoglobin M (IgM)–sensitive enzyme immunoassay (EIA); Fiebig II: RNA+, p24 antigen+, negative by IgM-sensitive EIA; Fiebig III: RNA+, positive by IgM-sensitive EIA, Western blot; Fiebig IV: RNA+, positive by IgM-sensitive EIA, Western blot indeterminate; and Fiebig V: RNA+, Western blot+ without p31 protein band.

ART regimen (n = 483): ART regimen, time from enrollment to ART onset, and time from estimated date of infection to ART. Before 2017, individuals received efavirenz, tenofovir disoproxil fumarate, and either lamivudine or emtricitabine, with a subset randomized to an intensified protocol that also included raltegravir plus maraviroc for 24 weeks. From 2017 forward, newly enrolled participants were prescribed abacavir, lamivudine, and dolutegravir (DTG), with a subset receiving maraviroc intensification for 96 weeks. Individuals enrolled before 2017 were switched to the DTG-based regimen. The change in ART regimen was implemented for the entire cohort in 2017 (unless medically contraindicated). Participants were virally controlled at the time of the switch. Prior work reveals similar clinical profiles before and after the switch to a DTG-based regimen (25).

Cellular immunophenotyping (n = 134): a subset of participants enrolled into RV254/SEARCH 010 completed optional procedures to facilitate cellular immunophenotyping. Plasma markers of inflammation and immune activation were quantified using either enzyme-linked immunoassay or multiplex immunoassay on a Luminex 200 (Millipore). Data were analyzed using a five-parameter fit logistic curve.

Routine laboratory assays (n = 480): total count and percent values from complete blood cell count analysis, antihepatitis C antibodies, hepatitis B surface antigen, and anti–hepatitis B Surface antigen antibodies were measured using chemiluminescent microparticle immunoassay (Abbott).

Mental health (n = 459), quality of life (QOL; n = 446), and substance use history (n = 446): participants completed the Patient Health Questionnaire-9 (26,27) and a self-report measure of QOL (28). Item-level responses and total scores were included in the analysis. Substance use history was determined via clinician interview and self-report. Past and current use (last 4 months) for each drug class was considered in the classification models (see Table, Supplementary Digital Content 1, http://links.lww.com/PSYMED/A870, for specific drug classes).

Cognitive performance (n = 358) and neurological clinical screen (n = 483): participants completed tests of psychomotor speed, cognitive flexibility, and fine motor speed and dexterity. The tests were translated into Thai in prior studies (19,29,30). Research nurses administered and scored the cognitive tests after completing a thorough training and certification program. Raw scores were included in the analyses. A neurological screen was conducted by a study protocol physician. Item-level results were included in the analysis.

Statistical Analysis

Group-based multitrajectory analysis (GBMTA) was used to identify subgroups of individuals who followed similar CD4+, CD8+, and CD4/CD8 T-cell profiles from enrollment to week 144. Details regarding the GBMTA method are provided elsewhere (31–35). Briefly, GBMTA is a specialized form of finite mixture modeling that identifies distinctive clusters of individual trajectories within a given sample. The approach uses a multinomial modeling strategy to designate the optimal solution based on the observed

Bayesian information criteria value. The first step explored fit for model solutions ranging from two to six clusters. Larger Bayesian information criteria are indicative of a better-fitting model (31,34). As a conservative approach, we also examined the average posterior probability, odds of correct classification defined by posterior probabilities of group membership for each cluster, and relative entropy to confirm the optimal model solution (32,33,35–39).

Participant characteristics at the time of enrollment were compared between the CD4/CD8 T-cell ratio trajectory subgroups defined by the clustering results using multivariate analysis of variance for continuous variables and χ^2 for categorical variables (Table 1). To minimize type I error, comparisons across clusters using traditional parametric methods focused on a subset of information from the enrollment visit (e.g., demographics, VL, Fiebig stage; see Table, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A870). Results were adjusted for multiple comparisons.

