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Heterogeneity of baseline immune activation and SARS-CoV-2 vaccine responses in people with HIV: a multicenter prospective study.

Short title: Baseline Inflammation and COVID-19 Responses

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Abstract

Objective: To determine whether baseline immune activation and inflammation contribute to heterogeneity in SARS-CoV-2 vaccine–induced immunity in antiretroviral therapy (ART)–treated people with HIV (PWH) compared to HIV-negative controls.

Methods: In this multicenter prospective study, 159 ART-treated PWH from two cohorts and 56 HIV-negative controls were enrolled. The two PWH cohorts differed in immunovirological control: one showed sustained viral suppression and $CD4^+$ T-cell recovery, the other persistent $CD4^+$ T-cell lymphopenia despite ART, sometimes with residual viremia. Baseline plasma levels of 20 cytokines, chemokines and soluble endothelial markers, were measured before SARS-CoV-2 mRNA vaccination. Post-vaccination anti-Spike IgG, neutralizing antibodies, and IFN-γ–producing T cells were quantified and correlated with baseline immune mediators.

Results: PWH had higher baseline levels of innate immune activation and endothelial inflammation markers than controls, particularly among immunological non-responders. Principal component analysis identified two inflammatory profile groups among PWH: one characterized by Th1/Th17-oriented cytokine profile, and the other with dominant monocyte activation and endothelial markers. Higher baseline inflammation in PWH was associated with reduced humoral vaccine responses and elevated ICAM-1 levels with decreased IFN-γ T-cell responses, irrespective of prior SARS-CoV-2 infection. In contrast, among HIV-negative participants with prior SARS-CoV-2 exposure, higher sCD14, IL-12p70, MCP-1, and E-selectin levels correlated with stronger humoral responses, whereas ICAM-1 was associated with increased IFN-γ T-cell responses.

Conclusion: Baseline inflammatory and endothelial profiles may constitute additional determinants of SARS-CoV-2 vaccine-induced immune responses in PWH. The opposite associations observed in controls highlight the context-dependent immunological effects of these pathways across chronic immune dysfunction and immunocompetent states.

Keywords: mRNA Vaccine, cytokines, HIV, COVID-19, inflammation, Immunogenicity, Vaccine.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has brought unprecedented attention to the determinants of effective vaccine-induced immunity, particularly in populations with compromised immune systems [1,2]. Although SARS-CoV-2 vaccination is highly effective in immunocompetent populations, infection and vaccine-induced immune responses in people with HIV (PWH) are characterized by substantial heterogeneity in both humoral and T-cell compartments, with variability in response magnitude, functionality, and persistence, even under long-term suppressive ART [3-6]. PWH receiving ART mostly restore their $CD4^+$ T cell counts, protecting them from developing AIDS-related complications [7]. However, they still experience HIV-related

immune activation and systemic inflammation, though with marked heterogeneity across individuals, increasing vulnerability to non-AIDS comorbidities such as cardiovascular disease [7-8]. Chronic immune activation and systemic inflammation in treated PWH have been associated with impaired immune function, including altered antigen-specific $CD4^+$ T-cell recall responses, reduced IFN-γ production, and features of T-cell exhaustion, as well as functional defects across both innate and adaptive immune compartments, despite durable viral suppression [9-11]. Among PWH with advanced disease or incomplete immune reconstitution, vaccine-induced immune responses may be quantitatively and qualitatively impaired, affecting both humoral and cellular compartments across multiple vaccine platforms [12-15]. In contrast, among virologically suppressed PWH, vaccine responsiveness appears more variable, with studies reporting heterogeneous immune outcomes that are not fully explained by $CD4^+$ T-cell counts alone [4-5,12-15]. Here, we sought to determine whether baseline immune activation and inflammatory profiles contribute to the heterogeneity in humoral and T-cell responses to SARS-CoV-2 vaccination in ART-treated PWH, compared with uninfected controls.

