Title

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Journal

International Journal of Epidemiology, 44(1)

ISSN

0300-5771

Authors

Geng, Elvin H
Neilands, Torsten B
Thièbaut, Rodolphe
et al.

Publication Date

2015-02-01

DOI

10.1093/ije/dyu271

Peer reviewed

International Journal of Epidemiology, 2015, 251–263
doi: 10.1093/ije/dyu271
Original article

Miscellaneous

CD4+ T cell recovery during suppression of HIV replication: an international comparison of the immunological efficacy of antiretroviral therapy in North America, Asia and Africa

Elvin H Geng,[1]* Torsten B Neilands,[1] Rodolphe Thièbaut,[2] Mwebesa Bosco Bwana,[3] Denis Nash,[4] Richard D Moore,[5] Robin Wood,[6] Djimon Marcel Zannou,[7] Keri N Althoff, [5] Poh Lian Lim,[8] Jean B Nachega,[9,10,11] Philippa J Easterbrook,[12] Andrew Kambugu,[12] Francesca Little,[6] Gertrude Nakigozi,[13] Damalie Nakanjako,[12] Valerian Kiggundu,[13] Patrick Chung Ki Li,[14] David R Bangsberg,[15] Matthew P Fox,[16,17] Hans W Prozesky,[18] Peter W Hunt,[1] Mary-Ann Davies,[6] Steven J Reynolds,[5,13,19] Matthias Egger,[20] Constantin T Yiannoutsos,[21] Eric V Vittinghoff,[1] Steven G Deeks[1] and Jeffrey N Martin[1]

[1]University of California, San Francisco, CA, USA, [2]INSERM U897, Bordeaux University, Bordeaux, France, [3]Mbarara University of Science and Technology, Mbarara, Uganda, [4]City University of New York, New York, NY, USA,[5]Johns Hopkins University, Baltimore, MD, USA, [6]University of Cape Town, Cape Town, South Africa, [7]Centre National Hospitalier Universitaire, Cotonou, Benin, [8]Institute of Infectious Disease, Tan Tock Seng Hospital, Singapore, Singapore, [9]Department of Epidemiology, Infectious Diseases Program, Pittsburgh University, Graduate School of Public Health, Pittsburg, PA, USA, [10]Departments of Epidemiology and International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [11]Department of Medicine & Center for Infectious Diseases, Stellenbosch University, Cape Town, South Africa, [12]Infectious Diseases Institute, Kampala, Uganda, [13]Rakai Health Sciences Program, Kalisizo, Uganda, [14]Queen Elizabeth Hospital, Hong Kong, China, [15]Center for Global Health, Massachusetts General Hospital, Harvard University, Boston, MA, USA, [16]Center for Global Health and Development, Boston University, Boston, MA, USA, [17]Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [18]Division of Infectious Diseases, Department of Medicine, University of Stellenbosch and Tygerberg Academic Hospital, Cape Town, South Africa, [19]National Institutes of Allergy and Infectious Diseases, Washington DC, USA, [20]University of Bern, Bern, Switzerland and [21]Indiana University, Indianapolis, IN, USA

*Corresponding author. Division of HIV/AIDS, San Francisco General Hospital, University of California at San Francisco, 995 Potrero Avenue, Building 80, Box 0874, San Francisco, CA 94110, USA. E-mail: genge@php.ucsf.edu

Accepted 15 December 2014

Abstract

Background: Even among HIV-infected patients who fully suppress plasma HIV RNA replication on antiretroviral therapy, genetic (e.g. CCL3L1 copy number), viral (e.g. tropism) and environmental (e.g. chronic exposure to microbial antigens) factors influence CD4 recovery. These factors differ markedly around the world and therefore the expected CD4 recovery during HIV RNA suppression may differ globally.

Methods: We evaluated HIV-infected adults from North America, West Africa, East Africa, Southern Africa and Asia starting non-nucleoside reverse transcriptase inhibitor-based regimens containing efavirenz or nevirapine, who achieved at least one HIV RNA level <500/μl in the first year of therapy and observed CD4 changes during HIV RNA suppression. We used a piecewise linear regression to estimate the influence of region of residence on CD4 recovery, adjusting for socio-demographic and clinical characteristics. We observed 28 217 patients from 105 cohorts over 37 825 person-years.

Results: After adjustment, patients from East Africa showed diminished CD4 recovery as compared with other regions. Three years after antiretroviral therapy initiation, the mean CD4 count for a prototypical patient with a pre-therapy CD4 count of 150/μl was 529/μl [95% confidence interval (CI): 517–541] in North America, 494/μl (95% CI: 429–559) in West Africa, 515/μl (95% CI: 508–522) in Southern Africa, 503/μl (95% CI: 478–528) in Asia and 437/μl (95% CI: 425–449) in East Africa.

Conclusions: CD4 recovery during HIV RNA suppression is diminished in East Africa as compared with other regions of the world, and observed differences are large enough to potentially influence clinical outcomes. Epidemiological analyses on a global scale can identify macroscopic effects unobservable at the clinical, national or individual regional level.

Key words: HIV, Africa, antiretroviral therapy, CD4 + T cell counts, immunological activation

Key Messages

- Globally, CD4 + T-cell recovery during suppressive antiretroviral therapy is not uniform.
- Patients in East Africa exhibit the most blunted CD4 recovery and differences were large enough to potentially influence clinical outcomes.
- We speculate that differences in the 'immunological efficacy' of antiretroviral therapy may be explained in part by differences in microbial exposure and immunological activation, as well as other viral and host factors.