We also used gradient-boosted multivariate regression (GBM) (40,41) to explore predictors of CD4/CD8 T-cell ratio trajectory cluster classification using the more diverse range of multidimensional information available in the RV254/SEARCH 010 biorepository (e.g., cytokine profiles, cognitive performance, mental health). GBM is a form of ensemble machine learning that yields similar classification accuracy to more computationally intensive methods such as Super Learner (42) while minimizing error due to overfitting (43–49). We used the Python-based program CatBoost (40,41) to build the GBM models. Feature selection used an in-house program based on SciKit-learn (50) and PDPBox (51). Class membership was determined using a probability score based on the sigmoid function ($1/(1 + e^{-x})$), 0.5 decision boundary, and gradient descent to minimize prediction error. Highly correlated features ($r > 0.65$) were managed by selecting the feature with the highest mutual information criterion value. Consistent with prior work (44–47), the number of features in the final algorithm was determined by model saturation, defined as the point at which inclusion of additional features resulted in <1 standard deviation gain in classification accuracy relative to the base model. For the current analysis, model saturation was achieved with 10 features. Validity of the classification algorithm was determined using fivefold cross-validation repeated five times (a total of 25 trials). The mean area under the curve (AUC) from the validation trials served as the final metric of model performance.

RESULTS

Demographic and HIV Clinical Indices at Enrollment

A total of 483 individuals (470 cisgender men and 13 cisgender women) were included in the analysis. The median age of the study participants was 26 (interquartile range [IQR] = 23–31 years), and the median years of educational attainment was 18 (IQR = 14–18). At enrollment, the median plasma CD4+ T-cell count was 368 (IQR = 266–495) cells/ml, median CD8+ T-cell count was 523 (IQR = 336–887) cells/ml, median CD4/CD8 T-cell ratio was 0.71 (IQR = 0.43–1.04), and median VL was 5.88 (IQR = 5.24–6.73) copies/ml. In terms of ART regimen, 216 (44.7%) participants underwent a change from an efavirenz-based regimen to a DTG-based regimen during the observation period. The switch occurred for all participants enrolled in the cohort in 2017. Individuals were identified as being virally suppressed at the time of the ART change. Published work by our team (25) revealed a modest increase in CD4+ T-cell count after the switch but no other clinically relevant outcomes after the ART regimen. The proportion of study participants who underwent the scheduled ART regimen change did not differ by cluster designation ($p = .19$).

CD4/CD8 T-Cell Ratio Trajectories From AHI Through 144 Weeks of ART

The GBMTA identified five distinct CD4/CD8 T-cell trajectory subgroups (average posterior probability of .92, average odds of correct classification of 17, and relative entropy of 0.93; Figure 1). Only one trajectory group (group 1; 3% of the participants) had a CD4/CD8 T-cell ratio ≥1.0 at each visit. The other four trajectory subgroups exhibited CD4/CD8 T-cell inversion at enrollment with different profiles extending through week 144. Trajectory groups 2 (18%) and 3 (29%) achieved CD4/CD8 T-cell ratio normalization within 4 and 12 weeks after ART initiation, respectively. The