Methods

This prospective, observational study included ART-treated PWH recruited from two Belgian hospitals. Participants were enrolled at the University Hospital of Liège between August 2021 and February 2022 (HIV-L cohort) and at Saint-Pierre University Hospital in Brussels between April 2021 and June 2021 (HIV-B cohort) (Fig.1A). All participants were ≥18 with documented HIV infection and were receiving ART. In the HIV-L cohort, T-cell and humoral immune responses were evaluated before (T3) and after (T4) a third dose of an mRNA SARS-CoV-2 vaccine as previously described [4], whereas the HIV-B cohort only assessed humoral immune responses before the first (T0) and after the second (T2) vaccine dose (Suppl. Materials, p1, http://links.lww.com/QAD/D901). An HIV-negative control group of vaccinated healthcare workers (HCWs) was also included and assessed longitudinally across all vaccination timepoints. Demographic, clinical, and HIV-related characteristics were collected from medical records. Baseline plasma immune mediator profiling was performed prior to vaccination at T0 and T3 for the HIV-B and HIV-L cohorts (Suppl. Materials, p1, http://links.lww.com/QAD/D901). Statistical analyses included group comparisons, Spearman correlation analyses, multivariable linear regression, principal component analysis (PCA), and longitudinal models of vaccine-induced responses, with adjustment for cohort and prior SARS-CoV-2 infection when appropriate. The study was approved by the ethics committee, and all participants provided written informed consent (Suppl. Materials, p2, http://links.lww.com/QAD/D901).

Results

Participants characteristics

A total of 159 ART-treated PWH (77 in HIV-L and 82 in HIV-B) and 56 HIV-negative HCWs were included (Table S1, http://links.lww.com/QAD/D900). The mean age across both HIV cohorts was 46.5 ± 10.5 years, with no significant demographic differences between groups. However, regarding HIV, the cohorts had distinct HIV-related profiles. Despite similar time since diagnosis, the HIV-L participants had longer ART exposure (10.9 vs. 8.5 years; $p < 0.05$), a higher proportion of

undetectable HIV viral load (VL) (<50 copies/mL) (94.8% vs 77.8%; $p < 0.005$), whereas the HIV-B cohort showed markedly impaired immune reconstitution, with substantially lower median $CD4^+$ T-cell counts (245 cells/μL vs. 741 cells/μL; $p < 0.0001$). Hypertension was also more prevalent in HIV-L cohort. All HIV-B participants received BNT162b2 for the first two doses, while third-dose regimens in HIV-L included BNT162b2 (51.9%) or mRNA-1273 (48.1%). Compared with PWH, HCWs included more women and had lower BMI (Table S2, http://links.lww.com/QAD/D900).

Distinct baseline immune activation profiles

Baseline inflammatory profiles reflected these clinical differences (Fig. 1B-E, Table S3, http://links.lww.com/QAD/D900). Overall, PWH showed higher median levels of many plasma immune mediators (IL-17A, IFN-γ, and IL-12p70, TNF-α, E-selectin, ICAM-1, MIP-1β, MCP-1, IP-10, and P-selectin) than controls. The HIV-L cohort had significantly higher median levels of Th1/Th17 cytokines and related mediators, including IFN-γ, IL-12p70, IL-17A, IL-1β, IL-6, IL-4, IL-13, IFN-α, and GM-CSF, compared with HIV-B ($p < 0.0001$) (Fig.1B-E). By contrast, the HIV-B cohort exhibited higher levels of innate immune activation and endothelial inflammation markers, including TNF-α, sCD14, IL-8, E-selectin, P-selectin, ICAM-1, MIP-1β, MCP-1, and IP-10, than the HIV-L cohort ($p < 0.01$).

PCA identified two principal components (PCs) that explained 71.1% of the variance in immune mediators (PC1, 39.2%; PC2, 31.9%) (Figure S1A). PC1 was driven by biomarkers of innate immune activation, endothelial inflammation and chemotactic signaling (ICAM-1, E-selectin, P-selectin, IL-8, MIP-1α/β) and low levels of IL-1β, IL-6, GM-CSF and Th2-associated cytokines (IL-4, IL-13), whereas PC2 reflected Th1/Th17 cytokine variability (IFN-γ, IL-12p70, IL-17A, IL-1β). HIV-B participants mainly characterized PC1, which was linked to advanced HIV disease indicators such as a CD4 nadir below 200/μL and a recent CD4 count under 500/μL ($p<0.0001$), as well as detectable viremia (PVL ≥50 copies/mL; $p<0.05$). HIV-L participants primarily defined PC2, along with a subset of controls. This group's cytokine signature was notably higher in females ($p<0.005$) and decreased with longer ART exposure ($p<0.05$).

