Clinical Nutrition 38 (2019) 1303–1309

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Effect of baseline micronutrient and inflammation status on CD4 recovery post-cART initiation in the multinational PEARLS trial

Rupak Shivakoti [a, *, 1], Erin R. Ewald [b, 1], Nikhil Gupte [a], Wei-Teng Yang [a], Cecilia Kanyama [c], Sandra W. Cardoso [d], Breno Santos [e], Khuanchai Supparatpinyo [f], Sharlaa Badal-Faesen [g], Javier R. Lama [h], Umesh Lalloo [i], Fatima Zulu [j], Jyoti S. Pawar [k], Cynthia Riviere [l], Nagalingeswaran Kumarasamy [m], James Hakim [n], Richard Pollard [o], Barbara Detrick [p], Ashwin Balagopal [a], David M. Asmuth [o], Richard D. Semba [q], Thomas B. Campbell [r], Jonathan Golub [a], Amita Gupta [a], for the NWCS 319 and ACTG PEARLS Study Team

[a] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA
[b] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[c] UNC Lilongwe, Lilongwe, Malawi
[d] STD/AIDS Clinical Research Laboratory, Instituto de Pesquisa Clinica Evandro Chagas, Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil
[e] Hospital Nossa Senhora de Conceição, Porto Alegre, Brazil
[f] Chiang Mai University, Chiang Mai, Thailand
[g] Department of Medicine, University of Witwatersrand, Johannesburg, South Africa
[h] IMPACT PERU Clinical Trials Unit, Asociacion Civil Impacta Salud y Educacion, Lima, Peru
[i] University of KwaZulu Natal, Nelson R Mandela School of Medicine, Durban, South Africa
[j] Malawi College of Medicine – Johns Hopkins Research Project, Kachere Rehabilitation Centre, Blantyre, Malawi
[k] National AIDS Research Institute, Pune, India
[l] Les Centres GHESKIO, Port-Au-Prince, Haiti
[m] YR Gaitonde Center for AIDS Research and Education, Chennai, India
[n] University of Zimbabwe, Harare, Zimbabwe
[o] Department of Medicine, University of California Davis, Sacramento, CA, USA
[p] Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[q] Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[r] Department of Medicine, Division of Infectious Diseases, University of Colorado School of Medicine, Aurora, CO, USA

ARTICLE INFO

Article history:
Received 13 February 2018
Accepted 22 May 2018

Keywords:
CD4 reconstitution
CD4 recovery
Micronutrients
Inflammation
HIV
Nutrition

SUMMARY

Background & aims: Nutritional deficiency and inflammation may impact CD4+ T cell recovery during combination antiretroviral therapy (cART), particularly in resource-limited settings where malnutrition is prevalent. The aim of this study was to investigate the relationship of micronutrient and inflammation biomarkers to CD4 recovery after cART initiation.

Methods: We conducted a secondary analysis of a random sub-cohort sample (n = 270) from a multinational randomized trial of cART regimen efficacy among 1571 cART-naïve adults. We measured pre-cART serum levels of micronutrients (Vitamin A, B_6, B_{12}, D, total carotenoids, selenium, and iron) and inflammation (C-reactive protein, soluble CD14 (sCD14), IFNγ, TNFα, Interleukin-6, and C-X-C motif chemokine 10 (CXCL10/IP10), EndoCab (IgM)) biomarkers. Biomarker status (i.e. micronutrient deficiency vs. sufficiency and elevated vs. low inflammation) was defined using established cutoffs or quartiles.

Aabbreviations: cART, Combination antiretroviral therapy; HIV, Human immunodeficiency virus; CD4, CD4+ T cells; sCD14, soluble CD14; CXCL10/IP10, C-X-C motif chemokine 10; CRP, C-reactive protein; IgM, EndoCab; IL6, Interleukin-6; IFNg, Interferon gamma; TNFa, Tumor necrosis factor alpha; 25-hydroxyvitamin D, vitamin D; BMI, body mass index.

* Corresponding author. Center for Clinical Global Health Education, 600 N Wolfe St, Phipps 521, Baltimore, MD, 21287, USA. Fax: +1 443 287 6440.
E-mail addresses: rshivak1@jhmi.edu (R. Shivakoti), erewald@gmail.com (E.R. Ewald), nikhil_jhumit@yahoo.com (N. Gupte), weiteng.yang@gmail.com (W.-T. Yang), ckanyama@unclilongwe.org (C. Kanyama), sandra.wagner@ipec.fiocruz.br (S.W. Cardoso), breno@ghc.com.br (B. Santos), khuanchai@rihes.org (K. Supparatpinyo), sfaesen@witshealth.co.za (S. Badal-Faesen), jrlama@impactaperu.org (J.R. Lama), umeshlalloo@gmail.com (U. Lalloo), nez4@cdc.gov (F. Zulu), jyotispawar.pawar@gmail.com (J.S. Pawar), cynthiariviere@yahoo.com (C. Riviere), kumarasamy@yrgcare.org (N. Kumarasamy), jhakim@mweb.co.zw (J. Hakim), rbpollard@ucdavis.edu (R. Pollard), bdetrick@jhmi.edu (B. Detrick), abalago1@jhmi.edu (A. Balagopal), dasmuth@ucdavis.edu (D.M. Asmuth), rdsemba@jhmi.edu (R.D. Semba), Thomas.Campbell@ucdenver.edu (T.B. Campbell), jgolub@jhmi.edu (J. Golub), agupta25@jhmi.edu (A. Gupta).
[1] Contributed equally.

https://doi.org/10.1016/j.clnu.2018.05.014

Mixed-effects linear regression models were used to determine the association of baseline (pre-cART) concentrations of individual biomarkers with CD4 recovery through 96 weeks post-cART initiation.
Results: In models adjusting for time-dependent viral load and baseline CD4 count, age, sex, body mass index, country, treatment regimen, anemia and hypoalbuminemia status, pre-cART vitamin D deficiency was associated with lower CD4 recovery (−14.9 cells/mm^3, 95% CI: −27.9, −1.8) compared to sufficiency. In contrast, baseline selenium deficiency (20.8 cells/mm^3, 95% CI: 3.3, 38.3), vitamin A deficiency (35.9 cells/mm^3, 95% CI: 17.6, 54.3) and high sCD14 (23.4 cells/mm^3, 95% CI: 8.9, 37.8) were associated with higher CD4 recovery compared to sufficient/low inflammation status.
Conclusions: In summary, baseline vitamin D deficiency was associated with diminished CD4 recovery after cART initiation; impaired CD4 recovery may contribute to the poor clinical outcomes recently observed in individuals with vitamin D deficiency. Vitamin A, selenium and sCD14 were associated with CD4 recovery but future studies are needed to further explore these relationships.