Introduction

Although the first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens widely used in resource-limited settings reliably suppress HIV RNA replication in adherent patients, less certainty exists about the equivalence of CD4 + T cell recovery during HIV RNA suppression—an outcome which also has a direct effect on clinical outcomes.[1] First, host genetic factors such as CCL3L1 copy number,[2] CCR5 and cytokine polymorphisms,[3,4] and mitochondrial DNA[5] can influence CD4 recovery during HIV RNA suppression. The prevalence of these genetic factors—as well as others not yet identified likely differ in human populations around the world. Second, characteristics of HIV itself, such as tropism, also influence CD4 recovery after HIV RNA suppression.[6] For example, the proclivity of subtype D for X4 tropism and the preponderance of subtype D in certain regions may influence CD4 recovery in those regions.[7,8] Finally, immunological activation due to environmental exposure to microbial antigens has emerged as a unifying theory that explains both CD4 loss before antiretroviral therapy (ART) initiation and attenuated CD4 rise on suppressive ART.[9] Implicated organisms include commensal gut flora,[10] hepatitis C virus,[11] *Mycobacterium tuberculosis*,[12] *Cryptococcus neoformans*,[13] helminths[14] and

herpesviruses such as cytomegalovirus.[15] Populations in resource-limited settings are exposed to a higher burden of many infections starting at a younger age.[16,17]

To date, CD4 recovery during ART-mediated HIV RNA suppression—which we call 'immunological efficacy'—has not been directly compared across geographically disparate populations. Most existing multi-regional studies have included all patients regardless of their virological response.[18] Although such designs provide a picture of population-level effectiveness of ART, they do not distinguish whether differences in CD4 recovery are due to socio-structural and behavioural determinants of medication adherence or to biological factors that act on the immune system. Most analyses which do restrict observation to CD4 recovery during HIV RNA suppression have been carried out within Europe and therefore did not assess wider geographical differences.[1,19] One cross-regional study carried out in the setting of a randomized trial found diminished CD4 recovery among South African patients as compared with Europeans, even though the South Africans had higher rates of HIV RNA suppression.[20] However, these intriguing results only included data from one country in Africa (South Africa), in which the socioeconomic setting differs markedly from the rest of sub-Saharan Africa.

In the present analysis, we sought to understand the effect of differences in host, virus and environment on CD4 recovery during ART-mediated HIV RNA suppression across geographically large regions of the world. We analysed patients from five regions participating in the International Epidemiological Database to Evaluate AIDS (IeDEA) Consortium: North America, West Africa, East Africa, Southern Africa and Asia. The size and reach of IeDEA allowed us to identify, and restrict the analysis to, patient populations followed with serial plasma HIV RNA testing in resource-limited settings. Regional differences in immunological efficacy—should they exist—may inform existing and spur additional hypotheses for biological researchers seeking to understand the mechanisms of immunological destruction by HIV and immunological restoration after ART initiation. Differences could also influence assessments about the risks and benefits of ART initiation at different CD4 thresholds. Finally, differences in immunological efficacy may inform public health scientists who seek to assess or model population-level health benefits of the global roll-out of ART.

Methods

Design

We conducted a multi-site cohort analysis using data collected from five regions in the IeDEA Consortium. Our objective was to assess the effect of region (with attendant but unmeasured differences in human genetics, HIV subtype and environmental exposures) on CD4 count recovery during ART-mediated suppression of plasma HIV RNA. We adjusted the effect of region on CD4 count recovery for factors already known to influence CD4 count recovery, such as sex, age, pre-therapy CD4 count, pre-therapy HIV RNA level, and ART regimen composition (e.g. the use of zidovudine). We used a directed acyclic graph (Figure 1) to formally express the research question in a causal framework[21] and to guide decisions about adjustment.[22]

Patients

IeDEA is an NIH-funded research consortium which pools data from geographically dispersed cohorts to address macroscopic epidemiological questions regarding the HIV epidemic. Cohorts from five regions participated in this analysis: North America (USA and Canada), West Africa (Ivory Coast, Senegal and The Gambia), East Africa (Uganda), Southern Africa (South Africa and Malawi) and Asia (China, Thailand, Vietnam, Indonesia,and Japan). Institutional review boards in the respective IeDEA regions approved the study. Within each region, we included all ART-naive adults (adults defined as age >17 years) who initiated NNRTI-based ART, had a pre-therapy CD4 count of $\leq$350 cells/μl, were monitored with routine HIV RNA testing, and achieved at least one plasma HIV RNA level <500 copies/ml in the first 48 weeks after initiation of ART. Observation began at ART initiation and continued as long as patients remained on an NNRTI-based regimen with a plasma HIV RNA of <1000 copies/ml. Observations were censored at the last HIV RNA level <1000 copies/ml that occurred before the first of any of the following: (i) HIV RNA rebound to $\geq$1000 copies/ml; (ii) switch to a protease inhibitor or other non-NNRTI-based regimen; (iii) an interval of 9 months without an HIV RNA determination (to minimize the risk of incorporating CD4 values obtained during unascertained HIV viraemia); (iv) death; (v) loss to follow-up (defined as 6 months without a clinic visit); or (vi) database closure.

Measurements

Socio-demographic and clinical variables such as sex, age, ART regimen and the dates of clinical events (e.g. ART initiation, follow-up visits etc.) were collected in the respective IeDEA-associated cohorts during the course of routine care and in research-based cohorts through protocols. CD4 counts and plasma HIV RNA levels were obtained from

