



## OPEN ACCESS

## EDITED BY

Sikhulile Moyo,  
Botswana Harvard AIDS Institute Partnership,  
Botswana

## REVIEWED BY

Robert L. Furler O'Brien,  
Feinstein Institute for Medical Research,  
United States  
Victor Riitho,  
University of Nairobi, Kenya

## \*CORRESPONDENCE

Peter Kojo Quashie  
✉ pquashie@ug.edu.gh

RECEIVED 24 November 2025

REVISED 02 January 2026

ACCEPTED 23 January 2026

PUBLISHED 10 February 2026

## CITATION

Appeaning M, Magomere E, Amoako NAY,  
Kouffie KE, Tapela K, Olwal CO,  
Amponsah JA, Nartey S, Baah-Danquah R,  
Frimpong ST, Quarshie ST, Efa-Quayson S,  
Broni F, Nenyewodey FE, Abugri J, Ansa GA,  
Bonney EY and Quashie PK (2026) JAK-STAT  
and IL-17 pathway dysregulation underlies  
persistent immune dysfunction in ART-  
experienced people living with HIV in Ghana.  
*Front. Immunol.* 17:1753475.  
doi: 10.3389/fimmu.2026.1753475

## COPYRIGHT

© 2026 Appeaning, Magomere, Amoako,  
Kouffie, Tapela, Olwal, Amponsah, Nartey,  
Baah-Danquah, Frimpong, Quarshie, Efa-  
Quayson, Broni, Nenyewodey, Abugri, Ansa,  
Bonney and Quashie. This is an open-access  
article distributed under the terms of the  
[Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/).  
The use, distribution or reproduction in other  
forums is permitted, provided the original  
author(s) and the copyright owner(s) are  
credited and that the original publication in  
this journal is cited, in accordance with  
accepted academic practice. No use,  
distribution or reproduction is permitted  
which does not comply with these terms.

# JAK-STAT and IL-17 pathway dysregulation underlies persistent immune dysfunction in ART-experienced people living with HIV in Ghana

Mark Appeaning<sup>1,2,3</sup>, Edwin Magomere<sup>1,2</sup>,  
Nana Ama Yeboaa Amoako<sup>1</sup>, Kirk Elorm Kouffie<sup>1</sup>,  
Kesego Tapela<sup>1</sup>, Charles Ochieng' Olwal<sup>1</sup>,  
Jones Amo Amponsah<sup>4</sup>, Stella Nartey<sup>4</sup>,  
Rosalynn Baah-Danquah<sup>5</sup>, Salome Tettey Frimpong<sup>6</sup>,  
Seyram Tetteh Quarshie<sup>7</sup>, Samuel Efa-Quayson<sup>8</sup>,  
Francis Broni<sup>9</sup>, Felix E. Nenyewodey<sup>9</sup>, James Abugri<sup>10</sup>,  
Gloria Akosua Ansa<sup>5</sup>, Evelyn Yayra Bonney<sup>1,4</sup>  
and Peter Kojo Quashie<sup>1,11\*</sup>

<sup>1</sup>West African Centre for Cell Biology of Infectious Pathogens (WACCBIP), College of Basic and Applied Sciences, University of Ghana, Accra, Ghana, <sup>2</sup>Department of Biochemistry Cell and Molecular Biology, School of Biological Sciences, College of Basic and Applied Sciences, University of Ghana, Accra, Ghana, <sup>3</sup>Department of Medical Laboratory Science, Faculty of Health and Allied Sciences, Koforidua Technical University, Koforidua, Ghana, <sup>4</sup>Noguchi Memorial Institute for Medical Research, University of Ghana, Accra, Ghana, <sup>5</sup>University of Ghana Health Services, Public Health Department, Accra, Ghana, <sup>6</sup>Fevers Unit, Greater Accra Regional Hospital, Accra, Ghana, <sup>7</sup>HIV Clinic, Ho Municipal Hospital, Ho, Ghana, <sup>8</sup>Upper East Regional Hospital, Bolgatanga, Ghana, <sup>9</sup>Biomedical Science Department, Navrongo Health Research Centre, Navrongo, Ghana, <sup>10</sup>Department of Biochemistry and Forensic Sciences, School of Chemical and Biochemical Sciences, C. K. Tedam University of Technology and Applied Sciences, Navrongo, Ghana, <sup>11</sup>The Francis Crick Institute, London, United Kingdom

**Introduction:** Chronic immune activation and inflammation are central to HIV pathogenesis and persist despite antiretroviral therapy (ART), contributing to non-AIDS comorbidities. The HIV epidemic in West Africa is distinct, marked by the coexistence of HIV-1, HIV-2 in circulation as well as recombinant forms, yet immune responses in this region remain under-investigated. This study examined how ART modulates cytokine and chemokine signaling in Ghanaian people living with HIV (PLWH), with emphasis on biomarkers of immune dysfunction and treatment response.

**Methods:** Plasma concentrations of 25 cytokines and chemokines were quantified using Luminex multiplex assays in 247 participants: ART-naïve (n=141), post-ART at 6-months (n=52) and 12-months (n=23), ART-experienced (n=74), and HIV-negative controls (n=32). Differentially expressed cytokines, cytokine network analysis, and pathway enrichment analyses, including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) were performed using R-anchored packages. Correlations between cytokine levels and viral load were also evaluated. Cox proportional hazards regression was applied to identify biomarker of HIV disease progression

and predictive modelling using Least Absolute Shrinkage and Selection Operator (LASSO) regression, Random Forest (RF), and Gradient Boosting Machine (GBM). **Results:** ART-naïve individuals exhibited elevated pro-inflammatory (IL-6, IL-12/IL-23p40, IL-2, IL-15, IL-2R), and chemotactic (MCP-1, IP-10, MIG) cytokines, alongside reduced IL-1 $\beta$  and IL-1Ra. ART significantly reduced inflammatory cytokines, but paradoxically increased RANTES and Eotaxin. IL-1Ra emerged as the central node in cytokine interaction networks, while IP-10 positively and RANTES negatively correlated with viral load. Lower IL-1 $\beta$  and IL-10 levels predicted virologic control, whereas elevated GM-CSF was linked to persistent viraemia. Machine learning modelling identified RANTES, IP-10, IL-12/IL-23p40, IL-7, and IL-2R as the strongest predictors of viral load. Pathway enrichment analysis revealed upregulation of chemokine-mediated signaling and eosinophil chemotaxis, but downregulation of leukocyte activation, IL-17, and JAK-STAT signaling.