In linear regression, the last $CD4^+$ T-cell count emerged as the most consistent determinant of plasma mediator levels, with a $CD4^+$ T-cell count <500 cells/μL being significantly associated with lower plasma concentrations of IFN-γ, IL-12p70, IL-17A, IL-10, IL-13, IL-4, GM-CSF, IL-6, and IL-1β and with higher plasma levels of sCD14, TNF-α, IL-8, MCP-1, P-selectin, MIP-1α, MIP-1β, IP-10, ICAM-1, and E-selectin (Table S4, http://links.lww.com/QAD/D900). In addition, women were significantly associated with median plasma concentrations of ICAM-1, MIP-1β, MIP-1α, P-selectin, MCP-1, and TNF-α, and negatively associated with GM-CSF and IL-6. Longer time on ART and African ethnicity were independently associated with lower plasma MCP-1 concentrations, whereas IL-4 levels were negatively associated with African ethnicity only. Conversely, African ethnicity was positively associated with plasma MIP-1α concentrations. Importantly, although selected comorbidities were associated with isolated changes in specific cytokines (Suppl. Materials, p.2, http://links.lww.com/QAD/D901, Stable S5, http://links.lww.com/QAD/D900), no consistent relationship was identified between comorbidities and the immune activation profile. These findings suggest that the differential immune activation patterns observed across cohorts, including Th1/Th17-

associated and endothelial activation signatures, are unlikely to be primarily driven by differences in comorbidity burden.

Baseline immune activation and SARS-CoV-2 vaccine–induced immune responses

We then evaluated whether baseline inflammatory profiles were associated with subsequent immune responses, using linear regression (Table S6-S7, http://links.lww.com/QAD/D900). Among HIV-L participants, higher baseline IL-4 levels correlated with a weaker anti-spike IgG response after a third vaccine dose ($p = 0.016$). Conversely, higher baseline E-selectin levels were associated with a greater magnitude of the anti-Wuhan IgG response ($p = 0.0048$).

We next conducted within-group Spearman analyses. In HIV-L cohort, higher levels of monocyte and endothelial activation markers were consistently associated with weaker vaccine responses (Fig. 2, S2, http://links.lww.com/QAD/D900): baseline sCD14 correlated negatively with anti-Wuhan ($p < 0.05$) and anti-Omicron($p < 0.005$) neutralizing antibody (nAb) evolution, IL-4 and P-selectin with anti-spike IgG ($p < 0.05$), and ICAM-1 with IFN-γ production ($p < 0.05$) (Fig. 2). These inverse associations were similarly observed in SARS-CoV-2-naïve and -experienced HIV-L participants (Fig.2-S2, http://links.lww.com/QAD/D900), including an inverse association between sCD14 and anti-Omicron nAbs ($p < 0.05$) and lower anti-spike IgG with higher IL-1β, IL-4, IL-6, GM-CSF, MCP-1, IFN-γ and IL-10 (all $p < 0.05$). In contrast, distinct patterns were observed in control participants, in whom higher baseline levels of sCD14, IL-12p70, MCP-1, and E-selectin were associated with higher humoral responses (Fig. S4, http://links.lww.com/QAD/D900), but these relationships were not observed in SARS-CoV-2–naïve controls (Fig. S3-S4, http://links.lww.com/QAD/D900). Correlations in HIV-B were more heterogeneous (Fig. S5), with higher baseline MIP-1β and MCP-1 each associated with stronger anti-spike IgG responses (both $p < 0.05$), whereas higher baseline E-selectin was associated with weaker anti-spike IgG ($p < 0.05$).

Discussion

Early during the COVID-19 pandemic, concern regarding SARS-CoV-2 vaccine responses in PWH primarily focused on individuals with untreated infection or incomplete immune reconstitution despite virologically suppressive ART, who were considered at highest risk of impaired immunogenicity. However, even under suppressive ART, PWH remain characterized by persistent immune activation and residual inflammation, as reflected by sustained elevations in circulating inflammatory, chemotactic and endothelial-associated mediators [16]. Yet, beyond these extremes, whether baseline inflammatory and immune activation states contribute to the heterogeneity of vaccine-induced responses remains poorly explored.