1. Introduction

CD4+ T cell recovery after initiation of combination antiretroviral therapy (cART) is essential for restoring immune function in HIV-positive individuals [1]. However, CD4 recovery is variable and is affected by factors such as biological sex [2,3], race [4], BMI [5], geographic region [4], intravenous drug use [6], and alcohol use [7]. Nutritional status (especially micronutrient deficiencies) and inflammation are known to affect CD4 number and function [8–10], but the association between inflammation or nutritional status and CD4 recovery in HIV-positive adults after cART initiation has not been well studied, particularly in low- and middle-income (LMIC) populations, where high levels of malnutrition have been observed.

Most people living with HIV are at risk for experiencing malnutrition and inflammation. In particular, undernourishment may worsen HIV outcomes [11]. There is substantial interest in using serum or plasma-based biomarkers to identify patients at risk for HIV progression. Markers of malnutrition and inflammation that have been previously associated with adverse HIV clinical outcomes may also be predictors of CD4 recovery post-cART.

Diminished nutritional status, especially micronutrient malnutrition, and inflammation have been associated with CD4 proliferation and function in HIV-positive patients [8–10]. In particular, micronutrient deficiencies of vitamin B_{12}, vitamin D, selenium, and carotenoids have antioxidant effects, which have been linked to HIV activation and disease progression in individuals not on cART [11–13]. Similarly, several markers of inflammation assessed in serum or plasma, including soluble CD14 (sCD14), C-reactive protein (CRP), CXCL10, and interleukin-6 (IL-6), have been associated with increased risk of mortality on cART [14–16]. However, whether such adverse clinical outcomes are mediated by differences in CD4 reconstitution remains unclear [17–19].

We hypothesize that elevated levels of inflammatory biomarkers, including CRP, IL-6, and sCD14, and that low levels of micronutrients, including selenium, vitamin D and vitamin A, will be associated with a detrimental effect on CD4 recovery post-cART initiation. This analysis of a case-cohort sample from the Prospective Evaluation of Antiretrovirals in Resource Limited Settings (PEARLS) trial aimed to determine whether baseline micronutrient and inflammation levels are associated with CD4 reconstitution post-cART initiation. Such data will inform efforts to understand the mechanisms through which post-cART CD4 recovery is achieved and contribute to a better understanding of the relationship between these biomarkers and CD4 recovery.

2. Methods

2.1. Study population

A random sub-cohort was selected from the PEARLS trial, a randomized clinical trial examining efficacy of three cART regimens among 1571 HIV-positive adults (≥18 years) with CD4 count < 300 cells/mm^3 (AIDS Clinical Trials Group A5175, clinicaltrials.gov NCT00084136). The PEARLS trial methods are described in detail elsewhere [20]. Briefly, eligible participants were enrolled from May 2005 to August 2007. Exclusion criteria included pregnancy, acute illness, and other co-morbidities. Patients were randomized equally to three treatment regimens (once-daily efavirenz with twice-daily lamivudine-zidovudine; once-daily atazanavir with didanosine EC and emtricitabine; and once-daily efavirenz with emtricitabine-tenofovir-DF) and followed through 96 weeks, or more, post-cART initiation.

The 270 individuals included in our study were a random sub-cohort of the PEARLS trial of 1571 individuals. This sub-cohort was stratified by country with 30 individuals each randomly selected from 9 countries (Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, United States and Zimbabwe); inclusion or exclusion criteria were not based on other criteria such as race or treatment regimen.

2.1.1. Ethics statement

This study was approved by the Institutional Review Board at the Johns Hopkins School of Medicine and at each of the study sites participating in the parent trial. Written, informed consent was obtained from each study participant, and human experimentation guidelines of the US Department of Health and Human Services were followed.

2.2. Data collection and laboratory methods

At PEARLS trial entry, participants underwent a complete physical exam, medical history review, serum chemistries, liver function tests, CD4 count, and plasma HIV RNA viral load (Roche Amplicor Monitor Assay [v1.5, Branchburg, NJ]). CD4 count was subsequently measured at weeks four and eight, then every eight weeks through week 96. All laboratory assays (serum chemistries, liver function tests, CD4 counts and viral loads) were measured at ACTG laboratories that were externally assured as part of the NIH Division of AIDS and ACTG Network lab quality assurance [20].

Serum collected at the PEARLS trial entry visit was stored at −80 °C. For all study sites, baseline biomarkers were measured at quality-assured certified laboratories at the Johns Hopkins Hospital

(Baltimore, MD), except for IL-6, IFNγ, TNFα and CXCL10, which were measured at the University of California, Davis School of Medicine (Davis, CA). Vitamin B_{12} was measured using Abbott AxSYM (Abbott Canada, Quebec, Canada), an automated immunochemical analyzer. All fat-soluble vitamins (i.e. vitamin A, α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene) were measured using high performance liquid chromatography-ultraviolet detection (HPLC-UV). Serum 25(OH)-vitamin D was measured using a chemiluminescence immunoassay (LAISION, DiaSorin, Stillwater, MN), which reports total serum 25(OH)-vitamin D concentration. Selenium was measured using a Perkin-Elmer AAnalyst 600 graphite furnace atomic absorption spectrometer. Ferritin was measured using the Alpco Ferritin ELISA kit (ALPCO Diagnostics, Salem, NH), and soluble transferrin receptor (sTfR) was measured using the Quantikine ELISA kit (R&D Systems, Minneapolis, MN). CRP was measured using the Quantikine ELISA kit (R&D Systems, Minneapolis, MN). ELISA assays were also used to measure sCD14 (R&D Systems, Minneapolis, MN) and EndoCAb IgM (Cell Sciences, Canton, MA). IL-6, IFNγ and TNFα was measured using the Luminex multiplex platform (R&D Systems, Minneapolis, MN), and CXCL10 was measured with the Human IP-10 (CXCL10) V-PLEX Kit (Meso Scale Discovery, Rockville, MD).