TABLE 1. Demographic and HIV Clinical Characteristics at Enrollment

	Total Sample	Trajectory Group 1	Trajectory Group 2	Trajectory Group 3	Trajectory Group 4	Trajectory Group 5
No. (%) participants	483 (100)	14 (2.9)	89 (18.4)	140 (29.0)	151 (31.3)	89 (18.4)
Age, y	26 (23–31)	29 (24–37)	29 (25–35)	26 (22–30)	25 (22–29)	26 (22–31)
Identify as cisgender men, *n* (%)	470 (97.3)	12 (85.7)	84 (94.4)	136 (97.1)	150 (99.3)	88 (98.9)
Fiebig I, *n* (%)	71 (14.7)	2 (14.7)	21 (23.6)	21 (15.0)	13 (8.6)	14 (15.9)
Fiebig II, *n* (%)	118 (24.5)	4 (28.6)	25 (28.1)	36 (25.7)	37 (24.5)	16 (18.2)
Fiebig III, *n* (%)	205 (42.5)	3 (21.4)	30 (33.7)	64 (45.7)	73 (48.3)	35 (39.8)
Fiebig IV, *n* (%)	57 (11.8)	4 (28.6)	10 (11.2)	15 (10.7)	17 (11.3)	11 (12.5)
Fiebig V, *n* (%)	31 (6.4)	1 (7.1)	3 (3.4)	4 (2.9)	11 (7.3)	12 (13.6)
Viral $load_{log10}$	5.88 (5.24–6.73)	5.55 (5.08–6.54)	5.42 (4.78–6.38)	5.94 (5.22–6.60)	6.20 (5.44–6.99)	5.81 (5.38–6.75)
PHQ-9 total	9 (6–13)	9 (6–15)	10 (7–14)	9 (5–14)	9 (5–12)	9 (6–13)
CD4+ T-cell count	368 (266–495)	573 (431–684)	449 (343–619)	335 (260–451)	279 (218–386)	488 (358–616)
CD8+ T-cell count	523 (336–887)	483 (243–788)	423 (253–672)	427 (270–640)	541 (380–973)	929 (576–1630)
CD4/CD8 T-cell ratio	0.71 (0.43–1.04)	1.53 (0.79–2.44)	1.18 (0.8–1.6)	0.87 (0.6–1.2)	0.54 (0.3–0.8)	0.52 (0.3–0.8)
Achieved CD4/CD8 T-cell ratio normalization, wk		0	4	12	n/a	n/a
Changed ART regimen, *n* (%)	216 (44.7)	5 (36)	41 (47)	52 (37)	72 (48)	46 (52)

PHQ-9 = Patient Health Questionnaire-9; ART = antiretroviral therapy.

Values are reported as medians (interquartile range) unless otherwise noted. Patient Health Questionnaire-9 (PHQ-9).