**Conclusion:** ART attenuates systemic inflammation and partially restores immune balance in PLWH in Ghana, but recovery remains functionally dysregulated, with persistent chemotactic signaling and impaired mucosal and JAK-STAT-mediated immunity. IL-1 $\beta$ , IL-10, GM-CSF, RANTES, and IP-10 emerge as prognostic markers of disease progression and potential targets for adjunctive immunotherapies. These findings underscore the need for immune-modulatory strategies to optimize ART outcomes in West Africa.

#### KEYWORDS

antiretroviral therapy, cytokines and chemokines, HIV, IL-17, immune activation, JAK-STAT, West Africa, WHICH study

## Introduction

The human immunodeficiency virus (HIV) epidemic in West Africa is uniquely characterized by the co-circulation of different HIV-1 subtypes, circulating recombinant forms (CRFs) predominantly CRF02\_AG, unique recombinant forms (URFs) and HIV-2, and (1, 2). Unlike other regions where a single subtype dominates, this viral heterogeneity complicates treatment strategies and epidemiological tracking. HIV-2, in particular, remains endemic in West Africa, where it overlaps with a high burden of co-infections such as tuberculosis and an increasing prevalence of non-communicable diseases—factors that collectively influence treatment response and disease progression (3).

The global scale-up of ART has dramatically improved the prognosis of people living with HIV (PLWH), transforming it into a manageable chronic condition, particularly in high-income countries (HICs) (4). However, the benefits of ART are not equitably distributed (5). In low- and middle-income countries (LMICs), including many in Sub-Saharan Africa, HIV remains associated with high morbidity and mortality. One major contributor to this disparity is unequal access to newer, less toxic, and more effective ART regimens (5–7).

Despite widespread access to antiretroviral therapy (ART), treatment response remains variable. While many individuals achieve viral suppression, persistent immune activation and systemic inflammation are common and contribute to virologic non-suppression and non-AIDS-related comorbidities (8). In Ghana, unusually high rates of viral non-suppression 6–12 months post-ART initiation have been reported, in contrast to findings from DTG-anchored therapy in other regions outside West Africa (9). Interestingly, immune recovery occurred despite persistent viremia, suggesting distinct immune response dynamics and regional differences in treatment efficacy that warrant further investigation. Similar trends in viral non-suppression (VNS) have been documented across sub-Saharan Africa among adolescents and young adults in Tanzania and Kenya, and a recent meta-analysis estimated that two in every ten people living with HIV on ART experience VNS, posing a major challenge to achieving the UNAIDS third 95% target (10–12).

Cytokine and chemokine dysregulation play a central role in HIV pathogenesis. Pro-inflammatory mediators such as TNF- $\alpha$ , IL-1, IL-2, IL-6, IL-12, and GM-CSF enhance viral replication, whereas others, including TGF- $\beta$ , IL-4, IL-10, IL-13, and IFN- $\gamma$ , may suppress it (13). Yet, in West Africa and particularly in Ghana, the immunopathogenesis of HIV remains understudied.

Given the region's complex epidemiology, characterized by diverse viral subtypes, high co-infection burden, and socioeconomic disparities, immunological investigations are essential. Therefore, we examine how ART modulates immune responses in people living with HIV (PLWH) in Ghana, focusing on cytokine and chemokine dynamics. We employed machine learning, performed survival analysis, cytokine interaction networks, and pathway enrichment to identify key immune mediators linked to virologic control or persistent replication, providing mechanistic insights and potential biomarkers to understand ART outcomes in the region.

## Materials and methods

### Study design and participant

This work was conducted as part of the West African Centre for Cell Biology of Infectious Pathogens (WACCBIP) Long-term HIV Infection Cohort (WHICH Study) (9). A longitudinal design was employed for ART-naïve (M0) participants—PLWH who were yet to start ART and then followed up at six- and twelve-months post ART. In parallel, a cross-sectional design was used for ART-experienced participants (T\_E0) who had received ART for at least six months at enrolment. Recruitment was conducted between July 2022 and September 2024 at Greater Accra Regional Hospital, University of Ghana Hospital–Legon, Tema General Hospital, Ho Municipal Hospital, Upper East Regional Hospital (Bolgatanga), and War Memorial Hospital (Navrongo). Healthy controls (CON) were recruited from the International Maritime Hospital and the West African Centre for Cell Biology of Infectious Pathogens. In total, the study enrolled 32 healthy controls, 141 ART-naïve, 52 at six months, 23 at twelve months, and 74 ART-experienced.

### Sample collection, processing and HIV-1 viral load quantification

Venous blood (10 mL) was collected into BD Vacutainer® K2EDTA and SST™ tubes (BD Biosciences, UK). Plasma and serum were separated by centrifugation (2500 rpm for 10 minutes) and stored at  $-80^{\circ}\text{C}$ . Peripheral blood mononuclear cells (PBMCs) and red blood cells (RBCs) were also isolated and cryopreserved.

Plasma viral RNA was extracted using the Quick-RNA Viral Kit (Zymo Research, Cat. No. R1035) following the manufacturer's protocol. HIV-1 viral load was quantified using the Bosphore® HIV-1 Quantification Kit (Anatolia Geneworks, Cat. No. ABHIQ3) on the QuantStudio™ 5 Real-Time PCR System (Applied Biosystems). Viral load values, initially obtained in International Units/mL (IU/mL), were converted to copies/mL using a conversion factor of  $1 \text{ IU} = 0.7 \text{ copies/ml}$ , as specified by the manufacturer, this was to ensure comparability with the WHO International Standard for HIV RNA NAT assays (NBSIC code 97/650).