2.3. Biomarker status definitions

The outcome of CD4 recovery is defined here as the change in CD4 count through 96 weeks post-cART initiation measured in cells/mm^3. In accordance with prior publications and clinically relevant standards based on serum concentration, deficiency was defined as: vitamin B_{12} < 148 pmol/L; vitamin B_6 < 19 nmol/L; vitamin A <1.05 μmol/L; vitamin D < 30 ng/mL and selenium <85 μg/L [19, 21–25]. Iron deficiency was defined based on either soluble transferrin receptor concentration (>8.3 mg/L) [26] or ferritin concentrations (ferritin <12 μg/L if CRP ≤ 5 mg/L or ferritin <30 μg/L if CRP >5 mg/L) [27].

For all biomarkers without defined cutoffs (total carotenoids, IFNγ, TNFα, sCD14, IL-6, CXCL10 and EndoCab IgM), biomarkers levels were analyzed by quartile. Total carotenoids were measured by summing α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene concentrations (all measured in μmol/L), and the lowest quartile (Q1) was defined as deficient. As elevated levels of various inflammatory biomarkers have been associated with disease progression [14–16], the highest quartile (Q4) of these markers was defined as high inflammation. We defined elevated CRP as CRP ≥ 10 mg/L based on definitions from prior studies [28], which was similar to the observed Q4 cutoff in our study (10.3 mg/L). sCD14 was Log_2 transformed given its distribution and our prior studies [29].

2.4. Statistical analysis

We completed a secondary analysis of the PEARLS study investigating the effect of baseline levels of biomarkers on CD4 reconstitution. Using a mixed-effects linear regression analysis with exchangeable correlation structure (equal variance for random effects and one common pairwise covariance) and a random slope and intercept, we estimated CD4 counts over time. Separate models were run for each micronutrient and inflammatory marker, and models were adjusted for time-dependent viral load and baseline covariates including CD4 count, age, sex, body mass index (BMI), country, treatment regimen, anemia and hypoalbuminemia status. As the baseline CD4 counts differed by baseline micronutrient and inflammation status, we followed an analytical approach used by other groups [30] to define the outcome variable as CD4 count after cART initiation (4 weeks and onwards) while adjusting for baseline CD4 counts in the multivariable models. All analyses were conducted using STATA, version 12.1 (StataCorp LP, College Station, TX) with a significance level of $\alpha = 0.05$.

3. Results

3.1. Study population characteristics at baseline

We conducted a nested cohort study of HIV-infected adults initiating ART within a randomized clinical trial assessing cART efficacy of 3 different regimens. In the nested cohort (n = 270), the median age was 35 years (IQR 29–41) and 50.0% were female. As the cohort was stratified by country, there were 30 individuals (11.1%) from each of the nine countries. Half of the cohort (50.0%) were black non-Hispanic, 22.6% were Asian, 21.5% were Hispanic, and 5.6% were white non-Hispanic (Table 1). The majority (64.4%) fell within the normal BMI range; 25 (9.3%) individuals were underweight, and 71 (26.3%) individuals were overweight or obese. The median baseline CD4 count was 178.5 cells/mm^3 (IQR 99–229), and the median baseline log_{10} viral load was 5.1 copies/mL (IQR 4.6–5.5). 138 individuals (51.3%) had anemia and 51 (19.0%) had hypoalbuminemia (albumin <3.5 g/dL) at baseline. Among the individuals in this cohort, 99 (36.7%) were randomized to receive 3TC/ZDV/EFV, 89 (33.0%) received ATV/FTC/DDI and 82 (30.4%) received FTC/TDF/EFV (Table 1).

3.2. Pre-cART biomarker status

Baseline prevalence of deficiency for several micronutrients, using established thresholds, has been previously described in

Table 1
Baseline study population characteristics (n = 270).

Characteristic	n (%)[a]
Median age (IQR)[b]	35 (29–41)
Median CD4 count (IQR)	178.5 (90–229)
Median Log viral load (IQR)	5.1 (4.6–5.5)
Gender	
Male	135 (50.0)
Female	135 (50.0)
BMI (kg/m^2)	
<18.5	25 (9.3)
18.5–25	174 (64.4)
>25	71 (26.3)
Race	
White	15 (5.6)
Black	135 (50.0)
Hispanic	58 (21.5)
Asian	61 (22.6)
Country	
Brazil	30 (11.1)
Haiti	30 (11.1)
India	30 (11.1)
Malawi	30 (11.1)
Peru	30 (11.1)
South Africa	30 (11.1)
Thailand	30 (11.1)
United States	30 (11.1)
Zimbabwe	30 (11.1)
Treatment assignment	
3TC/ZDV/EFV	99 (36.7)
ATV/FTC/DDI	89 (33.0)
FTC/TDF/EFV	82 (30.4)
Anemia (Male < 13, Female < 12.0 g/dL)	
No	131 (48.7)
Yes	138 (51.3)
Hypoalbuminemia (<3.5 g/dL)	
No	218 (81.0)
Yes	51 (19.0)

[a] Number and percent – n (%) for each category.
[b] For continuous variable, median and interquartile range (IQR) shown instead.

detail for this cohort [31]. Selenium deficiency was most common (53.2%) followed by vitamin D deficiency (46.4%) and vitamin B_6 deficiency (37.3%); 17.1% had vitamin A deficiency, 9.0% had vitamin B_{12} deficiency, and 7.6% had iron deficiency (Table 2). Elevated CRP levels were defined based on thresholds reported in prior studies; the prevalence of elevated CRP was 26.2%. For biomarkers without established thresholds, quartiles were used to create cutoffs, with the exposed group representing hypothesized harmful end of the range. For example, individuals in the lowest quartile of carotenoids were categorized as deficient whereas individuals in the highest quartile of inflammatory markers were categorized as high inflammation (Table 2).

