

Plasma inflammatory biomarkers predict CD4+ T-cell recovery and viral rebound in HIV-1 infected Africans on suppressive antiretroviral therapy

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Summary

In a prospective African cohort study of people living with HIV-1 on suppressive antiretroviral therapy plasma levels of sCD14 and CRP predicted subsequent poor CD4+ T-cell recovery, and plasma levels of CXCL10 and sCD163 predicted subsequent viral rebound.

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Abstract

This multi-country prospective study investigated whether persistent systemic inflammation, measured by eight plasma biomarkers, in HIV-1-infected Africans during suppressive antiretroviral therapy (ART) (viral load <50 copies/mL), was associated with CD4+ T-cell recovery and viral rebound (>1,000 copies/mL) during long-term treatment. On-ART sCD14 and CRP concentrations were inversely associated with subsequent CD4+ T-cell counts. Risk of viral rebound was increased for participants with higher on-ART CXCL10 concentrations, and reduced for those with a greater sCD163 decline during the first year of ART. Persistent systemic inflammation predicted CD4+ T-cell recovery and viral rebound, warranting further mechanistic research in relation to clinical outcomes.

Keywords

HIV-1, biomarkers, cytokines, immune activation, inflammation, sub-Saharan Africa, antiretroviral therapy

Introduction

The global scale-up of combination antiretroviral therapy (ART) has substantially improved life expectancy of people with HIV-1 (PLWH), including in sub-Saharan Africa [1]. By effectively suppressing viral replication, long-term ART allows immune reconstitution, although cohort data suggest that 30-60% have persistently incomplete CD4+ T-cell recovery of CD4+ (i.e. <500 cells/ μ L) [2,3].

PLWH, despite sustained ART-mediated viral suppression, remain at increased risk of non-AIDS complications, such as cardiovascular diseases, compared with the general population. These risks are greatest among those who initiate ART at advanced disease stage with low CD4+ T-cell counts and those who have incomplete CD4+ T-cell recovery [4].

Persistent underlying immune defects despite suppressive ART are thought to be the main drivers of suboptimal CD4+ T-cell recovery [5,6]. Studies in Western populations found that plasma markers of systemic immune activation and inflammation tend to predict non-AIDS complications more strongly than cellular markers of T-cell activation [7], and suggested that plasma markers of systemic inflammation after ART initiation are potentially more predictive of future non-AIDS complications than pretreatment levels [7,8]. Since interventions to reduce residual inflammation in PLWH have not been identified to date, further explorations are useful in the search for potential targets.

We previously reported that plasma biomarkers of monocyte/macrophage activation (sCD163, sCD14), inflammation (CXCL10, CRP) and microbial translocation (LBP) were persistently elevated during suppressive ART in a multi-country cohort of African adults with advanced HIV-1 [9]. With the hypothesis that those biomarkers were predictive of adverse long-term clinical outcomes, despite suppressive ART, we assessed CD4+ T-cell recovery and viral rebound during long-term ART in the same cohort.

Methods

Study design and population

Pan-African Studies to Evaluate Resistance Monitoring (PASER-M) is a multi-country cohort of PLWH receiving ART, as previously described [2,9]. All participants received local standard of care. For the present analysis, 398 participants from 8 study sites in Kenya, Nigeria, South Africa, Uganda and Zambia, were selected who had a plasma HIV viral load <50 copies/mL at 12 months after initiation of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line ART. The study protocol was approved by the research ethics committees at all collaborating sites. All participants provided written informed consent including for storing samples for future approved research.

Laboratory methods

As part of routine care, CD4+ T-cell counts were regularly measured in on-site laboratories using standard flow cytometry methods. Cryopreserved plasma samples were used for retrospective testing of: (i) annual HIV-RNA using NucliSens EasyQ v2.0 (bioMérieux, Marcy l'Etoile, France) or COBAS Ampliprep/COBAS Taqman (Roche, Pleasanton, CA, USA); (ii) 8 selected biomarkers pre-ART (D0) and 12 months after ART initiation (M12), i.e. soluble CD14 (sCD14) and CD163 (sCD163); C-reactive protein (CRP), C-X-C motif chemokine 10 (CXCL10), interleukin-6 (IL-6), chemokine (C-C motif) ligand 2 (CCL2), C-X-C chemokine ligand 9 (CXCL9) using Luminex® multiplex kits (R&D Systems, Minneapolis, USA) that were analyzed using a BioPlex 200 suspension array system and software (Bio-Rad Laboratories Inc., Hercules, CA, USA). Lipopolysaccharide-binding protein (LBP) was determined using the DuoSet enzyme-linked-immunosorbent assay (R&D Systems, Minneapolis, USA). Further details have been described elsewhere [9].