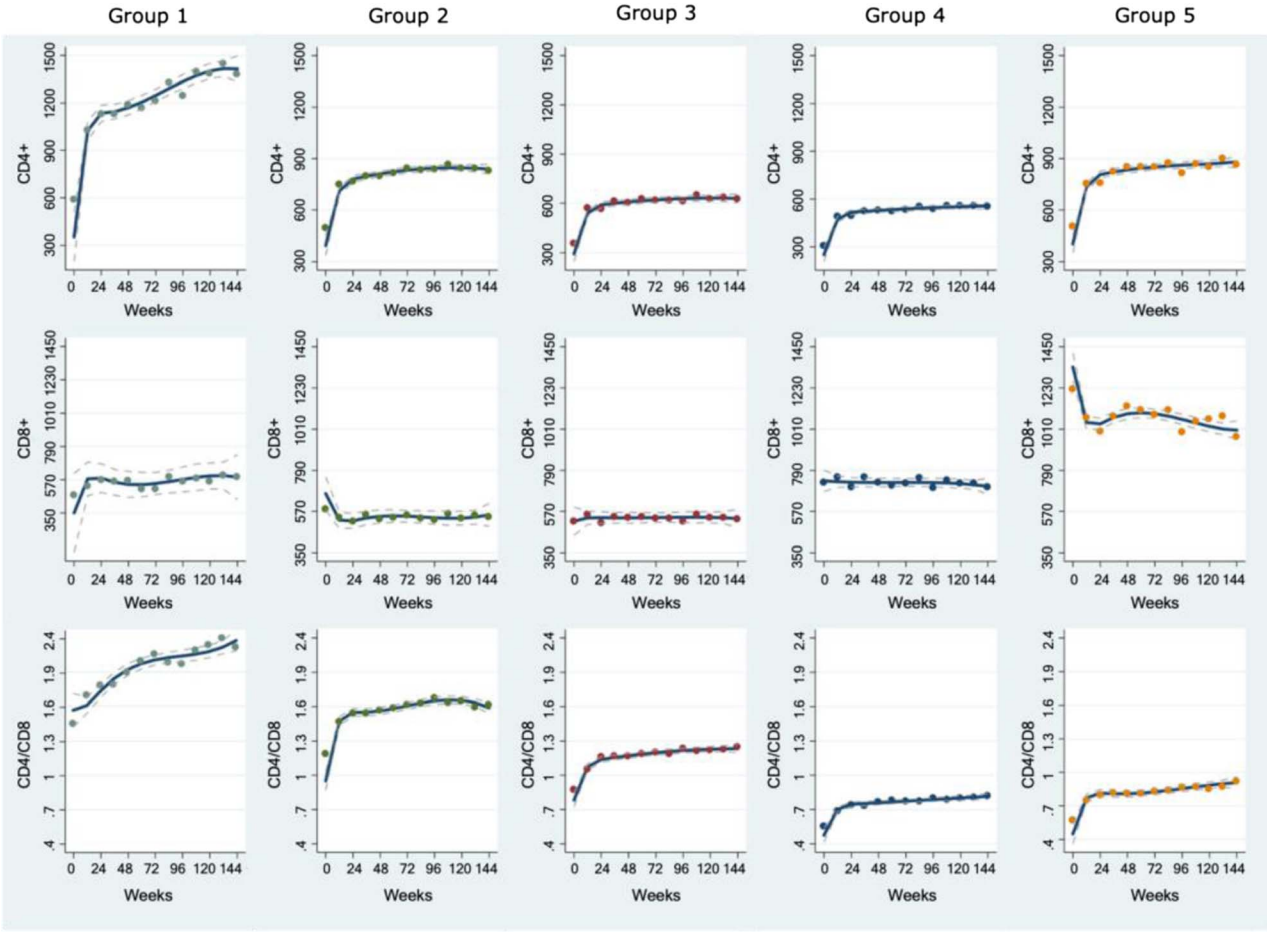

FIGURE 1. CD4+, CD8+, and CD4/CD8 T-cell ratio trajectories defined by the group based multitrajectory analysis. CD4+ T-cell (top row), CD8+ T-cell (middle row), and CD4/CD8 T-cell ratio (bottom row) trajectories. Trajectory group 1 includes individuals with CD4/CD8 T-cell ratio ≥1.0 at enrollment and each follow-up visit. Trajectory group 2 includes individuals who achieved normalization by week 4 after ART onset. Trajectory group 3 represents individuals who achieved normalization by week 12. Trajectory group 4 represents individuals with persistent inversion despite 144 weeks of ART due to slow CD4+ T-cell recovery after ART. Trajectory group 5 represents individuals with persistent inversion due to high CD8+ T-cell count. ART = antiretroviral therapy.

difference in time to normalization was due to a more rapid increase in CD4+ T-cell count for individuals in trajectory group 2. Trajectory groups 4 (31%) and 5 (18%) exhibited persistent CD4/CD8 T-cell ratio inversion through week 144, because of either slow CD4+ T-cell recovery after ART (group 4) or early and ongoing high CD8+ T-cell counts (group 5).

Comparisons Between CD4/CD8 T-Cell Ratio Normalization Versus Persistent Inversion

Because of the limited number of individuals with a CD4/CD8 T-cell ratio ≥1.0 at all visits (3% of the total sample), comparisons between the trajectory subgroups on initial risk profiles focused on the subgroups who exhibited CD4/CD8 T-cell ratio inversion at enrollment. Results from the multivariate analysis of variances revealed that individuals who initiated ART in Fiebig I or II were more likely to achieve CD4/CD8 T-cell ratio normalization (groups 2 and 3) compared with individuals who initiated treatment in Fiebig III–V (groups 4 and 5; $\chi^2 = 6.5$, $p = .011$). At enrollment, individuals who achieved normalization were older ($p = .005$), and had lower VL ($p < .001$), higher CD4+ T-cell count ($p < .001$), lower CD8+ T-cell count ($p < .001$), higher CD4/CD8 T-cell ratio ($p < .001$), higher total lymphocyte percent ($p = .030$), higher eosinophil percent ($p = .009$), and lower levels of sCD27 ($p = .018$) and TIM-3 ($p = .041$) compared with individuals with persistent inversion through week 144.

