Residual immune activation in Africans on antiretroviral therapy predicts CD4 T-cell recovery and viral rebound

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Background

- Residual systemic inflammation and immune activation during ART-induced viral suppression have been associated with poor clinical outcomes.
- There are limited data on the association between chronic immune activation during suppressive ART and clinical outcomes in sub-Saharan Africa.

Objectives

To explore associations between plasma biomarkers of immune activation and **(1)** CD4+ T-cell recovery, and **(2)** viral rebound

Methods

- 398 HIV-infected adults from Kenya, Nigeria, South Africa, Uganda and Zambia enrolled in the Pan-African Studies to Evaluate Resistance (PASER-M) cohort, were included
- Inclusion criteria:
  - –Initiation of first-line non-nucleoside-reverse-transcriptase-inhibitor-based ART
  - –Undetectable plasma HIV-RNA (<50 cps/mL) at 12 months after ART initiation
  - –Complete stored plasma sample set available at baseline and 12 months after ART initiation
- We measured 8 plasma biomarkers of monocyte activation (sCD14, sCD163), inflammation (CRP, IP-10/CXCL10, IL-6, MCP1/CCL2, MIG/CXCL9), and microbial translocation (LBP) using multiplex and ELISA at baseline and 12 months after ART initiation.

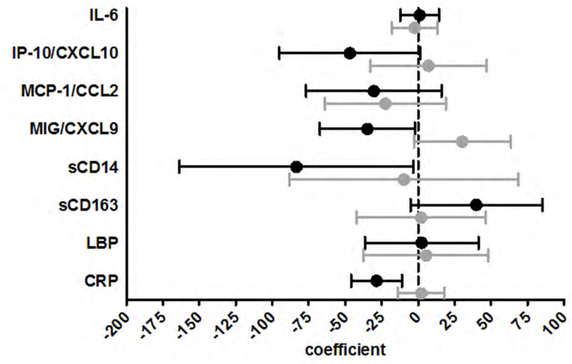
Statistical analysis

1) To estimate the association between the levels of each of the M12 or the D0-M12 (delta) biomarkers and subsequent CD4+ T-cell recovery, we fit a multivariable linear mixed model, incorporating all available follow-up CD4 cell count measurements. To incorporate patient-level variation in CD4 cell count time trends, the time variable was incorporated in the random part of the model.
2) To estimate the association between each of the M12 or the D0-M12 (delta) and biomarkers and the outcome virological rebound (defined as a single HIV-RNA>1000 cps/mL), we used multivariable interval-censored survival analysis.

M-PACT MARKERS OF PERSISTENT IMMUNE ACTIVATION DURING ANTIRETROVIRAL THERAPY IN AFRICA

PASER PAN-AFRICAN STUDIES TO EVALUATE RESISTANCE

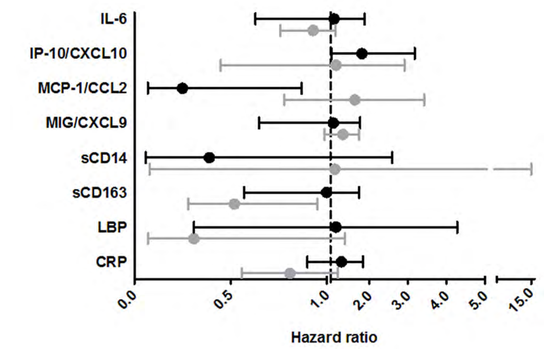
(1) Immune activation markers predict CD4+ T-cell recovery



- From a median CD4+ T-cell count at M12 of 291 cells/μL (IQR 216-395), there was a gradual linear rise up to a median of 458 (IQR 340-602) cells/μL at month 72 of ART.
- More likely to experience suboptimal CD4+ T-cell recovery: higher M12 levels of sCD14 (-83.38 95%CI -163.49 to -3.27, p=0.041), IP-10/CXCL10 (-46.79 95%CI -95.05 to 1.47, p=0.057), MIG/CLCX9 (-34.78 95%CI -67.27 to -2.29, p=0.036), CRP (-28.49, 95%CI -45.95 to -11.04; p=0.001).
- Less likely to experience suboptimal immune recovery: higher M12 levels of sCD163 (39.94 95%CI -5.34 to 85.23, p=0.084) or those with a greater D0-M12 decline of MIG/CXCL9 (30.36 95%CI -2.79 - 63.51, p=0.073).

Figure 1 Associations between immune activation markers during suppressive ART and CD4+ T-cell recovery. The figure shows the results of two analyses: (1) biomarkers measured at 12 months after ART initiation (M12) (black), and (2) the change in biomarker levels between start of ART (D0) and M12 (grey). The figure shows the regression coefficient with 95% CI of a multivariable linear mixed model for each of the markers (independent variables) and CD4 T-cell slope (dependent variable), adjusted for age, sex, ART regimen and virological rebound.

(2) Immune activation markers predict viral rebound



- From M12 onwards, we recorded 1148.0 person years of follow-up time, with 47 participants experiencing virological rebound, corresponding to an incidence rate of 40.9 (95%CI 30.8-54.5) per 1000 person-years.
- Increased risk of viral rebound: higher M12 levels of IP-10/CXCL10 (1.81 95%CI 1.03 to 3.18, p=0.038), and greater D0-M12 decline of MIG/CXCL9 (1.32 95%CI 0.99 to 1.74, p=0.056).
- Reduced risk of viral rebound: higher M12 levels of MCP-1/CCL2 (0.25 95%CI 0.07 to 0.87, p=0.030), and greater D0-M12 decline of sCD163 (0.52 95%CI 0.28 to 0.95, p=0.035).

Figure 2 Associations between immune activation markers and viral rebound. The figure shows the results of analyses: (1) biomarkers measured at 12 months after ART initiation (M12) (black), and (2) the change in biomarker levels between start of ART (D0) and M12 (grey). The figure shows ~~shows~~ the adjusted hazard ratio with 95% CI of the interval censored survival analysis of each of the biomarkers (independent variables) and viral rebound (dependent variable), adjusted for age, sex, ART regimen, and pre-treatment drug resistance.

Conclusion

- This study in African adults with advanced HIV infection highlights the negative effect of persistent systemic inflammation and immune activation during suppressive ART on long-term CD4 T-cell recovery and virological rebound.
- Measuring levels of sCD14, sCD163, IP-10/CXCL10, MIG/CXCL9, and/or CRP during suppressive ART could have prognostic value for HIV-infected patients receiving ART in predicting adverse outcomes.
- Further research needs to explore the potential for adjunct therapies targeting relevant inflammatory pathways.

Patient characteristics

Total N	**398 (100%)**
Sex	
Female	229 (58%)
Male	169 (42%)
Age	37 [33-43]
Country	
Kenya	92 (23%)
Nigeria	57 (14%)
South Africa	65 (16%)
Uganda	121 (30%)
Zambia	63 (16%)
CD4 cell count (cells/μL)	291 [216-395]
HIV viral load (cps/mL)	<50
Hemoglobin (g/dL)	12.8 [11.6-13.9]
BMI (kg/m²)	23.3 [21.0-26.6]
NNRTI	
Nevirapine	176 (44%)
Efavirenz	222 (56%)
NRTI	
Stavudine	69 (17%)
Zidovudine	157 (39%)
Tenofovir	161 (40%)
Abacavir	11 (3%)
HIV-1 subtype	
A	94 (24%)
C	131 (33%)
CRF02_AG	31 (8%)
D	92 (23%)
G	26 (7%)
Other	20 (5%)
Unspecified	4 (1%)

* Patient characteristics at 12 months of ART

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