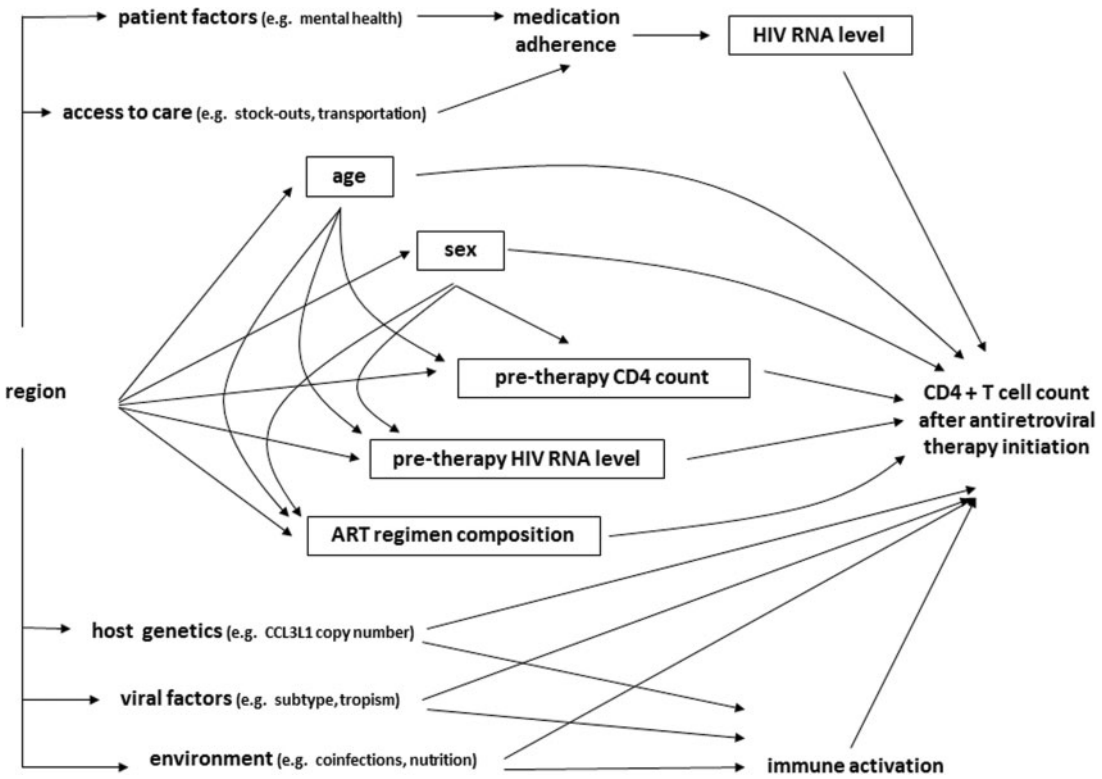

Figure 1. Directed acyclic graph depicting research question. We seek to estimate the direct effect of region on CD4 + T cell recovery during antiretroviral-mediated HIV RNA suppression, apart from other previously established mediators. Restriction, in the study design, to time during HIV RNA suppression closes pathways mediated by medication access and adherence. Statistical adjustment closes pathways mediated by factors known to influence CD4 + T cell recovery such as age and sex. We interpret any remaining association between region and CD4 + T cell recovery to represent the effect of additional regional host, viral and environmental factors that act through biological mechanisms.

the respective clinical or research laboratories associated with the various sites.

Analysis

First, we conducted a non-parametric comparison of region-specific median CD4 counts (and interquartile ranges) before ART and at 4, 12, 24 and 36 months after ART initiation. For patients with multiple CD4 count determinations within a 90-day window of the target date, we used the median value.

Second, we used a mixed-effects regression model to estimate the effect of region on mean CD4 count values after initiation of ART, adjusting for age, sex, pre-therapy CD4 count, pre-therapy plasma HIV RNA level and initial ART regimen composition. Random intercepts and slopes, with unstructured covariance, were used to accommodate patient-specific departures from the trajectories determined by the fixed effects. To best conform to the model assumptions of normality and homoscedasticity, we used the square root transformation of the on-therapy CD4 values. We subsequently back-transformed estimates into the native CD4 scale.[23,24] The pre-therapy CD4 value was treated as a predictor and not included as an outcome.[25] This analysis was performed using full information maximum likelihood estimation in M-plus version 6 (Muthén & Muthén, Los Angeles, CA), which provides consistent estimates under the assumption that missing predictor data were missing at random.[26]

Time was specified as a linear spline with knots at 4 months and 1 year to account for the different rates of CD4 count change known to occur in these periods.[27–30] We explored the significance of an additional knot at month 24. Interaction terms between region and time as well as pre-therapy CD4 and time were used to accommodate the influence of these factors on changes in CD4 slope, resulting in a distinct piecewise linear trajectory for each region and pre-therapy CD4 count. Pre-therapy CD4 count was specified as a restricted cubic spline with three knots, to accommodate non-linear associations between pre-therapy CD4 counts and CD4 counts over time. Two-way interactions between time and all other pre-therapy patient characteristics (e.g. age, sex) were also included to allow adjustment for these factors over time. We also explored a three-way interaction term between pre-therapy CD4 cell count, region and time, motivated by the hypothesis that regional differences in CD4 slope may differ by pre-therapy CD4 cell count. Our final model was

chosen based on examination of Akaike and Bayesian information criteria.

Age was treated as a continuous variable and pre-therapy HIV RNA level was categorized according to convention at $\log_{10}$ values of <4.0, 4.0–4.5, 4.51–5.0, 5.1–5.5 and >5.5 copies/ml.[31] The presence or absence of a particular antiretroviral medication in the initial regimen was classified using an indicator variable for the medication in question. For illustrative purposes, we estimated mean CD4 counts at 4 months, 1 year and 3 years after ART initiation for patients with pre-therapy CD4 counts of 25/μl, 50/μl, 100/μl, 150/μl, 200/μl and 300/μl in each region. CD4 recovery was estimated for a 'prototypical' patient, defined as having the mean value in the entire study population for age, sex, pre-therapy HIV RNA and composition of ART regimen. At each of the three follow-up time points and six pre-therapy CD4 count combinations, we generated between-region differences in mean CD4 count for a total of 180 contrasts.

Results

In total, 28 217 patients from 105 cohorts contributed a total of 37 825 patient-years of observation (Table 1). In the entire cohort, the median age at ART initiation was 36 years (IQR: 30–42), 59% were women and the median pre-therapy CD4 value was 116 cells/μl (IQR: 50–181). Patient characteristics differed across regions. Women, for example, comprised only 20% of the patients from North America but approximately 70% in the African regions. Each patient contributed a median of 12.7 months (IQR: 6.94 –24.0) of follow-up during HIV RNA suppression. During follow-up, the median number of CD4 determinations made was 3 (IQR: 2–5) and median time between CD4 determinations was 114 days (IQR: 84–168). The most common reason for censoring was database closure (i.e. administrative) in 41% of patients. Loss to follow-up occurred in 15% of patients. The reasons for censoring differed across regions: for example, observation end due to 9 months without an HIV RNA determination was present in 46% of persons in Asia compared with 13% in North America.

The unadjusted distribution of CD4 counts across regions demonstrated lower values in East Africa at most time points, and this difference was apparent in each of the pre-therapy CD4 categories (Figure 2). For example, after ART initiation for patients from East Africa with a pre-therapy CD4 value of ≤50/μl, the median CD4 count during HIV RNA suppression was 111/μl (IQR: 72–158) at 4 months, 191/μl (IQR: 139–265) at 1 year and 240/μl (IQR: 199–350) at 2 years. For a patient from Southern Africa with the same pre-therapy CD4 count of ≤50/μl, the median CD4 counts were 120/μl (IQR: 75–180) at 4 months, 219/μl (IQR: 158–301) at 1 year and 344/μl (IQR: 251–462) at 2 years. Similar trends were observed for patients who started ART at higher CD4 levels.