Comparisons Between Inversion Due to Slow CD4+ T-Cell Recovery Versus High CD8+ T-Cell Count

Individuals with persistent inversion due to slow CD4+ T-cell recovery (group 4) had lower CD4+ and CD8+ T-cell counts, white blood cell (WBC) count, total lymphocytes, and platelet count as well as higher VL (absolute), neutrophil count, and plasma IL-12 at enrollment compared with individuals in group 5 with high CD8+ T-cell count (p values < .05). The two trajectory subgroups with persistent inversion did not differ by Fiebig stage, VL ($\log_{10}$), or CD4/CD8 T-cell ratio at enrollment.

Machine Learning Classification of Slow CD4+ T-Cell Recovery Versus High CD8+ T-Cell Count

The algorithm to classify individuals into CD4/CD8 T-cell ratio normalization versus inversion subgroups yielded poor accuracy (AUC = 65%). Better results were obtained from the GBM model

that examined predictive features associated with slow CD4+ T-cell recovery (group 4) versus high CD8+ T-cell count (group 5). This model yielded an average AUC of 74% (accuracy = 69%, F1 score = 77%, precision = 73%, and recall = 81%; Figure 2). The classification algorithm was derived from the following 10 features (ranked by relative importance): a) total WBC, b) response to QOL item 15 ("How well are you able to get around?"), c) VL (absolute), d) Color Trails 1 performance, e) VL (log_{10}), f) response to QOL item 6 ("To what extent do you feel your life to be meaningful?"), g) response to QOL item 13 ("How available to you is the information that you need in your day-to-day life?"), h) randomization to standard ART versus intensified ART, i) basophil percent, and j) response to Patient Health Questionnaire-9 item 10 ("How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?").

Partial dependency plots (52) provided in Figure, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A871, depict the directionality of each feature in relation to trajectory risk group. Higher VL, lower WBC, worse performance on Color Trails 1, worse QOL ratings, and higher disruption from mental health symptoms predicted classification into trajectory group 4 (i.e., slow CD4+ T-cell recovery after ART). Absolute and log-transformed VL contributed to the performance of the algorithm. A post hoc analysis confirmed that the two VL indices were not redundant features ($r = 0.56$). The discordance between absolute and log-transformed VL is depicted in the partial dependency plots, which show that low absolute VL predicted inversion due to high CD8+ T-cell count (trajectory group 5), whereas low and high log-transformed VL predicted inversion due to slow CD4+ T-cell recovery (trajectory group 4).

Summary of Study Findings

There is substantial individual heterogeneity in CD4/CD8 T-cell ratio trajectories after ART initiated during the earliest stages of infection. We identified five distinct CD4/CD8 T-cell ratio trajectory subgroups, three of which led to CD4/CD8 T-cell ratio normalization and two led to persistent inversion. Furthermore, we identified unique immune risk profiles of persistent inversion, one that was characterized by slow CD4+ T-cell recovery after ART and a second that was characterized by early and ongoing high CD8+ T-cell count. Importantly, individuals who initiated ART after Fiebig II, when disease dynamics such as VL and cytokine induction intensify, were most likely to exhibit CD4/CD8 T-cell ratio inversion after 144 weeks of suppressive ART. Machine learning analysis identified a novel combination of viral, immune, and psychological indices at enrollment that predicted risk for CD4/CD8 T-cell ratio inversion due to slow CD4+ T-cell recovery after treatment, which accounted for the majority of cases of persistent inversion after ART.

DISCUSSION

We identified substantial individual differences in CD4/CD8 T-cell ratio outcomes after 144 weeks of ART initiated during AHI. Although the median CD4/CD8 T-cell ratio significantly improved from enrollment to week 144 (median ratio = 1.3), only 51% of the study participants achieved CD4/CD8 T-cell ratio normalization. The high frequency of persistent CD4/CD8 T-cell ratio inversion in this study is particularly concerning given that all study participants began treatment within the first 30 days of infection, and viral control was maintained for 144 weeks (excluding occasional blips).

Results from this study extend findings from previous work (9) that described CD4/CD8 T-cell ratio inversion in 30% of AHI participants after 2 years of ART commenced during early infection. The higher frequency of CD4/CD8 T-cell ratio inversion observed in this study may reflect the longer duration of follow-up and/or differences in participant characteristics at the time of treatment onset (e.g., Fiebig stage, VL). Additional studies using longer follow-up periods are needed to determine if the CD4/CD8 T-cell ratio profile among individuals who initiated early ART eventually approximates the frequency of persistent inversion that is typically reported among individuals who initiate treatment in chronic HIV.