Statistical analysis

We performed a principal component analysis and pairwise correlation to explore correlations between the biomarkers. To estimate the association between the concentrations of each of the M12 biomarkers and the subsequent CD4+ T-cell slope, we fitted a multivariable linear mixed model, incorporating all available follow-up CD4+ T-cell counts, adjusting for age, sex, ART regimen, adherence (poor adherence defined as <95% pills taken), and viral rebound during follow-up. To incorporate patient-level variation in CD4+ T-cell count time trends, the time variable was incorporated in the random part of the model. A negative (vs positive) regression coefficient indicates that participants with a higher concentration of the M12 biomarker are more (vs less) likely to have impaired CD4+ T-cell recovery, than those with lower M12 biomarker concentration. We performed two additional analyses: 1) to eliminate the influence of viral rebound, we censored subjects with viral rebound at time of their latest undetectable viral load; 2) to facilitate comparisons in effect sizes between biomarkers with different dynamic ranges, we repeated the analysis using IQR-normalised biomarkers. To estimate the association between each of the M12 biomarkers and viral rebound (defined as a single HIV-RNA >1000 cps/mL) after initial viral suppression at M12, we used multivariable interval-censored survival analysis, adjusting for age, sex, ART regimen, adherence and pre-ART drug resistance. A hazard rate between 0 and 1 (vs >1) indicates that participants with a higher concentration of the respective M12 biomarker are less (vs more) likely to experience viral rebound than those with a lower M12 biomarker concentration. Participants were censored at the earliest occurrence of death, loss to follow-up, or completion of cohort follow-up. In an additional analysis, we repeated the above two analyses replacing the M12 biomarkers concentration with the concentration change (delta) between before initiating ART to 12 months on ART (D0-M12). We imputed values below the assay detection limits using multiple imputations. $P < 0.05$ was considered statistically significant. All tests were two-sided. All analyses were performed using STATA 12 (StataCorp LP, College Station, TX, USA).

Results

Participant characteristics at month 12 after ART initiation

Of 398 participants, 57.5% (n=229) were women, with a median age of 37 years (IQR 33-43), and country of origin was Kenya (n=92, 23.1%), Nigeria (n=57, 14.3%), South Africa (n=65, 16.3%), Uganda (n=121, 30.4%) and Zambia (n=63, 15.8%) (**Table S1**). All participants who were diagnosed with tuberculosis (n=50, 12.6%) and/or chronic hepatitis B (defined as HBsAg-seropositivity, n=29, 7.3%) at ART initiation had received anti-TB treatment and/or anti-HBV-active ART, respectively. From M12 onwards, we recorded 1,148 person years of follow-up. The overall median time of follow-up from D0 onwards was 60 months (IQR 24-72). From M12 onwards, 48 (12.1%) participants reported poor adherence.

Biomarker correlations

For each of the 8 biomarkers, the median concentrations decreased significantly from pre-ART to M12 levels (**Table S2**). Principal component analysis suggested clustering of CRP with LBP for their D0-M12 change, but not for any of the other biomarkers measured at M12 or their D0-M12 change (**Figure S1**). Although none of the M12 biomarkers were correlated, several pairs were moderately correlated for their D0-M12 change: IL6 and CRP (0.4502), CXCL10 and CXCL9 (0.4375), IL6 and LBP (0.4044), LBP and CRP (0.3858), and CXCL10 and CCL2 (0.3405) ($p < 0.001$ for all) (**Figure 2**).