Results of the mixed-effects, piecewise linear regression of expected CD4 counts during ART-mediated suppression of HIV RNA showed that after adjustment for age, sex, composition of initial regimen, pre-therapy CD4 count and pre-therapy HIV RNA level, CD4 recovery was lower in East Africa as compared with the other regions across all pre-therapy CD4 levels (Figure 3). For example, for prototypical patients with 150 CD4 cells/μl at ART initiation, the mean CD4 value 3 years after ART initiation was 437/μl (95% CI: 425–449) in East Africa whereas it was 529/μl (95% CI: 517–541) in North America, 494/μl (95% CI: 429–559) in Western Africa, 515/μl (95% CI: 508–522) in Southern Africa and 503/μl (95% CI: 478–528) in Asia (Table 2).

We also expressed CD4 change as differences between mean values in each region for each given pre-therapy CD4 count at 4, 12 and 36 months after ART initiation (Table 3). Significant differences in CD4 recovery between East Africa and the other regions tended to occur after 4 months of therapy, and the observed differences tended to grow over time. For example, for patients with pre-therapy CD4 level of 150/μl, 4 months after ART initiation the mean CD4 level in North America was 13 cells/μl higher (95% CI: 4–22) than in East Africa. The difference rose to 51 cells/μl (95% CI: 41–61) at 12 months and 92 cells/μl (95% CI: 77–108) 36 months after ART initiation.

Addition of a knot in the piecewise regression at 24 months after ART initiation did not change results substantially. A comparison of each of the three sites from East Africa showed that all sites demonstrated diminished CD4 recovery as compared with other regions and therefore that observed differences were not driven by one site (data not shown).

Discussion

This study describes across geographical regions, for the first time, large and—especially in the case of East Africa as compared with other regions—potentially clinically meaningful differences in CD4 + T cell recovery among HIV-infected patients during ART-mediated suppression of plasma HIV RNA. These estimates may also inform modelling exercises to understand potential effects of ART treatment such as the UNAIDS investment framework and others. Patients from East Africa demonstrated the lowest CD4 recovery after adjustment for factors known to influence CD4 rise, including age, sex and pre-therapy CD4 count and plasma HIV RNA. The attenuated CD4 recovery in East Africa was consistent

Table 1. Patient characteristics

Characteristics	North America N = 4450	West Africa N = 649	East Africa N = 2,202	Southern Africa N = 20,323	Asia N = 593	Total N = 28,217
Pre-therapy						
Clinic sites, n	15	4	19	52	15	105
Age in years, median (IQR)	40 (34–46)	37 (31–44)	35 (30–41)	35 (30–41)	36 (31–42)	36 (30–42)
Female, n (%)	881 (20)	456 (70)	1451 (66)	13597 (67)	187 (32)	16572 (59)
CD4 + T cells/μl, median (IQR)	168 (62–250)	151 (75–223)	149 (71–210)	105 (48–165)	124 (34–200)	116 (50–181)
Plasma HIV RNA $\log_{10}$ copies/ml, median (IQR)[a]	4.9 (4.5–5.3)	5.4 (4.9–5.8)	5.12 (4.6–5.6)	4.79 (4.2–5.3)	5.08 (4.6–5.6)	4.9 (4.3–5.4)
Zidovudine in initial regimen, n (%)[b]	2415 (54)	198 (31)	1458 (66)	2972 (15)	115 (19)	7158 (26)
Nevirapine in initial regimen, n (%)[c]	841 (19)	415 (64)	646 (80)	6158 (30)	420 (71)	8480 (32)
ART initiation date, median (IQR and range)	2-Feb-03 (9-Mar-01 to 14-Apr-05; 15-Sep-96 to 5-May-09)	21-Jun-06 (10-Feb-06 to 3-Nov-06; 11-Jan-00 to 12-Apr-07)	13-Mar-05 (20-Feb-2005 to 8-May-08; 19-Apr-04 to 20-Nov-09	16-Mar-05 (2-Feb-05 to 27-Mar-07; 08-Apr-08 to 31-Aug-09)	5-May-04 (17-Feb-03 to 29-Jun-06; 12-Aug-99 to 29-Sep-08)	9-Jan-06 (19-Aug-04 to 2-Mar-07; 15-Sep-96 to 20-Nov-09)
Database closure date	03-Sep-09	27-Nov-07	05-Oct-09	15-Dec-09	23-Jun-09	
Follow-up						
Duration months, median (IQR)	31.7 (18.8–33.9)	12.1 (8.3–18.0)	33.2 (22.2–33.2)	20.9 (11.7–30.9)	26.0 (17.7–31.5)	12.7 (6.9–24.0)
Time between CD4 counts days, median (IQR)	98 (73–121)	175 (96–185)	112 (84–168)	134 (102–181)	89.5 (56–147)	114 (84–168)
CD4 determinations median (IQR)	5 (2–9)	2 (1–3)	6 (3–8)	2 (1–4)	4 (2–7)	3 (2–5)
Time between HIV RNA determinations days, median (IQR)	98 (71–119)	176 (128–184)	168 (85–168)	139 (110–182)	82 (56–160)	117 (87–168)
HIV RNA determinations, median (IQR)	4 (2–8)	1 (1–2)	4 (2–6)	2 (1–4)	3 (1–6)	2 (1–5)
Reasons for end of observation						
Administrative censor, n (%)	2048 (46)	440 (68)	1764 (80)	7198 (35)	219 (37)	11669 (41)
Nine-month gap without HIV RNA determination, n (%)	572 (13)	70 (11)	102 (5)	6802 (34)	271 (46)	7817 (28)
Loss to follow-up, n (%)	544 (12)	65 (10)	66 (3)	3561 (18)	25 (4)	4261 (15)
Switch or stop of ART, n (%)	333 (8)	3 (1)	9 (0.4)	443 (2)	5 (1)	793 (3)
HIV RNA rebound, n (%)	889 (20)	59 (9)	221 (10)	1947 (10)	71 (12)	3187 (11)
Death, n (%)	64 (1)	12 (2)	40 (2)	372 (2)	2 (0.3)	527 (2)