An important finding from this study is the observation that treatment onset after Fiebig stage II corresponded to persistent CD4/CD8 T-cell ratio inversion. Fiebig II defines a stage of HIV

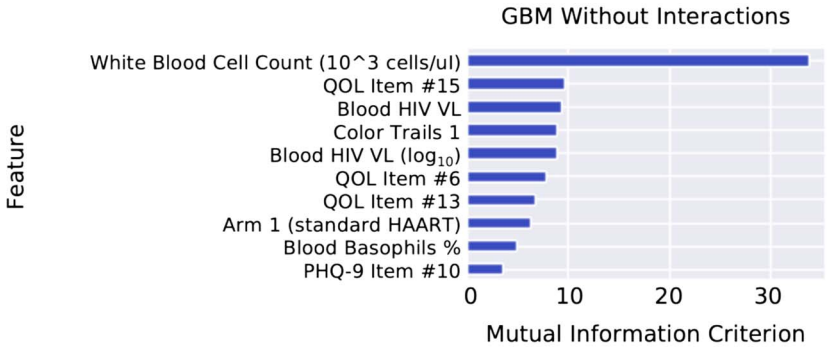

FIGURE 2. Machine learning classification of slow CD4+ T-cell recovery versus high CD8+ T-cell count. Variables at baseline that collectively classified individuals into trajectory group 4 (slow CD4+ T-cell recovery) versus trajectory group 5 (consistently high CD8 + T-cell count). Variables are listed in rank order of relevance to classification accuracy: a) total white blood cell count, b) QOL item 15 ("How well are you able to get around?"), c) VL (absolute), d) Color Trails 1 performance (psychomotor speed), e) VL (log10 transformed), f) QOL item 6 ("To what extent do you feel your life to be meaningful?"), g) QOL item 13 ("How available to you is the information that you need in your day-to-day life?"), h) ART randomization to a boosted regimen versus standard ART, i) basophil percent, and j) response to PHQ-9 item 10 ("If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?"). Unfavorable values predicted classification in trajectory group 4. Randomization to intensified ART predicted classification in trajectory group 5. GBM = gradient-boosted multivariate regression; HAART = highly active antiretroviral therapy; QOL = quality of life; PHQ-9 = Patient Health Questionnaire-9; VL = viral load.

infection that is characterized by an escalation of HIV disease pathogenesis. Numerous studies have documented that HIV VL, CD4+ T-cell depletion, and cytokine induction intensify after Fiebig I (53–55). It is possible that ART initiation in Fiebig II or later results in a larger latent viral reservoir and increased propensity for low-level viral replication and CD4/CD8 T-cell ratio inversion. Proviral DNA in CD4+ T cells correlates with CD4/CD8 T-cell ratio in some studies (56) but not others (57). Our findings suggest that the link between viral reservoir burden and CD4/CD8 T-cell ratio is most relevant to a specific subset of individuals (e.g., those with persistent inversion due to slow CD4+ T-cell recovery).

sCD27 and sTIM-3 levels at enrollment also differed between individuals who achieved normalization versus those with persistent CD4/CD8 T-cell inversion. These results are interesting given the known involvement of both markers with T-cell functionality and HIV disease pathogenesis (23). CD27 expression on T cells is functionally active (58,59), and elevated levels of sCD27 in plasma are a surrogate marker of immune activation and predictor of morbidity among PWH receiving suppressive ART (60,61). Although membrane-bound TIM-3 on T cells is a marker of exhaustion, the soluble form has been linked to HIV disease progression (62–64). Whether T-cell hyperactivation or exhaustion is involved in the persistence of CD4/CD8 T-cell ratio inversion is an important area for further study. This is particularly true for the subset of individuals (18% of the study participants) who exhibited a robust CD4+ T-cell response after ART but experienced persistent CD4/CD8 T-cell ratio inversion due to high CD8+ T-cell count before and after ART.