3.3. Impact of biomarker status on CD4 recovery

Univariable analysis was performed for each micronutrient and biomarker with CD4+ T cell recovery over 96 weeks post-cART initiation. In univariable models, deficiency in vitamin B_{12} ($p = 0.04$), vitamin B_6 ($p = 0.02$), total carotenoids ($p = 0.002$) and vitamin D ($p < 0.001$), but not selenium ($p = 0.97$), were associated with lower CD4 reconstitution compared to those with sufficient levels (Table 3). In contrast, sufficiency in vitamin A ($p = 0.04$) and iron ($p = 0.007$) were associated with lower CD4 reconstitution compared to those with deficient levels. In univariable models on the association of each inflammation marker with CD4 reconstitution, high levels of CRP ($p = 0.004$) and IFNγ ($p = 0.001$), but not IL-6 ($p = 0.29$), CXCL10 ($p = 0.11$), TNFα ($p = 0.28$), Log_2 sCD14 ($p = 0.98$), or endoCab IgM ($p = 0.91$) were associated with significantly lower CD4 reconstitution compared to those with normal levels (Table 3).

After adjusting for time-dependent viral load as well as baseline covariates, including CD4 count, age, sex, BMI, country, treatment regimen, anemia status, and hypoalbuminemia status, deficiency in vitamin D (−14.9, 95% CI: −27.9 to −1.8) was significantly associated with lower CD4 reconstitution (Table 3). Deficiency of vitamin A (35.9, 95% CI: 17.6–54.3) and selenium (20.8, 95% CI: 3.3–38.3), as well as high sCD14 (23.4, 95% CI: 8.9–37.8) were significantly associated with higher CD4 reconstitution in adjusted models (Table 3). High CRP and high IL-6 were associated with lower CD4 reconstitution but this association was not statistically significant ($p = 0.05$). The differences observed between the univariable and multivariable models were primarily driven by the adjustment for baseline CD4 counts.

While the focus of this analysis was to assess the relationship of micronutrients and inflammation with CD4 recovery, we also conducted secondary analyses to determine the association of BMI and anemia with CD4 recovery. In multivariable models that adjusted for the same variables as the primary analysis, low BMI (40.8, 95% CI: 20.1–61.6) was associated with higher CD4 reconstitution, while high BMI (−29.2, 95% CI: −43.1 to −15.3) was associated with lower reconstitution compared to those with normal BMI. Baseline anemia (28.1, 95% CI: 15.2–41.0) was also associated with higher CD4 reconstitution.

As circulating levels of micronutrients can often be affected by inflammation [9,32], we also further adjusted for CRP, a marker commonly used to adjust for inflammation in nutrition studies, in the micronutrient models but that did not change the direction or the significance of the results. Similarly, adjusting for baseline viral load instead of time-dependent viral load also did not affect our results (data not shown). Because there are considerable changes in CD4 counts during the first four weeks of cART and given our first time point in the outcome variable only starts at four weeks, we also assessed whether the gain in CD4 counts during the first four weeks were significantly different by biomarker status. However, for all of the biomarkers, the gain in CD4 counts over four weeks were not significantly different by baseline biomarker level (except for sCD14, but the direction of the effect was the same). Thus our conclusions remained the same even when gain during the first four weeks was taken into account (data not shown).

4. Discussion

Our analysis of adults initiating cART in multinational, resource-limited settings indicates that baseline levels of certain micronutrients and inflammation markers are associated with CD4 recovery post-cART initiation. Vitamin D deficiency was associated with lower CD4 reconstitution, while surprisingly, deficiencies in vitamin A and selenium, and high sCD14 were associated with higher CD4 reconstitution over 96 weeks. Our results suggest that implementing measures to correct pre-cART vitamin D deficiency may improve CD4 recovery while the relationship of other

Table 2
Baseline nutritional and inflammatory biomarker profiles.

Micronutrients	n	Median (IQR)	Deficient N (%)[a]
Vitamin B_{12} (pmol/L)	244	338 (253–338)	22 (9.0)
Vitamin B_6 (nmol/L)	225	23.3 (15.3–37)	84 (37.3)
Vitamin A (μmol/L)	251	1.52 (1.17–1.98)	43 (17.1)
Total carotenoids (μmol/L)	250	1.09 (0.81–1.47)	62 (24.8)
Vitamin D (ng/mL)	250	32 (24–39)	116 (46.4)
Selenium (μg/L)	252	83.0 (57.3–99.9)	134 (53.2)
Ferritin (μg/L)	249	79.9 (33.3–185.6)	19 (7.6)[b]
Soluble transferrin receptor (mg/L)	252	1.6 (1.3–2.1)	19 (7.6)[b]
Inflammation markers	**n**	**Median (IQR)**	**"High inflammation" N (%)**
CRP[c] (mg/L)	252	3.4 (1.4–10.3)	66 (26.2)
IFNγ (pg/mL)	241	17.5 (6.1–49.7)	61 (25.3)
TNFα (pg/mL)	241	19.1 (13.2–26.7)	61 (25.3)
sCD14 (pg/mL)	248	2.1×10^6 (5.5×10^5–2.7×10^6)	69 (27.8)
IL-6 (pg/mL)	241	23.8 (8.9–51.0)	61 (25.3)
CXCL10 (pg/mL)	241	1228.7 (584.5–2665.6)	61 (25.3)
EndoCab IgM (MMU/mL)	255	48.1 (29.7–71.5)	64 (25.1)

[a] Deficiency thresholds: 148 pmol/L (Vitamin B_{12}); 19 nmol/L (Vitamin B_6); 1.05 μmol/L (Vitamin A); 30 ng/mL (Vitamin D); 85 μg/L (Selenium); Carotenoids "deficiency" defined as lowest quartile as there is no established deficiency threshold for total carotenoids. "High" inflammation defined as highest quartile of inflammatory markers.

[b] n (%) shown for iron deficiency (ID); ID defined based on either soluble transferrin receptor concentration (>8.3 mg/L) or ferritin concentration (ferritin <12 μg/L if CRP ≤ 5 mg/L or ferritin <30 μg/L if CRP > 5 mg/L).

[c] High CRP defined as CRP ≥ 10 mg/L, which while similar to Q4 cutoff of CRP (10.3 mg/L), was chosen based on cutoffs from prior studies [28].

Table 3
Differences in CD4 counts by baseline biomarkers.