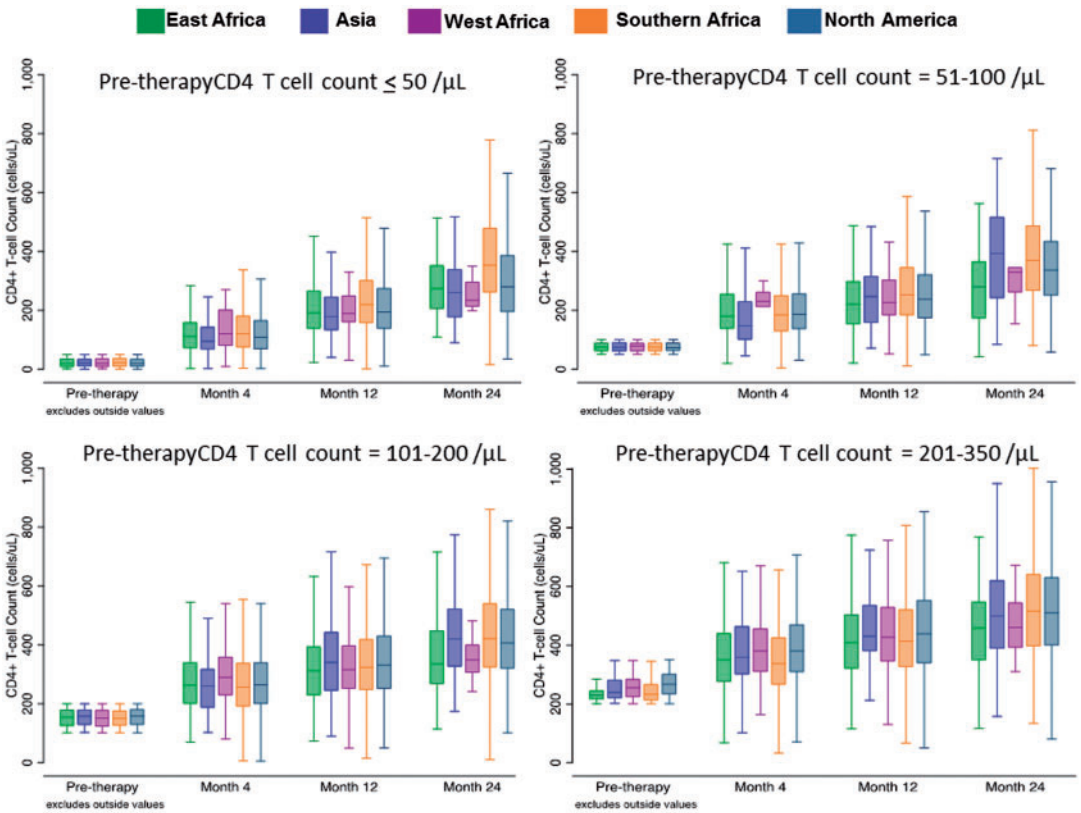

Figure 2. CD4 + T cell counts before and after antiretroviral therapy-mediated HIV RNA suppression. Distribution of CD4 + T cell values for given pre-therapy CD4 + T cell count strata at 4, 12 and 24 months after antiretroviral therapy initiation, stratified by region. These values are not adjusted for other patient characteristics.

across a range of pre-therapy CD4 counts. Differences were not clearly apparent during the first 4 months of therapy, a period in which changes mainly result from the redistribution of CD4 cells from lymphoid tissues,- but rather became increasingly pronounced during subsequent periods when *de novo* T cell production drives CD4 count increases in the peripheral blood.

Our findings extend existing analyses comparing CD4 recovery among different patient populations globally. Although a previous cross-regional comparison found that patients in high- and low-income countries experienced similar rates of CD4 recovery on ART, the comparison was limited to 6 months of observation after ART initiation[18] whereas we observed patients for up to 3 years. Previous work in The Netherlands that did follow patients for longer periods—for up to 5 years of HIV RNA suppression—found CD4 increases among patients who originated from sub-Saharan Africa to be on average 40 cells/µl lower than among patients originating from Europe or North America.[19] By including populations currently living in Africa, however, our analysis was able to capture the effects of ongoing environmental factors as well as genetic or past environmental exposures, which may explain the greater differences we observed.

Chronic exposure to microbial antigens may explain, at least in part, the observed differences in 'immunological efficacy' of ART. Population-based surveys have found that the distribution of CD4 levels in HIV-uninfected people in East Africa does not differ from other regions.[32] This implies that the diminished CD4 recovery in East Africa cannot be explained by different normal CD4 'set points', but rather represents poor recovery per se. Although this blunted recovery is consistent with a number of different hypotheses, the emerging paradigm—that immunological activation drives CD4 cell depletion during untreated HIV disease[10] as well as attenuating CD4 recovery after HIV replication is controlled by ART[9]—offers an intriguing potential explanation. Commensal microbial antigens from the gut as well as a variety of infections such as tuberculosis,[33] malaria, schistosomiasis[14] and herpesviruses such as cytomegalovirus[15] have all been implicated as causes of immunological activation. East Africans experience a higher occurrence of most of these infections from a younger age than North Americans.

Exposure to microbial antigens, however, does not fully explain diminished CD4 recovery in East Africa because residents of Southern and especially West Africa experience a similar prevalence of infections but exhibited more