### Plasma cytokine and chemokine measurement

Plasma concentration of various cytokines and chemokines were evaluated using the Human Cytokine Magnetic 25-Plex Panel (Invitrogen, Thermo Fisher Scientific, USA). The cytokines assessed were granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon alpha (IFN- $\alpha$ ), interferon beta (IFN- $\beta$ ), interleukin-1 receptor antagonist (IL-1Ra), IL-1 beta (IL-1 $\beta$ ), IL-2, IL-2 receptor (IL-2R), IL-4, IL-5, IL-6, IL-8 (CXCL8), IL-10, IL-12/IL-23p40, IL-13, IL-15, IL-17A, and tumor necrosis factor alpha (TNF- $\alpha$ ). The chemokines were regulated on activation, normal T cell expressed and secreted (RANTES/CCL5), macrophage inflammatory protein-1 alpha (MIP-1 $\alpha$ /CCL3), Eotaxin (CCL11), macrophage inflammatory protein-1 beta (MIP-1 $\beta$ /CCL4), monocyte chemoattractant protein-1 (MCP-1/CCL2), monokine induced by gamma interferon (MIG/CXCL9) and interferon gamma-induced protein 10 (IP-10/CXCL10).

The assay was conducted following the manufacturer's instructions and as previously reported by Tapela et al. (14). Briefly, in a 96-well plate, 25  $\mu\text{L}$  of antibody-coated beads were added and washed. Then, 100  $\mu\text{L}$  of samples, standards, and blanks were added and incubated for 2 hours with shaking at 250 rpm on a MicroPlate Shaker (Thermo Scientific, Korea). Subsequently, 100  $\mu\text{L}$  of biotinylated detector antibody was added and incubated for 1 hour. Thereafter 100  $\mu\text{L}$  of streptavidin-RPE was added incubated for 30 minutes, wells were washed, and 150  $\mu\text{L}$  of wash buffer was added. The assay was read using a Luminex MAGPIX system (Luminex Corporation, Austin, TX, USA) and data analyzed using xPONENT™ software (v4.3.229), according to the manufacturer's protocol.

### Cytokines and chemokines as predictors of HIV progression

Cox proportional hazards regression was used to evaluate associations between cytokine levels and HIV progression at baseline, six months, and twelve months. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with the survival package in R and visualized with forest plots generated using the survminer package (15). Model significance was assessed with the log-rank test.

### Modelling cytokines and chemokines as predictors of viral load

To identify cytokine predictors of viral load, we applied three machine learning modelling approaches: Least Absolute Shrinkage and Selection Operator (LASSO) regression to select cytokines with strong linear associations, Random Forest (RF) to capture non-linear interactions and estimate variable importance based on percentage increase in mean squared error (%IncMSE) and Gradient Boosting Machine (GBM) to assess relative influence

across sequential decision trees (16, 17). Model performance was evaluated by comparing predicted versus observed log viral load on the test set. Variable importance plots identified top predictors. Partial dependence plots (PDPs) were used to visualize non-linear effects of the top 10 cytokines.

## Network and pathway analysis

Cytokine–protein interaction networks were constructed using the STRING database (STRINGdb) (18); <https://string-db.org/>, focusing on cytokines differentially expressed between ART-naïve and ART-experienced groups. To ensure high-confidence interactions, only experimentally validated and high-confidence STRING interactions (confidence score > 0.7) were used.

Network structure was analyzed by computing key centrality measures, including degree centrality and betweenness centrality, to identify highly interconnected and functionally influential cytokines. The network was visualized using the *igraph* package in R (19). Functional enrichment was performed with *clusterProfiler* (20), using Gene Ontology (GO) (biological process, molecular function, cellular component) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases (21, 22). Gene names were retrieved from UniProt (23), and terms with false discovery rate (FDR) < 0.05 were considered significant.

## Data processing and statistical analysis

Cytokines and chemokines were categorized into three functional groups based on their established roles in HIV pathogenesis. Pro-inflammatory cytokines were IL-1 $\beta$ , IL-5, IL-6, TNF- $\alpha$ , IL-12/IL-23p40, GM-CSF, IFN- $\gamma$ , IFN- $\alpha$ , IL-2, IL-7, IL-15, IL-2R, and IL-17. Anti-inflammatory; IL-10, IL-1Ra, IL-4 and IL-13. Chemokines were MIP-1 $\alpha$  (CCL3), MIP-1 $\beta$  (CCL4), RANTES, Eotaxin, MCP-1, IL-8, MIG, and IP-10 (24–26). Raw data was processed in Microsoft Excel and analyzed using GraphPad prism software Inc version 8 (GraphPad Software, San Diego, CA, USA) and open resource packages anchored in R software version 4.1.0 (R Development Core Team, Vienna, Austria, and R studio Version 2024.12.0.467). Cytokine and chemokine concentrations were expressed as Net Median Fluorescence Intensity (net MFI). Viral load, cytokine, and chemokine data were log<sub>10</sub>-transformed. Group comparisons were made using the Kruskal–Wallis test with Dunn's *post hoc* test. Spearman's correlations assessed associations between cytokines and viral load. Significance was set at  $p < 0.05$ .

## Results

### Participant characteristics and HIV-1 viral load dynamics

HIV-1 viral load remained high and unsuppressed among ART-naïve their longitudinal follow-up pairs (Table 1). In contrast, viral

suppression was observed in ART-experienced participants at the time of recruitment, the majority of whom had been on treatment for more than five years.

### Cytokine alterations in ART-naïve and ART-experienced participants

ART-naïve participants had significantly elevated levels of several pro-inflammatory cytokines, particularly IL-6 and IL-12/IL-23p40, whereas IL-1 $\beta$  was significantly reduced compared to the control group (Figure 1). Additionally, cytokines involved in T-cell homeostasis and activation, including IL-15, IL-2, IL-2R, and IL-7, were significantly higher in ART-naïve individuals than in uninfected controls (Figure 1). In contrast, levels of the anti-inflammatory cytokine IL-1Ra were significantly lower in ART-naïve individuals (Figure 2). Chemotactic cytokines such as MCP-1, IP-10, and MIG were also significantly elevated in ART-naïve individuals compared to controls (Figure 3).