Micronutrient deficient[a]	Unadjusted		Adjusted[b]	
	CD4 differences (95% CI)	P-value[b]	CD4 differences (95% CI)	P-value[b]
Vitamin B_{12}	−37.9 (−73.3 to −2.5)	0.04	7.1 (−15.0 to 29.2)	0.53
Vitamin B_6	−26.0 (−47.7 to −4.2)	0.02	−7.0 (−20.2 to 6.2)	0.30
Vitamin A	27.6 (0.9–54.2)	0.04	35.9 (17.6 to 54.3)	<0.001
Total carotenoids	−36.4 (−59.1 to −13.6)	0.002	−0.5 (−15.4 to 14.4)	0.95
Vitamin D	−36.6 (−56.7 to −16.5)	<0.001	−14.9 (−27.9 to −1.8)	0.03
Selenium	0.5 (−19.7 to 20.6)	0.97	20.8 (3.3–38.3)	0.02
Iron	52.6 (14.7–90.5)	0.007	−12.4 (−46.0 to 11.2)	0.30
High inflammation[a]				
CRP	−33.3 (−56.0 to −10.5)	0.004	−12.2 (−24.6 to 0.1)	0.05
IFNγ	−38.9 (−62.6 to −15.2)	0.001	−14.3 (−31.0 to 2.3)	0.09
TNFα	−13.1 (−36.6 to 10.5)	0.28	−5.9 (−21.1 to 9.3)	0.45
Log_2 (sCD14)	−0.3 (−22.6 to 22.0)	0.98	23.4 (8.9–37.8)	0.001
IL-6	−12.8 (−36.5 to 11.0)	0.29	−15.2 (−30.6 to 0.1)	0.05
CXCL10	−19.3 (−43.1 to 4.5)	0.11	−0.9 (−16.2 to 14.5)	0.91
EndoCab IgM	1.3 (−21.8 to 24.4)	0.91	−3.1 (−16.5 to 10.4)	0.66

[a] Same Cutoffs for deficiency and high inflammation as defined in Table 1. Reference/comparison groups for micronutrient deficiencies are “Not Deficient” and for high inflammation is “Not high inflammation”.
[b] P-values were calculated using mixed-effects linear regression models; Multivariable models adjusted for time-dependent viral load and baseline CD4 count, age, sex, BMI, country, treatment regimen, anemia and hypoalbuminemia status.

biomarkers (e.g. selenium, vitamin A and sCD14) with CD4 recovery seem more complex.

The WHO has long recognized nutrition as an important factor in HIV progression [33]. Micronutrient deficiencies are very common in HIV-positive individuals, and deficiencies in selenium and 25(OH)-vitamin D have been associated with HIV disease progression [9,34–36]. However, the effect of micronutrient deficiencies on longitudinal CD4 recovery after cART initiation has not been adequately studied.

Our analysis found that lower concentrations of baseline vitamin D are associated with lower long-term CD4 recovery; utilizing a global cohort of participants in this study adds a wider scope to these previously reported results. Both cross-sectional and supplementation studies indicate that, in the context of HIV, vitamin D insufficiency and deficiency can lead to adverse outcomes, such as mortality and progression to AIDS in patients on cART and not on cART [37,38]. Our group has previously reported in this cohort that baseline Vitamin D insufficiency and deficiency are associated with increased risk of HIV disease progression post-ART initiation [36]; this may be in part related to the reduced CD4 recovery we observed in this analysis and as suggested by other recent studies [39]. Vitamin D sufficiency could potentially help with CD4 recovery as recent studies have shown that vitamin D is essential for immune function. It has been reported that sufficient vitamin D levels can reduce inflammation and T cell activation (both of which have been associated with CD4 loss) while improving the efficiency of antigen presenting cells to induce CD4 T cell proliferation [10,37,40].

From a supplementation standpoint, however, the evidence for the association of vitamin D levels and CD4 recovery is not as strong. For instance, a small 2011 study conducted in HIV-positive children on ART in Toronto (n = 54; 75% of whom were vitamin D insufficient or deficient) observed no increase in CD4 count compared to placebo after a six-month regimen of high-level vitamin D supplementation [41]. The children in this study, however, had relatively preserved immunological function; mean CD4 count at study entry was 927 cells/mm^3, which is a much healthier population than our study population. It is possible that any effect of vitamin D supplementation on CD4 count was masked by the high baseline values for CD4 or that supplementation is most beneficial for patients with lower baseline immunological functionality; for example, vitamin D could reduce inflammation and T cell activation, levels of which are often highest in more advanced disease. In contrast, a study of HIV-infected adults on cART with varying ranges of CD4 counts showed a positive effect of vitamin D supplementation on CD4 count [42]. Despite the high prevalence of vitamin D deficiency in HIV-positive adults, the exact relationship between vitamin D and CD4 recovery remains unclear [12]. Additional studies are ongoing and needed to further understand the role of supplementation in CD4 recovery and HIV disease progression.

Our results on the association of selenium deficiency and vitamin A deficiency being associated with greater CD4 recovery during treatment were surprising. As we had hypothesized a relationship in the opposite direction (deficiency being associated with lower CD4 recovery), we can only reflect on potential reasons for these observations. We would like to emphasize that our data is not necessarily suggesting that baseline deficiency in selenium or vitamin A is ‘beneficial’ in terms of CD4 recovery; instead, we hypothesize that the observed pattern in CD4 recovery may reflect a ‘catching up’ mechanism (e.g. in the setting of inflammation resolution with cART initiation [43]) in individuals with baseline deficiencies, who had a lower starting CD4 count to begin with. For example, despite the increased CD4 recovery in individuals with selenium deficiency, the total CD4 counts in selenium deficient and selenium sufficient individuals were similar at week 96 (412 vs. 416, respectively); this is explained by the lower baseline CD4 counts in selenium deficient individuals. Similar ‘catching up’ also occurs in those with low BMI and baseline anemia; the results with high BMI are interesting and future studies will need to study this in greater detail. Another possible explanation for the relationship between micronutrients and CD4 recovery may be that the deficiency status itself may improve with ART, resulting in further increases in CD4 count. However, the vitamin A, but not selenium results can be explained through this reason as our previous data from this cohort showed reduction in vitamin A but not selenium deficiency after 48 weeks of cART [31].