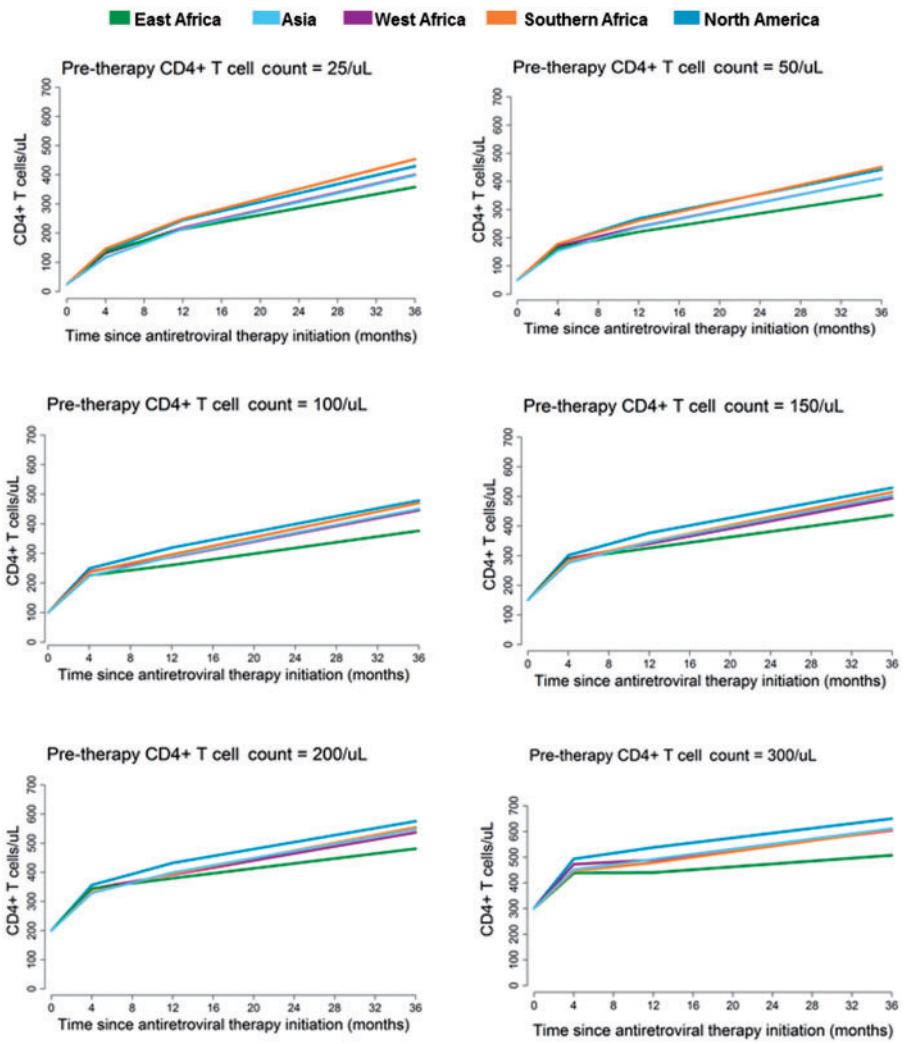

Figure 3. Model estimated CD4 + T cell counts during antiretroviral therapy-mediated HIV RNA suppression. Mean CD4 + T cell counts for prototypical patients by region and pre-therapy CD4 + T cell count, at 4, 12 and 36 months after antiretroviral therapy initiation. Estimates were derived from piecewise mixed effects linear regression with knots at 4 and 12 months. Estimates are shown for a patient with mean values in the entire population for age, sex, medication regimen composition and pre-therapy HIV RNA level.

robust CD4 recovery. Viral factors, therefore, might play a role. HIV subtype D, which is rare in other regions of the world—including in other areas of Africa—accounts for 30–50% of HIV infections in some areas of East Africa.[34,37] Subtype D has a greater predilection for X4 tropism[7] and X4 tropism, in turn, has been associated with suboptimal CD4 recovery after HIV RNA suppression.[6] Nutrition may also play a role. A randomized trial in the USA suggested that protein intake was associated with better CD4 recovery, and populations in rural East Africa may have particularly low protein intake.[38] The effect of trimethoprim-sulfamethoxazole—a medication that can impair haematopoiesis—may be magnified in populations with low protein intake. Host genetic characteristics unique to East Africa may also contribute to diminished capacity for CD4 + T cell restoration.[4,5] Further studies to elucidate the mechanisms that determine the differences we observed between regions—which may be multifactorial—are needed.

The diminished CD4 recovery in East Africa is large enough to potentially influence health outcomes. A large cohort analysis from the Collaboration of Observational HIV Epidemiological ResearchEurope (COHERE) found reductions in AIDS progression and mortality: by 65% per rise of 100 CD4 cells/μl among patients with a most recent CD4 level <200/μl; by approximately 20% for patients with CD4 levels from 201/μl to 500/μl; and by 4% for those with a CD4 level >500/μl.[1] Given our observation of an approximately 100-cell/μl difference between East Africa and North America at 3 years following ART initiation, the results of COHERE suggest that the poorer CD4 recovery in East Africa is likely clinically meaningful across a range of CD4 counts. Inpatient health systems in Africa, furthermore, often lack sophisticated and expensive

Table 2. Average CD4 + T cell counts for patients for given pre-therapy CD4 levels. Values are shown in each region at 4, 12 and 36 months after antiretroviral therapy initiation and during HIV RNA suppression. Estimates were obtained from a piecewise mixed-effects linear regression with knots at 4 and 12 months. Values are adjusted for sex, age, composition of initial regimen, pre-therapy CD4 level and pre-therapy HIV RNA level

	North America		West Africa		East Africa		Southern Africa		Asia	
Pre-therapy CD4 count	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
	Month 4									
25	137	133 to 141	132	120 to 143	136	130 to 142	147	144 to 149	117	108 to 125
50	177	173 to 182	170	158 to 182	164	158 to 170	178	176 to 181	154	144 to 164
100	249	243 to 256	240	224 to 256	226	218 to 234	237	234 to 240	224	209 to 238
150	301	296 to 307	290	276 to 305	289	281 to 296	284	281 to 287	276	263 to 289
200	356	351 to 362	343	329 to 358	344	337 to 352	333	329 to 336	329	316 to 342
300	493	479 to 508	473	431 to 515	439	408 to 470	447	434 to 460	452	409 to 494
	Month 12									
25	245	239 to 251	218	202 to 234	214	206 to 221	249	246 to 252	215	203 to 226
50	268	262 to 274	239	224 to 254	221	214 to 229	260	258 to 263	237	224 to 250
100	320	312 to 328	287	268 to 305	261	252 to 269	296	293 to 300	288	272 to 305
150	377	370 to 384	340	324 to 357	326	318 to 334	347	344 to 350	346	331 to 361
200	432	425 to 439	392	375 to 409	380	372 to 387	395	391 to 399	399	384 to 414
300	538	522 to 554	489	446 to 532	440	409 to 471	479	465 to 493	492	447 to 537
	Month 36									
25	429	418 to 441	400	340 to 461	358	345 to 371	454	447 to 461	398	376 to 421
50	442	430 to 453	411	351 to 472	352	341 to 364	452	445 to 458	411	388 to 435
100	479	466 to 492	446	382 to 510	376	363 to 389	470	463 to 478	450	423 to 478
150	529	517 to 541	494	429 to 559	437	425 to 449	515	508 to 522	503	478 to 528
200	575	564 to 586	537	470 to 604	481	469 to 493	554	547 to 562	548	523 to 573
300	650	626 to 674	605	520 to 689	508	471 to 544	608	585 to 630	611	555 to 666

diagnostic and treatment options available in Europe, thus magnifying potential consequences of attenuated CD4 recovery in East Africa. Finally, diminished CD4 recovery after ART initiation in East Africa—and therefore a longer period of immunosuppression—implies that the benefits of initiating ART at higher CD4 levels may be greater in East Africa than in other regions of the world.