In this study, we identified distinct baseline immune activation profiles across two HIV cohorts that differed in the degree of immune reconstitution achieved under ART. Individuals with sustained $CD4^+$ T-cell reconstitution (HIV-L cohort) exhibited a cytokine milieu enriched for Th1/Th17-associated markers, including IL-12p70, IFN-γ and IL-17A, whereas immunological non-responders (HIV-B cohort) displayed a dominant innate and endothelial inflammatory signature characterized by elevated TNF-α, sCD14, IL-8, adhesion molecules (ICAM-1, E-selectin, P-selectin) and chemokines involved

in leukocyte recruitment (MCP-1, MIP-1β, IP-10). These observations are consistent with recent data showing that ART only partially restores monocyte function, as early treatment initiation may transiently preserve monocyte antiviral function and IL-12p70 production, whereas prolonged treated HIV infection remains associated with persistent alterations in monocyte inflammatory programming despite virological suppression [17,18]. Nevertheless, the relative enrichment in IL-12p70, IFN-γ- and IL-17A-associated mediators observed in the HIV-L cohort suggests that earlier ART initiation and sustained $CD4^+$ T-cell reconstitution may be associated with partial preservation of Th1/Th17-associated immune function despite residual immune activation [19-26]. In parallel, the increased expression of E-selectin, P-selectin and ICAM-1 in the HIV-B cohort supports persistent endothelial activation, a recognized feature of chronic treated HIV infection. Experimental studies have shown that inflammatory cytokines, microbial translocation-derived products such as LPS, and HIV proteins, including Tat and gp120, can directly induce endothelial activation, oxidative stress and adhesion molecule expression, while clinical studies in ART-treated PWH demonstrate correlations between monocyte activation markers such as sCD14/sCD163 and endothelial activation markers including ICAM-1 and VCAM-1 [27-30].

These baseline immune activation profiles were associated with subsequent vaccine-induced immunity [31]. Higher baseline markers of monocyte and endothelial activation were associated with weaker humoral and T-cell responses following vaccination, even among individuals with normal $CD4^+$ T-cell counts (HIV-L cohort). This observation is consistent with previous studies linking persistent inflammation and innate immune activation to reduced recall T-cell responses to prior vaccine antigens, while pre-vaccine inflammatory markers such as sCD14, IL-6, IP-10 and sCD163 negatively predict antibody responses to hepatitis A/B virus and tetanus vaccination [31–34]. Persistent activation of the innate immune compartment may impair antigen-presenting cell function, reduce dendritic-cell maturation, alter T follicular helper-cell differentiation and disrupt germinal center, thereby limiting effective B-cell priming, affinity maturation and the generation of durable plasma-cell and memory B-cell responses [31-33]. In parallel, endothelial activation may also contribute to impaired cellular immunity, as elevated baseline ICAM-1 levels likely reflected chronic endothelial inflammation, and excessively high ICAM-1 expression may impair coordinated T-cell responses through altered immune synapse dynamics, abnormal leukocyte trafficking, and reduced IFN-γ production. Previous studies have also shown that ICAM-1 is involved in long-lasting cognate T–B cell interactions required for the selection of low-affinity B-cell clones during T cell-dependent antibody responses, suggesting that dysregulated ICAM-1 expression could additionally contribute to suboptimal adaptive immune responses [35-42]. Collectively, these data indicate that residual immune and endothelial inflammation may represent an additional and previously underappreciated determinant of vaccine responsiveness in PWH, even in the context of long-term ART.

The opposite associations observed between baseline inflammatory markers and vaccine-induced immunity in controls versus PWH highlight the context-dependent nature of innate and endothelial immune activation. Higher baseline ICAM-1 levels were associated with enhanced IFN-γ responses in controls, whereas the opposite association was observed in PWH. At steady state, ICAM-1 is minimally expressed on endothelial and immune cells, where it stabilizes antigen-presenting cell interactions and facilitates TCR engagement, thereby promoting effector T-cell function [31-36]. ICAM-1 also sustains T–B cell interactions in secondary lymphoid tissues, influencing B-cell selection

and differentiation [35-42]. In chronic infection, however, persistent ICAM-1 signaling might instead disrupt immune synapses via excessive LFA-1 engagement, prompting premature effector T-cell contraction and fostering exhausted memory T cells [31, 38]. Thus, in healthy controls, moderate endothelial activation may facilitate leukocyte trafficking and antigen presentation, whereas in PWH, persistently elevated ICAM-1 could instead represent chronic immune dysregulation. Further studies are needed to validate these findings in independent cohorts and to delineate how ICAM-1 regulation influences vaccine-induced immune responses in HIV infection.