While studies are limited on the relationship of vitamin A deficiency and CD4 recovery, there are some studies that have examined the relationship between selenium and CD4 counts [17,44–46]. Our results appear to contradict findings from these prior studies. While there were important differences between these studies and ours based on cART status [44], use of supplements including multiple micronutrients [46], and study design

[47], the more significant point to consider is that this relationship was observed in our analysis only after adjusting for baseline CD4 levels; in fact, a model that did not adjust for baseline CD4 levels showed that baseline selenium deficiency was associated with lower CD4 recovery (data not shown). To assess the relationship between baseline selenium deficiency and CD4 recovery, we believe that adjusting for baseline CD4 is important as it will ensure that any differences in CD4 recovery by deficiency status is not actually due to pre-existing baseline CD4 differences. Future studies should investigated whether this positive association of baseline selenium deficiency with CD4 recovery can be replicated in other populations and also whether a different type of relationship (e.g. a U-shaped relationship as seen in other studies [9,48]) might be possible.

Ongoing inflammation, as assessed by markers including CRP and sCD14, has been previously associated with HIV disease progression [49–53]. In our study, high sCD14 was the only inflammation marker found to be significantly and positively associated with CD4 recovery in the multivariable model. In contrast, other studies have associated a higher sCD14 level with an increase in markers of HIV progression after cART initiation [16,54], although these studies focused on clinical outcomes rather than CD4+ T cell recovery. Notably, similar to our results, Rajasuriar and colleagues observed faster CD4 recovery with higher baseline sCD14 levels [53]. The authors suggested a potential biological explanation for this relationship whereby under certain circumstances, such as a high ratio of sCD14 compared to LPS-binding protein, elevated sCD14 may be protective against LPS-induced immune activation [53]. While previous studies have shown that inflammation is not always resolved after cART [55], it is possible that cART impacts levels of inflammatory biomarkers. Further investigation is needed to more fully understand this relationship.

Our study has some limitations. While our study provides data from a diverse multi-country setting, we did not have a sufficient sample size to investigate whether the relationship of micronutrients and inflammation with CD4 recovery differed by country. We relied on measurement of deficiencies based on measurement in serum, which may not represent 'true' deficiency in an individual at the level of the tissue; however, serum samples are commonly used to measure micronutrient deficiency and are clinically relevant in most instances. Additionally, we investigated the effect of single deficiencies and did not explore the effects of concurrent deficiencies on CD4 recovery (e.g., both selenium and vitamin D deficiencies). We also had few cases of immunologic failure in our cohort ($n = 14$) and could not assess factors associated with immunologic failure. This may indicate that our clinical trial cohort is generally healthier than the population of individuals starting cART treatment in routine program settings. Therefore, we may have underestimated some associations. Further, small numbers of participants were deficient in some biomarkers, such as vitamin B_{12}; thus our analysis was not powered to detect significant differences in CD4 count among B_{12} deficient and non-deficient participants. Other trace minerals, such as zinc and copper, which may be important in HIV immune reconstitution were not measured in this study because the parent study did not collect and store the samples in a way that was required to assess these appropriately. Despite these acknowledged limitations, we had a high quality dataset with robust longitudinal CD4 data allowing us to address CD4 recovery adequately over a two-year period.

In conclusion, lower baseline levels of serum vitamin D in HIV-positive patients at cART initiation was associated with reduced CD4 recovery, while deficiencies in selenium and vitamin A were associated with increased CD4 recovery. Among inflammatory markers, elevated sCD14 levels were associated with improved CD4+ T cell recovery. Despite the heterogeneity of the nested cohort, deriving from nine low, intermediate, and high-income countries on four continents, the findings were still discriminatory, lending power to the study and supporting these findings on a global scale. While more investigation is needed, our findings suggest that correcting baseline deficiency of vitamin D may improve CD4 recovery. In addition, these results also suggest that specific micronutrients and inflammation biomarkers may play a role in the CD4 recovery pathway post-cART initiation in resource-limited settings.

Conflict of interest

Thomas B Campbell has served on advisory boards for Gilead Sciences, ViiV and Theratechnologies. Amita Gupta and Rupak Shivakoti has received grant funding from Gilead Foundation. All authors declare no conflicts of interest. This work was supported by the National Institutes of Health, National Institute of Allergy and Infectious Diseases [UM1 AI069465, R01 AI080417]. RS was supported by National Institute of Child Health and Human Development [grant numbers K99 HD089753] of the National Institutes of Health. The parent study was supported by NIAID grants UM1 AI068634, UM1 AI068636 and UM1 AI106701. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The parent trial A5175 was also supported in part by Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, and GlaxoSmithKline. Funders had no role in study design, data collection, analysis, publication decision, or manuscript preparation.

Acknowledgements

RS and ERE conducted the data analysis and wrote the primary version of the manuscript. NG conducted the data analysis and contributed to data interpretation. JG contributed to data interpretation and manuscript review. WY, CK, SWC, BS, KS, SB, JL, UL, FZ, JSP, CY, NK, JH, RP, BD, AB, and DA contributed to data collection and manuscript review. RDS contributed to study design, laboratory testing, and review of manuscript. TBC contributed to study design, data collection, oversight of study implementation, and manuscript review. AG obtained funding and contributed to study design, manuscript writing, and review. All authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and were fully responsible for all aspects of manuscript development.

References

[1] Li TS, Tubiana R, Katlama C, Calvez V, Ait Mohand H, Autran B. Long-lasting recovery in CD4 T-cell function and viral-load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. Lancet 1998;351(9117):1682–6. Epub 1998/09/12.

[2] Farzadegan H, Hoover DR, Astemborski J, Lyles CM, Margolick JB, Markham RB, et al. Sex differences in HIV-1 viral load and progression to AIDS. Lancet 1998;352(9139):1510–4. Epub 1998/11/20.

[3] Hawkins C, Chalamilla G, Okuma J, Spiegelman D, Hertzmark E, Aris E, et al. Sex differences in antiretroviral treatment outcomes among HIV-infected adults in an urban Tanzanian setting. AIDS 2011;25(9):1189–97. Epub 2011/04/21.

[4] Meditz AL, MaWhinney S, Allshouse A, Feser W, Markowitz M, Little S, et al. Sex, race, and geographic region influence clinical outcomes following primary HIV-1 infection. J Infect Dis 2011;203(4):442–51. Epub 2011/01/20.

[5] Palermo B, Bosch RJ, Bennett K, Jacobson JM. Body mass index and CD4+ T-lymphocyte recovery in HIV-infected men with viral suppression on antiretroviral therapy. HIV Clin Trials 2011;12(4):222–7. Epub 2011/11/03.