Several limitations were present in this study. First, we did not conduct the CD4 measurements ourselves in a centralized laboratory, and therefore regional differences in assay performance cannot be addressed. In East Africa, however, CD4 testing was carried out in three administratively and geographically distinct laboratories, thus making laboratory artefact unlikely. Second, losses to follow-up occurred in 15% of patients and raise concerns about selection bias. Our analysis, however, restricted observation to time during HIV RNA suppression, and this strategy provides stronger protection against bias due to informative censoring. Also, conditions such as tuberculosis that could cause both losses to follow-up as well as diminished CD4 recovery during HIV RNA suppression—and therefore informative censoring—are more likely to occur in East Africa than in the USA and would lead to underestimates of the differences observed. In addition, the longer interval between HIV RNA determinations in East Africa as compared with North America may have allowed longer periods of undetected rebound HIV RNA viraemia and therefore biased estimates of CD4 recovery during HIV RNA suppression downward in East Africa. The interval between HIV RNA measurements, however, was also relatively long in West and Southern Africa, yet those regions exhibited more robust CD4 responses as compared with East Africa. Therefore, we believe that artefact due to interval of CD4 measurements is an unlikely explanation for our findings. In North America, restriction of the cohort to patients starting NNRTI-based regimens implies that many patients (e.g. those starting protease inhibitor-based regimens) were excluded, thus introducing the possibility they were unlike other patients who were included in unmeasured ways. A final limitation is that all our sites in East Africa were located in Uganda and we lacked data from Kenya or Tanzania, thus potentially compromising the generalizability of the findings.

In summary, we found notable regional differences in CD4 count recovery on suppressive ART, with patients in

Table 3. Cross-regional differences in expected CD4 levels between patients. Values are shown for patients with given pre-therapy CD4 + T cell counts at 4, 12 and 36 months after ART initiation. Patients are assumed to have population-averaged characteristics of sex, age, composition of initial regimen and pre-therapy plasma HIV RNA levels. The value in each cell represents the estimated difference in CD4 recovery between an individual in the region indicated in the column and the region indicated in the row. For example the first value of 6 in the top left cell indicates that the average CD4 rise in North America is 6 cells higher than in West Africa 4 months after ART initiation for patients who initiate antiretroviral therapy with a CD4 count of 25 cells/μl

Pre-therapy CD4 Count = 25

	WA			EA			SA			AS		
Country	Diff.	95% CI	*P*-value	Diff.	95% CI	*P*-value	Diff.	95% CI	*P*-value	Diff.	95% CI	*P*-value
						Month 4						
NA	6	−7 to 18	0.385	1	−6 to 9	0.710	−9	−14 to −5	0.000	21	11 to 30	0.000
WA				−4	−17 to 9	0.537	−15	−27 to −3	0.014	15	1 to 29	0.039
EA							−11	−17 to −4	0.001	19	9 to 29	0.000
SA										30	22 to 38	0.000
						Month 12						
NA	27	10 to 44	0.002	32	22 to 41	0.000	−4	−10 to 3	0.288	30	17 to 43	0.000
WA				4	−13 to 22	0.632	−31	−47 to −15	0.000	3	−17 to 23	0.766
EA							−35	−44 to −27	0.000	−1	−15 to 12	0.847
SA										34	22 to 46	0.000
						Month 36						
NA	29	−32 to 90	0.349	71	56 to 87	0.000	−25	−37 to −12	0.000	31	7 to 55	0.012
WA				42	−19 to 104	0.178	−54	−114 to 7	0.082	2	−62 to 66	0.955
EA							−96	−109 to −82	0.000	−40	−65 to −15	0.001
SA										56	33 to 79	0.000

Pre-therapy CD4 Count = 50

	WA			EA			SA			AS		
	Diff.	95% CI	P-value	Diff.	95% CI	P-value	Diff.	95% CI	P-value	Diff.	95% CI	P-value
						Month 4						
NA	7	−6 to 20	0.285	13	6 to 21	0.000	−1	−6 to 4	0.671	23	12 to 34	0.000
WA				6	−7 to 20	0.367	−8	−21 to 4	0.188	16	0 to 32	0.044
EA							−14	−21 to −8	0.000	10	−2 to 21	0.097
SA										24	14 to 34	0.000
						Month 12						
NA	29	13 to 46	0.000	47	37 to 56	0.000	8	1 to 14	0.029	31	17 to 45	0.000
WA				17	1 to 34	0.041	−22	−37 to −6	0.006	2	−18 to 21	0.857
EA							−39	−47 to −31	0.000	−16	−30 to −1	0.032
SA										23	11 to 36	0.000
						Month 36						
NA	30	−31 to 92	0.329	90	75 to 104	0.000	−10	−22 to 3	0.124	31	6 to 55	0.016
WA				59	−2 to 120	0.060	−40	−101 to 20	0.194	0	−64 to 65	0.996
EA							−99	−112 to −87	0.000	−59	−84 to −34	0.000
SA										40	17 to 64	0.001

Pre-therapy CD4 Count = 100

	WA			EA			SA			AS		
	Diff.	95% CI	P-value	Diff.	95% CI	P-value	Diff.	95% CI	P-value	Diff.	95% CI	P-value
						Month 4						
		−8 to 27	0.278	23	13 to 33	0.000	12	5 to 19	0.001	25	10 to 41	0.002
WA				14	−4 to 32	0.125	3	−13 to 19	0.741	16	−6 to 37	0.148
EA							−11	−19 to −3	0.008	2	−14 to 18	0.815
SA										13	−2 to 28	0.079