CD4+ T-cell recovery

From a median CD4+ T-cell count at M12 of 291 cells/ μ L (IQR 216-395), there was a gradual linear rise to a median of 458 (IQR 340-602) cells/ μ L at month 72 of ART. The multivariable linear mixed model found that M12 levels of sCD14 (coefficient -83.37, 95%CI -163.48 to -3.26; $p=0.041$), and CRP (-28.49, 95%CI -45.95 to -11.03; $p=0.001$) were inversely associated with the slope of CD4+ T-cell counts during follow-up. We did not find any associations for M12 levels or for the D0-M12 change of any of the other biomarkers (**Figure 1A and Table S3**). The first additional analysis that censored patients with viral rebound corroborated the observed associations, and additionally found

an inverse association for M12 levels of CXCL10 (-48.73, 95%CI -97.01 to -0.46; $p=0.048$) (**Table S5**). The second additional analysis using IQR-normalised biomarkers is shown in **Table S6**.

Viral rebound

From M12 onwards, 47 (11.8%) participants experienced viral rebound, corresponding to an incidence rate of 40.9 (95%CI 30.8-54.5) per 1000 person-years. Genotypic resistance results were available for 33 of the 47 (70.2%) viremic samples, of which 21 (63.6%) harboured any drug resistance mutation, including 20 (60.6%) NNRTI-associated and 18 (54.5%) NRTI-associated. The risk of viral rebound was increased for participants with a higher M12 level of CXCL10 (aHR 1.85 per \log_{10} pg/mL unit increase, 95%CI 1.03-3.32; $p=0.040$) (**Figure 1B** and **Table S4**). The risk of viral rebound was reduced for participants with a greater D0-M12 decline of sCD163 (aHR 0.49 per \log_{10} ng/mL unit increase, 95%CI 0.26-0.94; $p=0.031$). We did not find any independent associations for the M12 levels or D0-M12 change of any of the other biomarkers (**Table S4**).

Discussion

This study of 398 African PLWH, who had achieved ART-mediated viral suppression during the first year of ART, identified several plasma cytokines and chemokines, indicative of persistent systemic immune activation and inflammation, with prognostic value in predicting long-term CD4+ T-cell and virological responses. First, individuals who had persistently elevated plasma levels of sCD14 or CRP, measured after one year of suppressive ART, were more likely to have diminished CD4+ T-cell restoration. Second, the risk of viral rebound was increased for participants who had higher levels of on-ART CXCL10, and reduced for participants who had a greater decline of sCD163 during the first year of ART.

Previous reports from Western populations support the hypothesis that monocyte and macrophage related inflammation has clinical consequences for PLWH. Increased plasma levels of sCD14 in PLWH during suppressive ART have been associated with unfavourable outcomes such as

diminished CD4+ T-cell restoration and death [5,7], and can potentially be attributed to various inflammatory stimuli, such as lipopolysaccharide (LPS), indicative of microbial translocation in the gut, which is considered a major driving force of mucosal CD4+ T-cell depletion during advanced HIV infection [10].

Activated inflammation, as measured by IL-6 and CRP, has been linked to AIDS and non-AIDS-associated morbidities [11], although the association between CRP and cardiovascular events has been found to be inconsistent in Western populations with HIV [12]. Further confirmation is required, including whether CRP could be used as an inexpensive tool to predict HIV-related inflammatory adverse outcomes in sub-Saharan Africa.

Elevated CXCL10 levels have been previously shown to be correlated with plasma HIV-RNA levels, predictive of HIV disease progression, and has been suggested as a potential practical monitoring tool to identify PLWH at risk of viral rebound in resource-limited settings [13].

Persistently elevated sCD163 in ART-treated PWLH have been reported in Western studies, especially if ART was started late, and have been associated with atherosclerosis [14]. The attenuated ART-mediated decrease in sCD163 plasma concentrations in some of our cohort participants could be attributed to several potential underlying mechanisms including residual low-level HIV replication, microbial translocation, and unmeasured co-infections such as cytomegalovirus or HCV [14,15].