Following ART initiation, cytokine and chemokine profiles shifted markedly. In ART-experienced individuals, there was a significant reduction in pro-inflammatory cytokines including GM-CSF, IL-12/IL-23p40, IL-6, IL-15, IL-17, and TNF- $\alpha$  compared to ART-naïve participants (Figure 1). Notably, anti-inflammatory cytokines IL-10 and IL-1Ra were also significantly reduced in ART-experienced individuals compared to ART-naïve (Figure 2). Among chemokines, Eotaxin and RANTES were significantly increased in ART-experienced whereas MCP-1, IL-8, MIG, and IP-10 were significantly decreased compared to ART-naïve (Figure 3).

### Cytokines and chemokines as biomarkers for HIV progression

A Cox proportional hazards regression was used to assess the predictive capacity of cytokines and chemokines for HIV disease progression among ART-naïve, six and twelve months follow up participants (Supplementary Figure 1). The model demonstrated strong predictive performance (AIC = 679.94, concordance index = 0.84) with a highly significant global log-rank  $p$ -value ( $p = 7.07 \times 10^{-5}$ ). Notably, lower levels of IL-1 $\beta$  (HR = 0.111, 95% CI: 0.0231–0.54,  $p = 0.006$ ) and IL-10 (HR = 0.176, 95% CI: 0.0551–0.56,  $p = 0.003$ ) were significantly associated with a higher likelihood of achieving virologic control. In contrast, elevated levels of GM-CSF (HR = 2.992, 95% CI: 1.118–8.01,  $p = 0.029$ ) were associated with uncontrolled viraemia.

### Modelling cytokines and chemokines as predictors of viral load

To evaluate cytokine predictors of HIV viral load, we applied LASSO regression, Random Forest (RF), and Gradient Boosting Machine (GBM) models. All three models demonstrated moderate

TABLE 1 Participant characteristics and HIV-1 viral load dynamics.

Participant/ Sample Description	Age median (IQR)	Log <sub>10</sub> viral load median (IQR)	Mean treatment duration
Control (n=32)	27 (23.4 - 31.8)	NA	NA
ART-Naïve/M0 (n= 141)	35(29 - 43)	5.2(4.7 - 5.7)	0
M06 (n=52)		4.6(3.3 - 4.9)	6 months
M12 (n=23)		3.9 (3.4 - 4.8)	12 months
ART-Experienced (n=74)	42 (35 - 51.5)	2.8 (2.5 - 3.0)	> 5 years

NA, not applicable; IQR, Interquartile range; M06, six-month follow up; M12, twelve-month follow up.

predictive performance, with predicted versus observed log viral load showing good calibration (Supplementary Figure 2). RANTES and IP-10 were the strongest predictors, followed by IL-12/IL-23p40, Eotaxin, and IL-7 (Figure 4). Partial dependence analyses

further highlighted non-linear cytokine–viral load relationships. RANTES exhibited an inverse association with viral load, while IP-10 and IL-12/IL-23p40 displayed positive effects, and Eotaxin and IL-7 showed threshold-dependent influences (Supplementary Figure 3).

### Cytokine and chemokine network in HIV pathogenesis

The cytokine interaction network in HIV pathogenesis revealed a complex web of interactions between key pro-inflammatory and immunoregulatory cytokines (Figure 5). IL-1Ra emerged as a central regulatory node, exhibiting the highest betweenness centrality. Other highly connected cytokines included TNF-α, IL-6, IL-17, and IL-10. Chemokines such as RANTES, MIG, and IP-10 formed strongly interconnected nodes, with Eotaxin also showing notable centrality. IFN-γ, IL-2, IL-7, GM-CSF, IL-1β, and MIP-1α were also integrated into the network (Figure 5).