Consistent with this interpretation, prior SARS-CoV-2 infection differentially modulated the relationship between baseline inflammation and vaccine-induced immunity in controls and PWH. In controls, positive associations between inflammatory markers and post-vaccination responses were observed only in previously infected individuals, suggesting effective immune priming and cumulative antigenic exposure. In contrast, inflammation in PWH remained negatively associated with vaccine-induced responses regardless of prior infection, supporting the notion that chronic inflammation in treated HIV primarily reflects persistent immune dysregulation rather than functional immunological memory. Impaired germinal center activity, dysfunctional T follicular helper-cell responses and chronic inflammation-driven T-cell exhaustion may collectively contribute to reduced immune responsiveness upon antigen re-exposure in PWH [43-47].

Several limitations should be acknowledged, including the limited cohort size, the single pre-vaccination inflammatory assessment, and the exploratory nature of the correlation analyses, which were not adjusted for multiple testing. In addition, differences in vaccination schedules and number of doses between cohorts may have influenced baseline inflammatory states and subsequent vaccine responses, although no significant effect of vaccine dose number on baseline immune parameters was observed in the control cohort.

Overall, these findings move beyond the established association between vaccine responsiveness and $CD4^+$ T-cell reconstitution, and identify persistent innate and endothelial activation as a potential additional determinant of vaccine-induced immunity in treated PWH. Whereas inflammatory signals in immunocompetent individuals may reflect effective immune priming capacity, in PWH, similar pathways may instead indicate persistent immune dysregulation despite suppressive ART. Collectively, these observations highlight the importance of the baseline inflammatory milieu in shaping vaccine responsiveness in PWH and support further investigation of residual endothelial and innate immune activation as potential contributors to the heterogeneity of vaccine-induced immunity [48].

Contributions

Majdouline El Moussaoui: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. Nathalie Maes: statistical analysis, Writing – review & editing. Aurélie Ladang: Formal analysis, Writing – review & editing; Etienen Cavalier: Formal analysis, Writing – review & editing. Francesco G. Genderini: Investigation, Funding acquisition, Writing – review & editing. Hafid Dahma: Fornal analysis, Investigation, Funding acquisition, Writing – review & editing. Charlotte Martin: Conceptualization – review & editing. Nicolas Dauby:

Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. Gilles Darcis: Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Conflicts of interest

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Figure 1. (A) Study design and sampling timeline across cohorts. ART-treated people with HIV (PWH) from two cohorts (HIV-L, n = 77; HIV-B, n = 82) and HIV-negative controls (n = 56) were included. Baseline immune mediator profiling was performed prior to vaccination at T0 (HIV-B and controls) and T3 (HIV-L and controls). The HIV-B cohort was evaluated before (T0) and after (T2) a two-dose mRNA vaccine regimen, whereas the HIV-L cohort was assessed before (T3) and after (T4) a third (booster) dose. HIV-negative controls were assessed longitudinally across all vaccination timepoints. **(B–D)** Baseline plasma immune mediator concentrations are expressed as Z-scores. Violin plots show distributions across cohorts for **(B)** adaptive (Th1/Th17) cytokines, **(C)** endothelial activation and adhesion markers, and **(D)** myeloid-inflammatory mediators. Dots indicate medians, with interquartile ranges (Q1–Q3). **(E)** Heatmap showing median Z-scores of immune mediators across cohorts. Statistical significance is indicated as * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