The main study strengths were its longitudinal design with long-term follow-up and broad geographic coverage within Africa, and that models controlled for ongoing viral replication and poor adherence. We measured a broad panel of relevant immune biomarkers associated with unfavourable clinical outcomes in PLWH [9]. There are some study limitations. First, because of the observational nature of the study, the associations do not necessarily indicate causality. Whether the elevated biomarkers are a cause or consequence of chronic immune dysregulation, or confounded by some other related

immunologic pathway, remains to be elucidated. An important caveat is that direct comparisons between studies in Western and African populations are confounded by differences in pre-ART CD4+ T-cell count, age distribution, genetic factors, pathogen exposure, and lifestyle. Second, our study was not able to control for some factors believed to contribute to chronic inflammation in PLWH receiving ART, such as low-level HIV replication, viral coinfection, and lifestyle factors such as tobacco and alcohol use.

In conclusion, we established that African adults with advanced HIV-1 infection who had a signature of persistent systemic inflammation and monocyte/macrophage activation during suppressive ART were at risk of suboptimal long-term CD4+ T-cell recovery and viral rebound. Measuring levels of sCD14, sCD163, CXCL10 and/or CRP in PLWH with suppressed viremia on ART may be useful in predicting adverse clinical inflammatory outcomes. To improve the long-term prognosis of African PLWH, further research is needed to increase our understanding of inflammatory pathways and explore the potential for adjunctive therapeutic interventions targeting these pathways.

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Competing interests

PR through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co, and ViiV Healthcare; he has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, Merck & Co, and Teva pharmaceutical industries for which his institution has received remuneration, all unrelated to the current manuscript. TR received travel support from Merck and payment for lectures from Merck and Abbott, all unrelated to the current manuscript. RLH through his institution has received independent scientific grant support from Gilead Sciences, unrelated to the current manuscript.

All other authors declare that they have no conflict of interest.

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Meeting presentation

These data have been presented at the Conference on Retroviruses and Opportunistic infections, March 8-11, 2020, Boston, Massachusetts, Abstract number 222.

Authors' contributions

TFRW is the PASER principal investigator. CMK, MS, SA, KM, MdJ, TFRW and RLH established the cohort and supervised data collection. SK and HCS performed the laboratory testing, supervised by TMR and NK. SK and RLH conceived the immunology study. SK performed the statistical analyses, with advice from FWW and RLH. SK and RLH drafted the manuscript. All authors provided valuable input to interpretation of the data and critically reviewed the paper for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Figure 1 Association between plasma biomarkers measured after the first year of suppressive ART and (A) CD4+ T-cell recovery and (B) viral rebound during the subsequent 5 years of ART.

Panel **A** shows the results of two analyses: (1) biomarkers measured at 12 months after ART initiation (M12) (black), and (2) the change in biomarker concentrations between start of ART and M12 (grey). The figure shows a multivariable linear mixed model of each of the biomarkers (independent variable) and CD4 T-cell slope (dependent variable), adjusted for age, sex, ART regimen, viral rebound and adherence. Dots and error bars represent the regression coefficients, each with 95% confidence intervals. The regression coefficients express difference in mean CD4 cell count per 1 unit increase for each biomarker. Biomarkers are expressed as \log_{10} pg/mL (IL-6, CXCL10, CCL2, CXCL9), \log_{10} ng/mL (sCD14, sCD163, LBP) or \log_{10} mg/L (CRP).

Panel **B** shows the results of two analyses: (1) biomarkers measured at 12 months after ART initiation (M12) (black), and (2) the change in biomarker concentrations between start of ART and M12 (grey). The figure shows the interval censored survival analysis of each of the biomarkers (independent variable) and viral rebound (dependent variable), adjusted for age, sex, ART regimen, pre-treatment drug resistance and adherence. Dots and error bars represent the hazard ratios, each with 95% confidence intervals. Biomarkers are expressed as \log_{10} pg/mL (IL-6, CXCL10, CCL2, CXCL9), \log_{10} ng/mL (sCD14, sCD163, LBP) or \log_{10} mg/L (CRP).

Figure 2 Correlation matrix of plasma biomarkers concentrations measured at month 12 of ART (M12) and differences measured between pre-ART and month 12 of ART (D0-M12). We performed pairwise correlation on all \log_{10} transformed biomarkers. Values are expressed as correlation coefficients. Darker colors indicate stronger correlation, whereas lighter color indicate weaker correlation.

Figure 1

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Figure 2

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