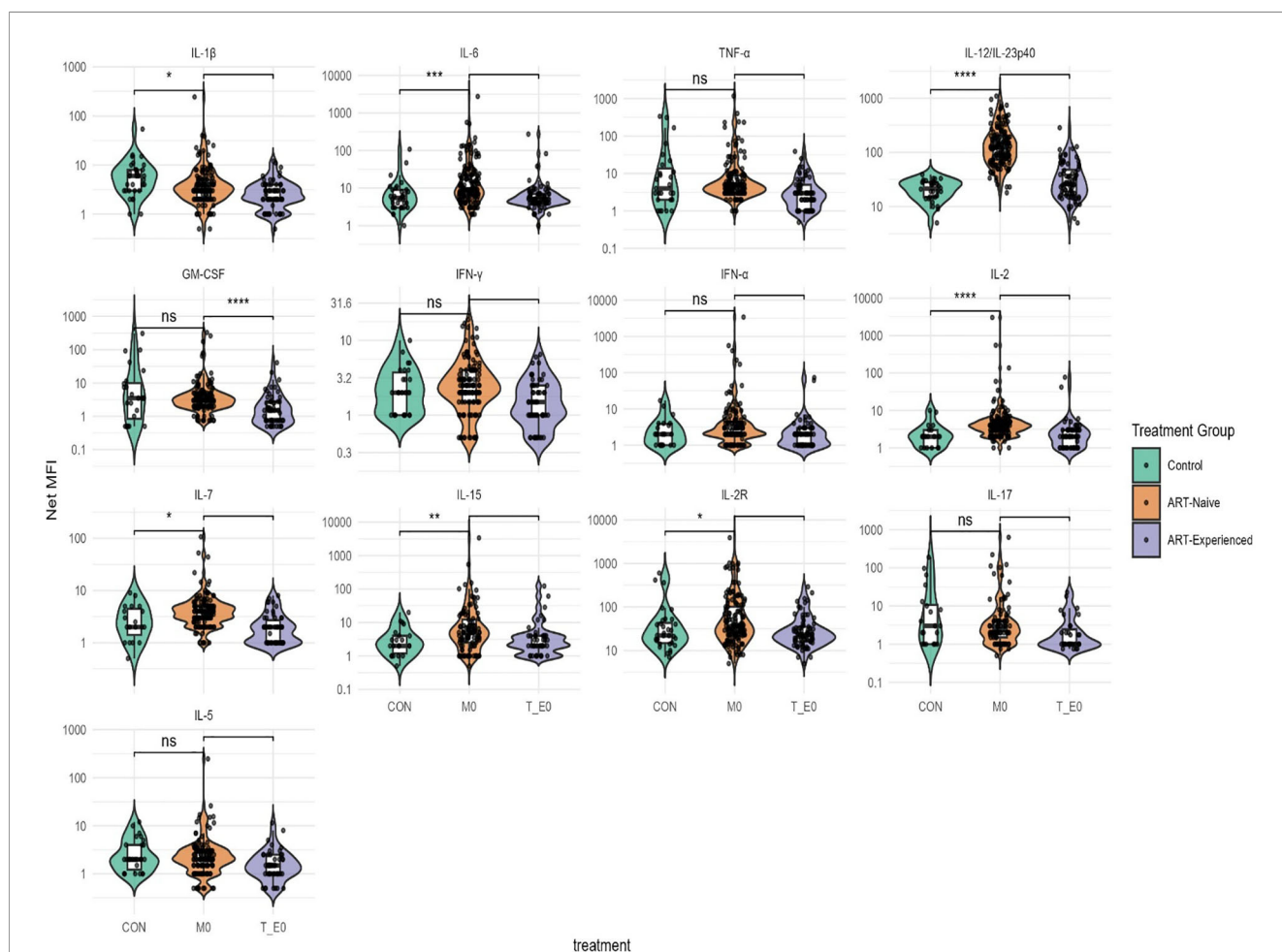
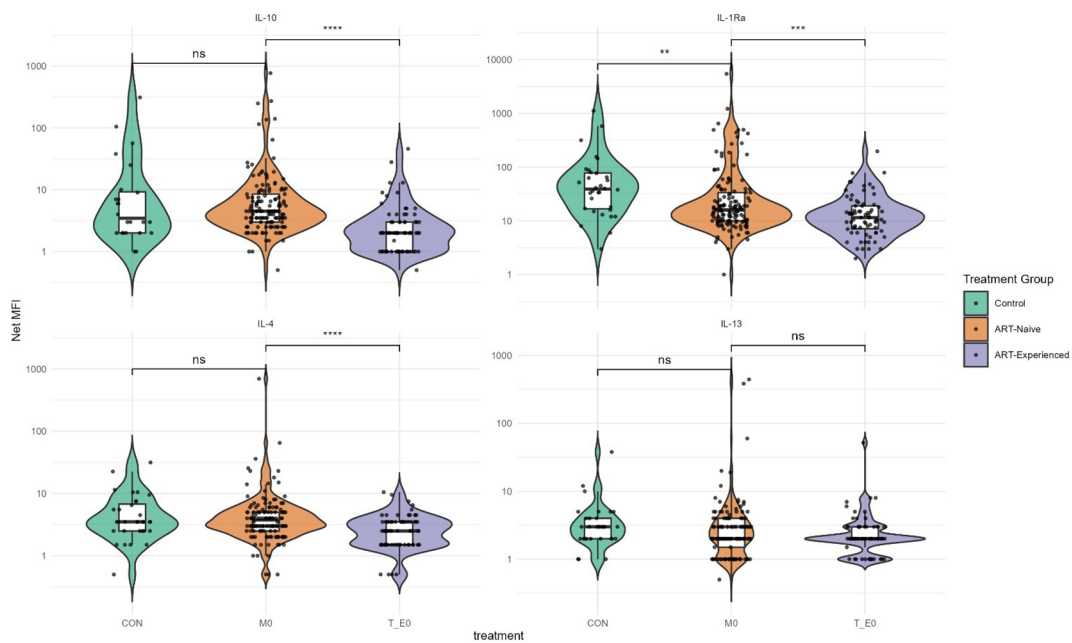
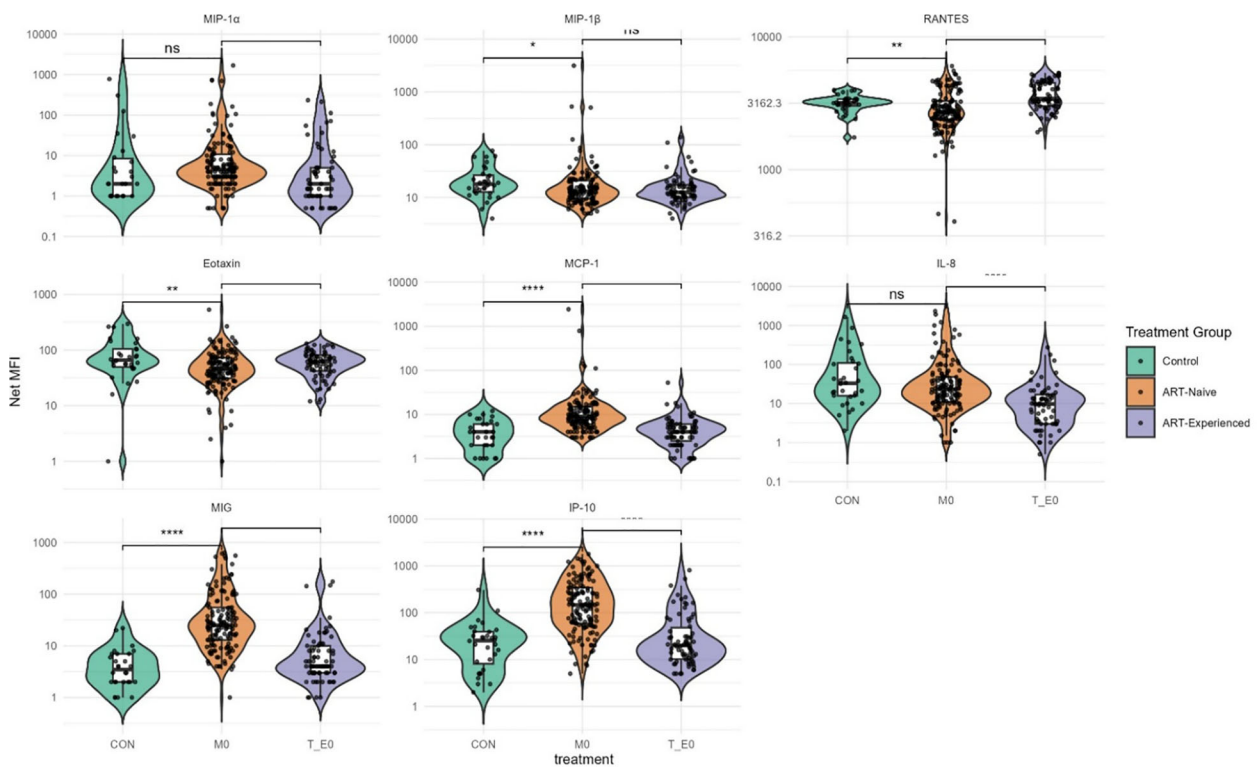