[6] Poundstone KE, Chaisson RE, Moore RD. Differences in HIV disease progression by injection drug use and by sex in the era of highly active antiretroviral therapy. AIDS 2001;15(9):1115–23. Epub 2001/06/21.

[7] Baum MK, Rafie C, Lai S, Sales S, Page JB, Campa A. Alcohol use accelerates HIV disease progression. AIDS Res Hum Retrovir 2010;26(5):511–8. Epub 2010/05/12.

[8] Eller MA, Blom KG, Gonzalez VD, Eller LA, Naluyima P, Laeyendecker O, et al. Innate and adaptive immune responses both contribute to pathological CD4 T cell activation in HIV-1 infected Ugandans. PLoS One 2011;6(4):e18779. Epub 2011/04/29.
[9] Rayman MP. Selenium and human health. Lancet 2012;379(9822):1256–68. Epub 2012/03/03.
[10] Lake JE, Adams JS. Vitamin D in HIV-infected patients. Curr HIV/AIDS Rep 2011;8(3):133–41. Epub 2011/06/08.
[11] Ivers LC, Cullen KA, Freedberg KA, Block S, Coates J, Webb P. HIV/AIDS, undernutrition, and food insecurity. Clin Infect Dis: Off Publ Infect Dis Soc Am 2009;49(7):1096–102. Epub 2009/09/04.
[12] de Pee S, Semba RD. Role of nutrition in HIV infection: review of evidence for more effective programming in resource-limited settings. Food Nutr Bull 2010;31(4):S313–44. Epub 2011/01/11.
[13] Nkengfack GN, Torimiro JN, Englert H. Effects of antioxidants on CD4 and viral load in HIV-infected women in sub-Saharan Africa - dietary supplements vs. local diet. Int J Vitam Nutr Res 2012;82(1):63–72. Epub 2012/07/20.
[14] Jiao Y, Zhang T, Wang R, Zhang H, Huang X, Yin J, et al. Plasma IP-10 is associated with rapid disease progression in early HIV-1 infection. Viral Immunol 2012;25(4):333–7. Epub 2012/07/14.
[15] Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 2008;5(10):e203. Epub 2008/10/24.
[16] Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. J Infect Dis 2011;203(6):780–90. Epub 2011/01/22.
[17] Stone CA, Kawai K, Kupka R, Fawzi WW. Role of selenium in HIV infection. Nutr Rev 2010;68(11):671–81. Epub 2010/10/22.
[18] Keating SM, Golub ET, Nowicki M, Young M, Anastos K, Crystal H, et al. The effect of HIV infection and HAART on inflammatory biomarkers in a population-based cohort of women. AIDS 2011;25(15):1823–32. Epub 2011/05/17.
[19] Baum MK, Shor-Posner G, Lai S, Zhang G, Lai H, Fletcher MA, et al. High risk of HIV-related mortality is associated with selenium deficiency. J Acquir Immune Defic Syndr Hum Retrovirol: Off Publ Int Retrovirol Assoc 1997;15(5):370–4. Epub 1997/08/15.
[20] Campbell TB, Smeaton LM, Kumarasamy N, Flanigan T, Klingman KL, Firnhaber C, et al. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. PLoS Med 2012;9(8). e1001290. Epub 2012/09/01.
[21] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol 2011;96(7):1911–30. Epub 2011/06/08.
[22] Baeten JM, Mostad SB, Hughes MP, Overbaugh J, Bankson DD, Mandaliya K, et al. Selenium deficiency is associated with shedding of HIV-1–infected cells in the female genital tract. J Acquir Immune Defic Syndr 2001;26(4):360–4. Epub 2001/04/24.
[23] Campa A, Shor-Posner G, Indacochea F, Zhang G, Lai H, Asthana D, et al. Mortality risk in selenium-deficient HIV-positive children. J Acquir Immune Defic Syndr Hum Retrovirol: Off Publ Int Retrovirol Assoc 1999;20(5):508–13. Epub 1999/05/04.
[24] Jiang T, Christian P, Khatry SK, Wu L, West Jr KP. Micronutrient deficiencies in early pregnancy are common, concurrent, and vary by season among rural Nepali pregnant women. J Nutr 2005;135(5):1106–12. Epub 2005/05/04.
[25] Semba RD, Graham NM, Caiaffa WT, Margolick JB, Clement L, Vlahov D. Increased mortality associated with vitamin A deficiency during human immunodeficiency virus type 1 infection. Arch Intern Med 1993;153(18):2149–54. Epub 1993/09/27.
[26] Grant FK, Martorell R, Flores-Ayala R, Cole CR, Ruth LJ, Ramakrishnan U, et al. Comparison of indicators of iron deficiency in Kenyan children. Am J Clin Nutr 2012;95(5):1231–7. Epub 2012/03/30.
[27] Kupka R, Msamanga GI, Mugusi F, Petraro P, Hunter DJ, Fawzi WW. Iron status is an important cause of anemia in HIV-infected Tanzanian women but is not related to accelerated HIV disease progression. J Nutr 2007;137(10):2317–23. Epub 2007/09/22.
[28] Drain PK, Kupka R, Msamanga GI, Urassa W, Mugusi F, Fawzi WW. C-reactive protein independently predicts HIV-related outcomes among women and children in a resource-poor setting. AIDS 2007;21(15):2067–75. Epub 2007/09/22.
[29] Shivakoti R, Gupta A, Ray JC, Uprety P, Gupte N, Bhosale R, et al. Soluble CD14: an independent biomarker for the risk of mother-to-child transmission of HIV in a setting of preexposure and postexposure antiretroviral prophylaxis. J Infect Dis 2015;213(7):111–23. Epub 2015/10/08.
[30] Kowalski S, Colantuoni E, Lau B, Keruly J, McCaul ME, Hutton HE, et al. Alcohol consumption and CD4 T-cell count response among persons initiating antiretroviral therapy. J Acquir Immune Defic Syndr 2012;61(4):455–61. Epub 2012/09/08.
[31] Shivakoti R, Christian P, Yang WT, Gupte N, Mwelase N, Kanyama C, et al. Prevalence and risk factors of micronutrient deficiencies pre- and post-antiretroviral therapy (ART) among a diverse multicountry cohort of HIV-infected adults. Clin Nutr 2016;35(1):183–9. Epub 2015/02/24.
[32] Craig GM, Evans SJ, Brayshaw BJ. An inverse relationship between serum zinc and C-reactive protein levels in acutely ill elderly hospital patients. Postgrad Med 1990;66(782):1025–8. Epub 1990/12/01.