The two risk profiles for persistent CD4/CD8 T-cell ratio inversion (i.e., slow CD4+ T-cell recovery versus early and ongoing elevation in CD8+ T-cell count) did not differ at enrollment in terms of Fiebig stage, VL, or CD4/CD8 T-cell ratio. However, individuals in the slow CD4+ T-cell recovery trajectory group were more likely to identify as cisgender women and to have lower CD4+ and CD8+ T-cell counts, lower WBC and total lymphocyte counts, lower platelet count, higher neutrophil count, and higher plasma IL-12. The number of cisgender female participants in the study was limited, and therefore, more firm conclusions regarding potential sex-related outcomes cannot be ascertained from these data. Additional studies are needed to further explore potential sex-specific mechanisms on CD4/CD8 T-cell ratio outcomes after ART initiation.

We used machine learning to explore a larger array of potential predictors from the data acquired at the time of enrollment into RV254/SEARCH 010. Specifically, ensemble machine learning was used to ascertain whether information acquired at enrollment could predict CD4/CD8 T-cell ratio subgroup trajectories after 144 weeks of sustained ART. The analysis aimed at differentiating CD4/CD8 T-cell normalization versus inversion did not yield a clear classification algorithm. By contrast, the analysis focused on differentiating persistent CD4/CD8 T-cell inversion due to slow CD4+ T-cell recovery (group 4) versus high CD8 T-cell count (group 5) yielded a robust classifier based on a combination of WBC, VL, cognitive performance, affective profiles, and randomization to standard ART, with worse values on these features (e.g., more severe emotional distress) corresponding to classification in the slow CD4+ T-cell recovery subgroup (trajectory group 4).

To our knowledge, this is the first study to identify psychological factors as important determinants of CD4/CD8 T-cell ratio outcomes among individuals who initiated suppressive ART during the earliest stages of infection. The finding is not surprising given the known interplay between mental distress and immune abnormalities (65–70), mediated by the neuroimmune axis (71–73). Our finding that mental health indices corresponded to persistent CD4/CD8 T-cell inversion due to slow CD4+ T-cell recovery is important. Although high CD8+ T-cell count represents a risk profile consistent with chronic inflammation, the most common pathway to CD4/CD8 T-cell ratio inversion observed among individuals enrolled in RV254/SEARCH 010 involved slow CD4 + T-cell recovery after ART. It will be important to determine if brief mental health interventions implemented during early infection precipitate CD4+ T-cell recovery after treatment onset.

This is also the first study to use a data-driven approach to model CD4/CD8 T-cell ratio trajectory subgroups from acute infection through 144 weeks of suppressive treatment. Unique to this study, the RV254/SEARCH 010 study enrolled individuals with a range of Fiebig stages, which was important for the study findings. Participants were also similar in terms of demographic profiles, and they reported minimal confounding factors (e.g., severe substance use disorders). However, it should be noted that most participants were Thai men who have sex with men, and therefore, the results may not generalize to other populations. Furthermore, we did not compare the results to demographically similar individuals who initiated ART during chronic infection, and risk profiles were limited to information acquired at enrollment. Additional studies are needed to examine the contribution of risk factors that emerge after ART (e.g., sexually transmitted disease, hepatitis C infection). Cellular immunophenotyping data were not available for all participants included in this analysis. As such, additional studies are needed to investigate the reliability of the predictive algorithms using nested cross-validation.

In summary, the present study reveals that nearly half of all individuals who complete 144 weeks of ART initiated within the first 30 days of HIV infection do not achieve a CD4/CD8 T-cell ratio ≥1.0. Failure to normalize the CD4/CD8 T-cell ratio resulted from distinct perturbations in either CD4+ or CD8+ T-cell populations, which correspond to unique viral, immune, and psychological risk profiles evident at the time of treatment onset in AHI. These findings provide important clinical insights into the potential pathways and underlying mechanisms that explain individual heterogeneity in CD4/CD8 T-cell ratio outcomes in the context of suppressive ART. Further research is needed to investigate the potential for adjunctive treatment strategies to improve CD4/CD8 T-cell ratio profiles at the time of initial HIV diagnosis and initiation of ART.

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