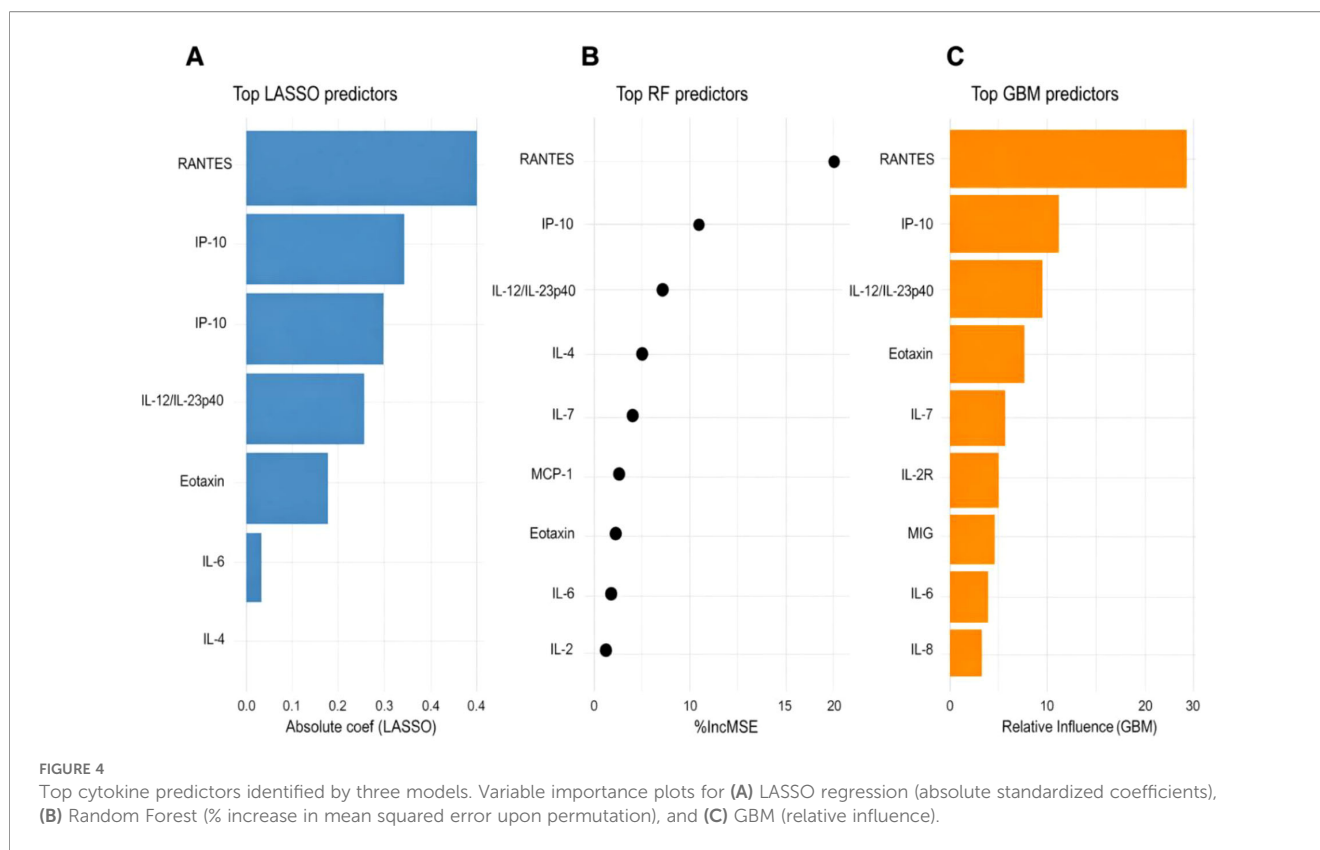
FIGURE 1 Pro-inflammatory cytokine levels in ART-naïve, ART-experienced, and control. Cytokine concentrations were measured by multiplex immunoassay and are expressed as Net MFI (log scale). The median is shown by the horizontal line within each box, while the lower and upper bounds represent the 25th and 75th percentiles, respectively. Violin plots illustrate the overall distribution of values within each group. Statistical comparisons were performed using Kruskal–Wallis test with Dunn’s *post hoc* correction. Significance thresholds are denoted as follows: \*\*\*\**p* < 0.0001; \*\*\**p* < 0.001; \*\**p* < 0.01; \**p* < 0.05; ns, not significant.



**FIGURE 2**  
Anti-inflammatory cytokine levels in ART-naïve, ART-experienced, and control. Concentrations of IL-10, IL-1Ra (interleukin-1 receptor antagonist), IL-4, and IL-13 were measured by multiplex immunoassay and expressed as Net MFI (log scale). The median is shown by the horizontal line within each box, with the lower and upper bounds representing the 25th and 75th percentiles, respectively. Violin plots illustrate the overall distribution of values within each group. Statistical comparisons were performed using Kruskal–Wallis test with Dunn’s *post hoc* correction, with significance thresholds indicated as follows: \*\*\*\* $p < 0.0001$ ; \*\*\* $p < 0.001$ ; \*\* $p < 0.01$ ; \* $p < 0.05$ ; ns, not significant.