(Continued)

Table 3. Continued

Pre-therapy CD4 Count = 100

	WA			EA			SA			AS		
	Diff.	**95% CI**	**P-value**	**Diff.**	**95% CI**	**P-value**	**Diff.**	**95% CI**	**P-value**	**Diff.**	**95% CI**	**P-value**
						Month 12						
NA	33	13 to 53	0.001	59	48 to 70	0.000	23	15 to 32	0.000	31	13 to 49	0.001
WA				26	6 to 46	0.010	−10	−28 to 9	0.312	−2	−26 to 23	0.897
EA							−36	−45 to −27	0.000	−28	−46 to −9	0.003
SA										8	−9 to 25	0.354
						Month 36						
NA	33	−32 to 97	0.317	103	86 to 119	0.000	9	−5 to 22	0.223	29	0 to 57	0.050
WA				70	5 to 134	0.034	−24	−88 to 39	0.455	−4	−73 to 64	0.902
EA							−94	−108 to −81	0.000	−74	−103 to −45	0.000
SA										20	−7 to 47	0.151

Pre-therapy CD4 Count = 150

	WA			EA			SA			AS		
	Diff.	**95% CI**	**P-value**	**Diff.**	**95% CI**	**P-value**	**Diff.**	**95% CI**	**P-value**	**Diff.**	**95% CI**	**P-value**
						Month 4						
NA	11	−4 to 26	0.156	13	4 to 22	0.005	18	11 to 24	0.000	25	11 to 39	0.000
WA				2	−14 to 18	0.816	7	−8 to 21	0.369	14	−5 to 33	0.147
EA							5	−3 to 13	0.243	12	−2 to 27	0.103
SA										8	−6 to 21	0.259
						Month 12						
NA	36	18 to 54	0.000	51	41 to 61	0.000	30	22 to 37	0.000	31	15 to 47	0.000
WA				14	−4 to 33	0.120	−6	−23 to 10	0.457	−6	−28 to 17	0.623
EA							−21	−29 to −13	0.000	−20	−36 to −4	0.016
SA										1	−14 to 16	0.907
						Month 36						
NA	35	−30 to 101	0.293	92	77 to 108	0.000	14	1 to 28	0.033	26	0 to 53	0.054
WA				57	−8 to 123	0.088	−21	−86 to 44	0.531	−9	−78 to 60	0.796
EA							−78	−91 to −65	0.000	−66	−93 to −39	0.000
SA										12	−14 to 37	0.370

Pre-therapy CD4 Count = 200

	WA			EA			SA			AS		
	Diff.	**95% CI**	**P-value**	**Diff.**	**95% CI**	**P-value**	**Diff.**	**95% CI**	**P-value**	**Diff.**	**95% CI**	**P-value**
						Month 4						
NA	13	−2 to 29	0.096	12	3 to 21	0.009	24	17 to 30	0.000	28	14 to 42	0.000
WA				−1	−17 to 15	0.896	11	−4 to 25	0.157	33	−33 to 98	0.332
EA							12	4 to 20	0.004	15	1 to 30	0.042
SA										4	−10 to 17	0.580
						Month 12						
NA	40	22 to 58	0.000	52	42 to 62	0.000	37	29 to 45	0.000	33	17 to 49	0.000
WA				12	−6 to 31	0.187	−3	−20 to 14	0.725	9	−58 to 76	0.790
EA							−15	−24 to −7	0.000	−19	−36 to −3	0.020
SA										−4	−19 to 11	0.606
						Month 36						
NA	38	−30 to 106	0.270	94	79 to 109	0.000	21	7 to 34	0.002	27	1 to 54	0.044
WA				56	−12 to 124	0.105	−17	−84 to 50	0.614	3	−76 to 82	0.939

(Continued)

Table 3. Continued

	Pre-therapy CD4 Count = 200											
	WA			EA			SA			AS		
	Diff.	95% CI	P-value	Diff.	95% CI	P-value	Diff.	95% CI	P-value	Diff.	95% CI	P-value
EA							−73	−87 to −60	0.000	−67	−94 to −40	0.000
SA										6	−19 to 32	0.621

	Pre-therapy CD4 Count = 300											
	WA			EA			SA			AS		
	Diff.	95% CI	P-value	Diff.	95% CI	P-value	Diff.	95% CI	P-value	Diff.	95% CI	P-value
	Month 4											
NA	20	−24 to 64	0.363	54	21 to 87	0.001	46	28 to 64	0.000	42	−3 to 86	0.068
WA				34	−18 to 85	0.200	26	−17 to 69	0.244	21	−38 to 81	0.484
EA							−8	−41 to 25	0.632	−12	−65 to 40	0.642
SA										−4	−49 to 40	0.845
	Month 12											
NA	49	4 to 94	0.032	98	65 to 132	0.000	60	40 to 79	0.000	46	−1 to 93	0.053
WA				49	−3 to 101	0.066	10	−34 to 54	0.649	−3	−65 to 58	0.920
EA							−39	−71 to −6	0.020	−52	−106 to 2	0.058
SA										−13	−60 to 33	0.570
	Month 36											
NA	46	−39 to 130	0.291	142	105 to 180	0.000	43	19 to 66	0.000	39	−16 to 95	0.167
WA				97	8 to 186	0.033	−3	−87 to 81	0.943	−6	−105 to 92	0.900
EA							−100	−137 to −63	0.000	−103	−166 to −41	0.001
SA										−3	−58 to 52	0.909

Diff., difference; NA, North America; WA, West Africa, EA, East Africa; SA, South Africa; AS, Asia.

East Africa experiencing a clinically significant attenuation as compared with other regions. We speculate that the differences in the 'immunological efficacy' of ART globally may be explained in part by the notion that HIV pathogenesis both before ART and after ART is driven by microbial exposure and immunological activation. Epidemiological analyses carried out on a global level, made possible for the first time by large research consortia such as IeDEA, can identify macroscopic effects otherwise unobservable at the clinical, national or individual regional level.

Funding

Funding has been provided by the National Institutes of Health [K23 AI084544, U01 AI069918, U01 AI069919, U01 AI069924, U01 AI069911, U01 AI069907, R01 MH054907 and P30 AI027763] and the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Conflict of interest: None declared.

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