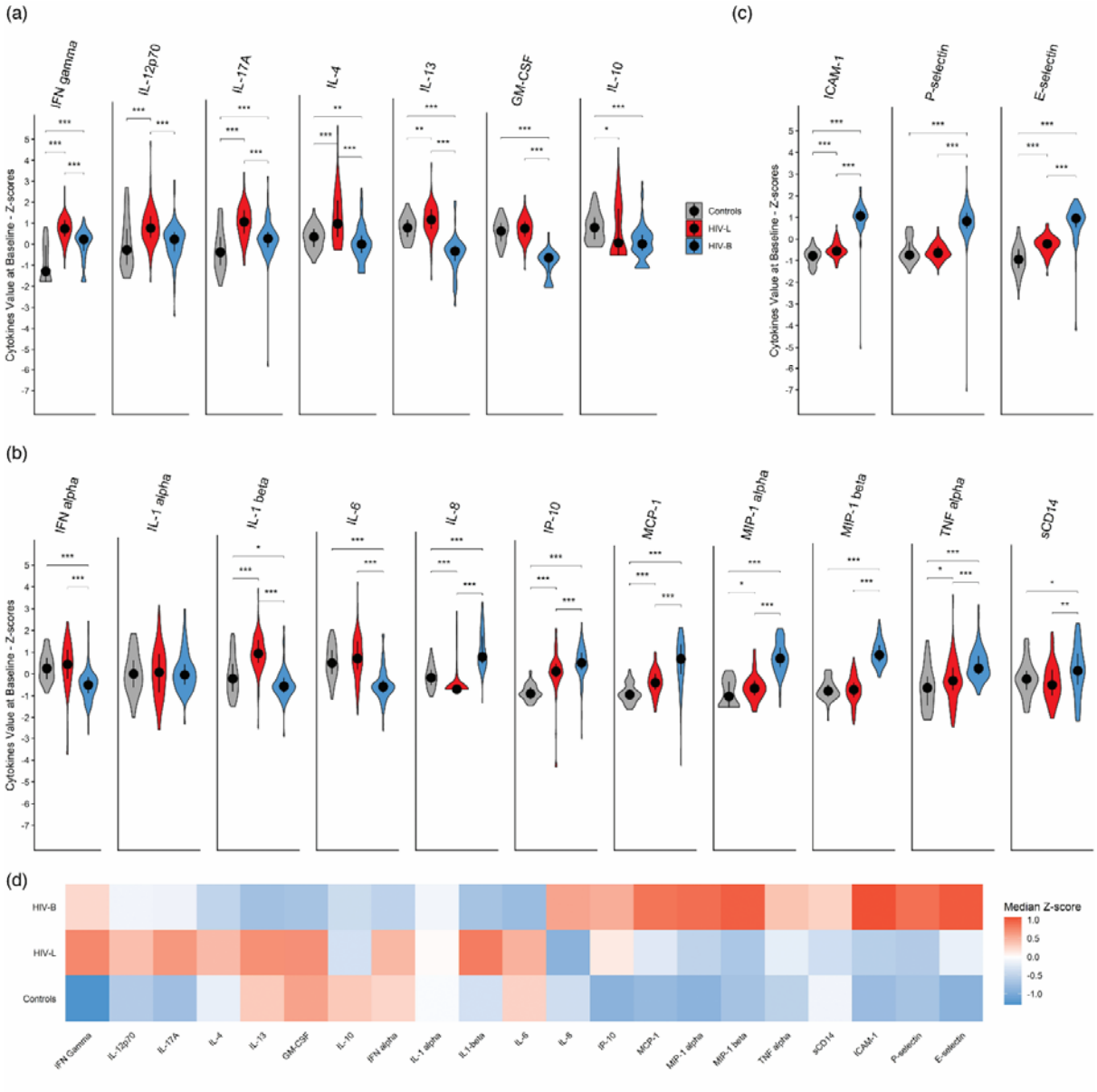
(a)
IFN gamma
IL-12p70
IL-17A
IL-4
IL-13
GM-CSF
IL-10
Cytokines Value at Baseline - Z-scores
Controls
HIV-L
HIV-B
(c)
ICAM-1
P-selectin
E-selectin
Cytokines Value at Baseline - Z-scores
(b)
IFN alpha
IL-1 alpha
IL-1 beta
IL-6
IL-8
IP-10
MCP-1
MIP-1 alpha
MIP-1 beta
TNF alpha
sCD14
Cytokines Value at Baseline - Z-scores
(d)
HIV-B
HIV-L
Controls
IFN Gamma
IL-12p70
IL-17A
IL-4
IL-13
GM-CSF
IL-10
IFN alpha
IL-1 alpha
IL-1 beta
IL-6
IL-8
IP-10
MCP-1
MIP-1 alpha
MIP-1 beta
TNF alpha
sCD14
ICAM-1
P-selectin
E-selectin
Median Z-score
1.0
0.5
0.0
-0.5
-1.0

Figure 2. Baseline immune activation and SARS-CoV-2 vaccine-induced immune response evolution in HIV-L individuals. Spearman correlations were computed between baseline circulating immune activation markers (T3) and changes in SARS-CoV-2–specific immune responses following the third vaccine dose (ΔT4–T3). Spearman correlation coefficients (ρ) are shown within each cell, with blue and red indicating positive and negative correlations, respectively. Statistical significance is indicated as * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. P-values are not adjusted for multiple comparisons and should be interpreted as exploratory.