**FIGURE 3**  
Chemokine levels in ART-naïve, ART-experienced, and control individuals. Violin plots show distributions of MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, Eotaxin, MCP-1, IL-8, MIG, and IP-10 across study groups. Data are expressed as Net MFI (log scale). Horizontal lines represent medians with 25th and 75th percentiles. Statistical comparisons were performed using nonparametric tests, with significance thresholds denoted as \*\*\*\* $p < 0.0001$ ; \*\*\* $p < 0.001$ ; \*\* $p < 0.01$ ; \* $p < 0.05$ ; ns, not significant.



## IP-10 and RANTES correlate with viral load

Spearman correlation analysis identified IP-10 as the strongest positive correlate of viral load, while RANTES showed a significant negative correlation ( $\rho \approx -0.45$ ) (Figure 6). Additional positive correlations with viral load were observed for IL-12/IL-23p40, MIG, MCP-1, IL-6, IL-2R, IL-2, and IFN- $\alpha$ .

## Gene ontology enrichment analysis

Gene ontology (GO) enrichment analysis revealed distinct immune processes altered between ART-naïve and ART-experienced groups (Figures 7, 8; Supplementary Figure 4). Upregulated biological processes included chronic inflammatory response, eosinophil migration, chemokine-mediated signaling, granulocyte chemotaxis, and antimicrobial humoral responses. In contrast, pathways related to leukocyte activation, differentiation, and lymphocyte activation were downregulated.

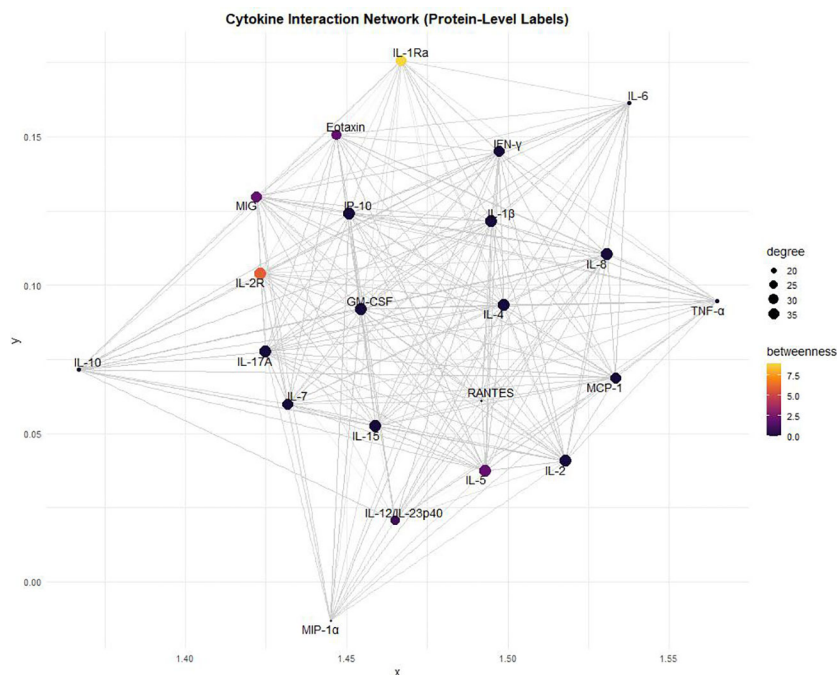
At the molecular function level, chemokine activity, cytokine receptor binding, and G protein-coupled receptor binding were enriched, along with phospholipase activator activity. Downregulated functions included cytokine activity, growth factor receptor binding, and CXCR chemokine receptor interactions. In the cellular component category, downregulated pathways were mainly associated with the external plasma membrane and receptor complexes.

## KEGG pathway enrichment analysis

KEGG pathway enrichment analysis of cytokines and chemokines that differed significantly between ART-naïve and ART-experienced groups revealed enrichment of immune pathways, including viral protein-cytokine interactions, chemokine signaling, and cytokine-cytokine receptor interactions (Figure 9). Downregulated pathways included IL-17 and JAK-STAT signaling, along with those related to inflammatory bowel disease, rheumatoid arthritis, malaria, Chagas disease, hematopoietic lineage differentiation, and allograft rejection.

## Discussion

Cytokine and chemokine variations across the study groups highlight the dual roles of immune activation and regulation in HIV pathogenesis, disease progression, and ART response. In ART-naïve individuals, elevated pro-inflammatory cytokines, particularly IL-6 and IL-12/IL-23p40, reflected a state of chronic immune activation, a hallmark of HIV pathogenesis (27). Persistent inflammation drives viral replication, CD4+ T cell depletion, and accelerated disease progression (28). Similarly, higher levels of IL-15, IL-2, IL-2R, and IL-7, suggest attempts at immune reconstitution, even in the absence of ART. This sustained activation promotes T-cell exhaustion and dysregulation (29).



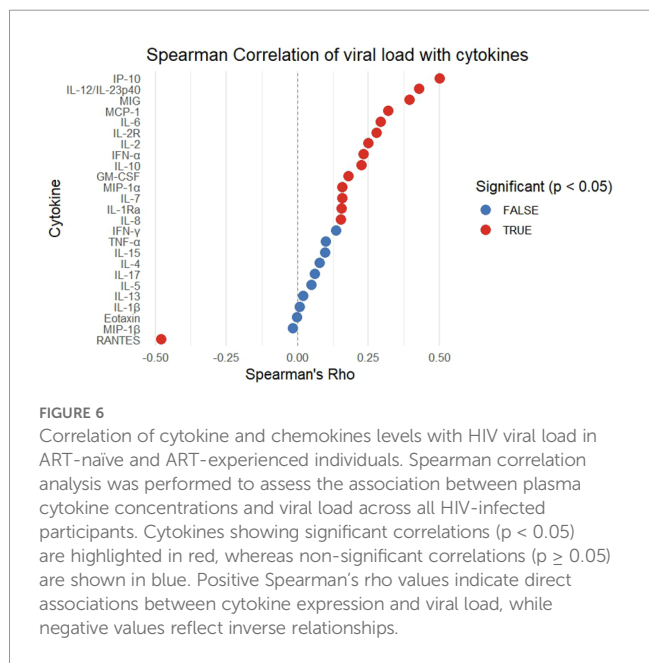
**FIGURE 5** Cytokine interaction network for HIV pathogenesis. Nodes represent cytokines, with size proportional to degree (number of connections) and color gradient indicating betweenness centrality. Edges denote cytokine–cytokine interactions, highlighting key bridging cytokines within the network.