[33] WHO. Nutrient requirements for people living with HIV/AIDS: report of a technical consultation. Geneva: World Health Organization; 2003. p. 1–26.
[34] Nixon DE, Landay AL. Biomarkers of immune dysfunction in HIV. Curr Opin HIV AIDS 2010;5(6):498–503. Epub 2010/10/28.
[35] Kupka R, Msamanga GI, Spiegelman D, Morris S, Mugusi F, Hunter DJ, et al. Selenium status is associated with accelerated HIV disease progression among HIV-1-infected pregnant women in Tanzania. J Nutr 2004;134(10):2556–60. Epub 2004/10/07.
[36] Havers F, Smeaton L, Gupte N, Detrick B, Bollinger R, Hakim J, et al. 25-hydroxyvitamin D insufficiency and deficiency is associated with HIV disease progression and virological failure post-antiretroviral therapy initiation in diverse multinational settings. J Infect Dis 2014;210(2):244–53. Epub 2014/05/07.
[37] Aziz M, Livak B, Burke-Miller J, French AL, Glesby MJ, Sharma A, et al. Vitamin D insufficiency may impair CD4 recovery among Women's Interagency HIV Study participants with advanced disease on HAART. AIDS 2013;27(4):573–8. Epub 2012/10/26.
[38] Viard JP, Souberbielle JC, Kirk O, Reekie J, Knysz B, Losso M, et al. Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study. AIDS 2011;25(10):1305–15. Epub 2011/04/28.
[39] Ezeamama AE, Guwatudde D, Wang M, Bagenda D, Kyeyune R, Sudfeld C, et al. Vitamin-D deficiency impairs CD4+T-cell count recovery rate in HIV-positive adults on highly active antiretroviral therapy: a longitudinal study. Clin Nutr 2016;35(5):1110–7. Epub 2015/09/16.
[40] von Essen MR, Kongsbak M, Schjerling P, Olgaard K, Odum N, Geisler C. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. Nat Immunol 2010;11(4):344–9. Epub 2010/03/09.
[41] Kakalia S, Sochett EB, Stephens D, Assor E, Read SE, Bitnun A. Vitamin D supplementation and CD4 count in children infected with human immunodeficiency virus. J Pediatr 2011;159(6):951–7. Epub 2011/08/09.
[42] Coelho L, Cardoso SW, Luz PM, Hoffman RM, Mendonca L, Veloso VG, et al. Vitamin D3 supplementation in HIV infection: effectiveness and associations with antiretroviral therapy. Nutr J 2015;14:81. Epub 2015/08/19.
[43] Sandler NG, Sereti I. Can early therapy reduce inflammation? Curr Opin HIV AIDS 2014;9(1):72–9.
[44] Burbano X, Miguez-Burbano MJ, McCollister K, Zhang G, Rodriguez A, Ruiz P, et al. Impact of a selenium chemoprevention clinical trial on hospital admissions of HIV-infected participants. HIV Clin Trials 2002;3(6):483–91. Epub 2002/12/26.
[45] Hurwitz BE, Klaus JR, Llabre MM, Gonzalez A, Lawrence PJ, Maher KJ, et al. Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. Arch Intern Med 2007;167(2):148–54. Epub 2007/01/24.
[46] Baum MK, Campa A, Lai S, Sales Martinez S, Tsalaile L, Burns P, et al. Effect of micronutrient supplementation on disease progression in asymptomatic, antiretroviral-naive, HIV-infected adults in Botswana: a randomized clinical trial. JAMA: J Am Med Assoc 2013;310(20):2154–63. Epub 2013/11/28.
[47] Passaretti C, Gupta A. Selenium and HIV-1: hope or hype? Arch Intern Med 2007;167(22):2530–1. Epub 2007/12/12.
[48] Shivakoti R, Gupte N, Yang WT, Mwelase N, Kanyama C, Tang AM, et al. Pre-antiretroviral therapy serum selenium concentrations predict WHO stages 3, 4 or death but not virologic failure post-antiretroviral therapy. Nutrients 2014;6(11):5061–78. Epub 2014/11/18.
[49] Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006;12(12):1365–71. Epub 2006/11/23.
[50] Boulware DR, Hullsiek KH, Puronen CE, Rupert A, Baker JV, French MA, et al. Higher levels of CRP, D-dimer, IL-6, and hyaluronic acid before initiation of antiretroviral therapy (ART) are associated with increased risk of AIDS or death. J Infect Dis 2011;203(11):1637–46. Epub 2011/05/20.
[51] Ledwaba L, Tavel JA, Khabo P, Maja P, Qin J, Sangweni P, et al. Pre-ART levels of inflammation and coagulation markers are strong predictors of death in a South African cohort with advanced HIV disease. PLoS One 2012;7(3), e24243. Epub 2012/03/27.
[52] Balagopal A, Asmuth DM, Yang WT, Campbell TB, Gupte N, Smeaton L, et al. Pre-cART elevation of CRP and CD4+ T-cell immune activation associated with HIV clinical progression in a multinational case-cohort study. J Acquir Immune Defic Syndr 2015;70(2):163–71. Epub 2015/05/29.
[53] Rajasuriar R, Booth D, Solomon A, Chua K, Spelman T, Gouillou M, et al. Biological determinants of immune reconstitution in HIV-infected patients receiving antiretroviral therapy: the role of interleukin 7 and interleukin 7 receptor alpha and microbial translocation. J Infect Dis 2010;202(8):1254–64. Epub 2010/09/04.
[54] Longenecker CT, Jiang Y, Orringer CE, Gilkeson RC, Debanne S, Funderburg NT, et al. Soluble CD14 is independently associated with coronary calcification and extent of subclinical vascular disease in treated HIV infection. AIDS 2014;28(7):969–77. Epub 2014/04/03.
[55] Shivakoti R, Yang WT, Berendes S, Mwelase N, Kanyama C, Pillay S, et al. Persistently elevated C-reactive protein level in the first year of antiretroviral therapy, despite virologic suppression, is associated with HIV disease progression in resource-constrained settings. J Infect Dis 2016;213(7):1074–8. Epub 2015/12/02.