Reduced IL-1 $\beta$  in ART-naïve individuals suggests impaired innate immune signaling, which weakens early antiviral responses and facilitates viral persistence (30). Likewise, the decreased IL-1Ra, a key anti-inflammatory cytokine, points to a limited capacity to counterbalance inflammation, further fueling immune activation, exhaustion and disease progression (31). Elevated chemotactic cytokines, including MCP-1, IP-10, and MIG, likely enhance

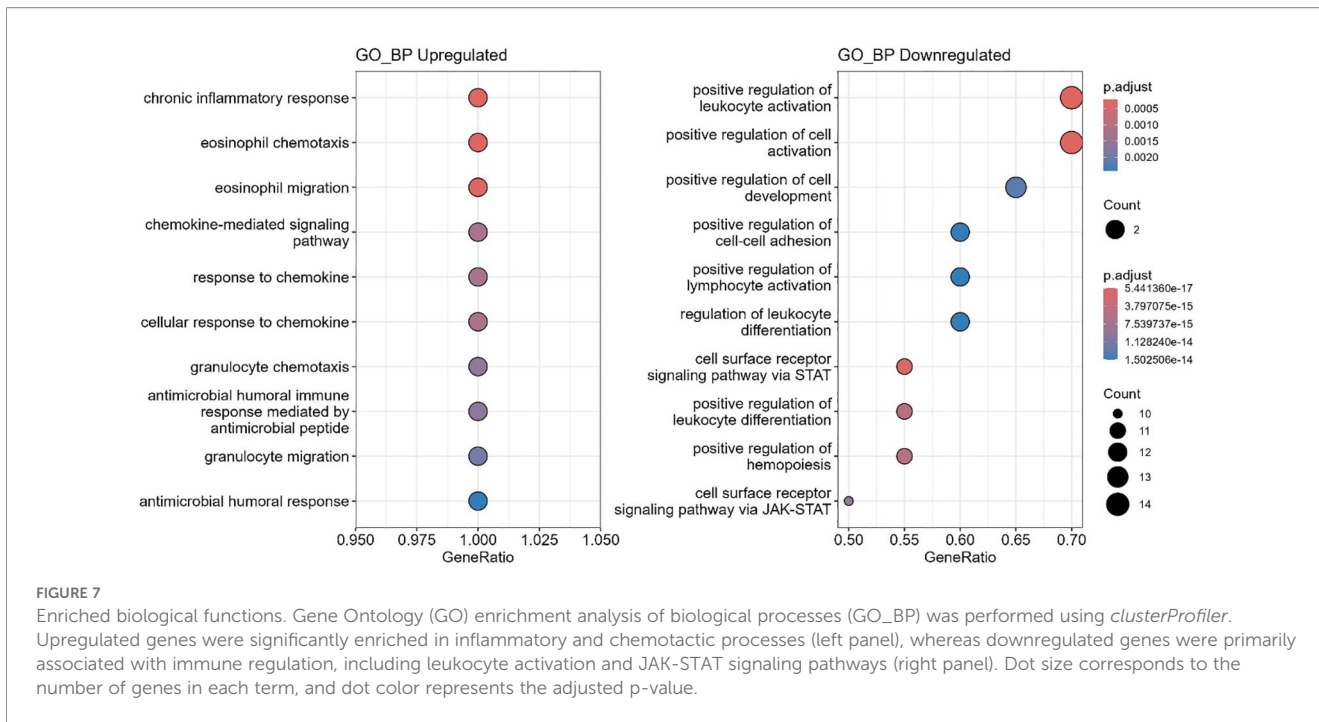
recruitment of activated immune cells to sites of infection, providing more target cells for HIV replication and enhancing viral dissemination (28). This contributes to systemic inflammation, ultimately enhancing the establishment and maintenance of viral reservoirs.

ART initiation resulted in significantly reduced pro-inflammatory cytokines, including GM-CSF, IL-6, IL-12/IL-23p40, IL-1 $\beta$ , and TNF- $\alpha$ . This indicates a restoration of regulatory balance by the suppression of immune hyperactivation as similarly reported in other cohorts (32). As treatment reduces circulating virus, immune stimulation diminishes, leading to a downstream reduction in multiple inflammatory and chemotactic pathways. Reduced IL-15 and other Th1 cytokines (IFN- $\gamma$ , IFN- $\alpha$ , IL-2, IL-7, IL-15, IL-2R) highlight downregulation of immune activation, critical for preserving long-term immune competence. Importantly, lower IL-10 and IL-1Ra in ART-experienced individuals likely reflect diminished need for compensatory immunosuppression following viral suppression (33). Conversely, chemokines with HIV entry-blocking properties, such as Eotaxin and RANTES, were significantly elevated post-ART, consistent with protective roles against viral re-entry (32). Reduced chemotactic cytokines (MCP-1, IL-8, MIG, and IP-10) indicates decreased immune cell trafficking and inflammation, contributing to overall immune stabilization.

Of note, ART-experienced individuals showed reduced IL-17, a Th17 cytokine essential for maintaining mucosal immunity, particularly in the gastrointestinal tract. This suggests incomplete restoration of gut-associated lymphoid tissue (GALT), consistent



**FIGURE 6** Correlation of cytokine and chemokines levels with HIV viral load in ART-naïve and ART-experienced individuals. Spearman correlation analysis was performed to assess the association between plasma cytokine concentrations and viral load across all HIV-infected participants. Cytokines showing significant correlations ( $p < 0.05$ ) are highlighted in red, whereas non-significant correlations ( $p \geq 0.05$ ) are shown in blue. Positive Spearman's rho values indicate direct associations between cytokine expression and viral load, while negative values reflect inverse relationships.

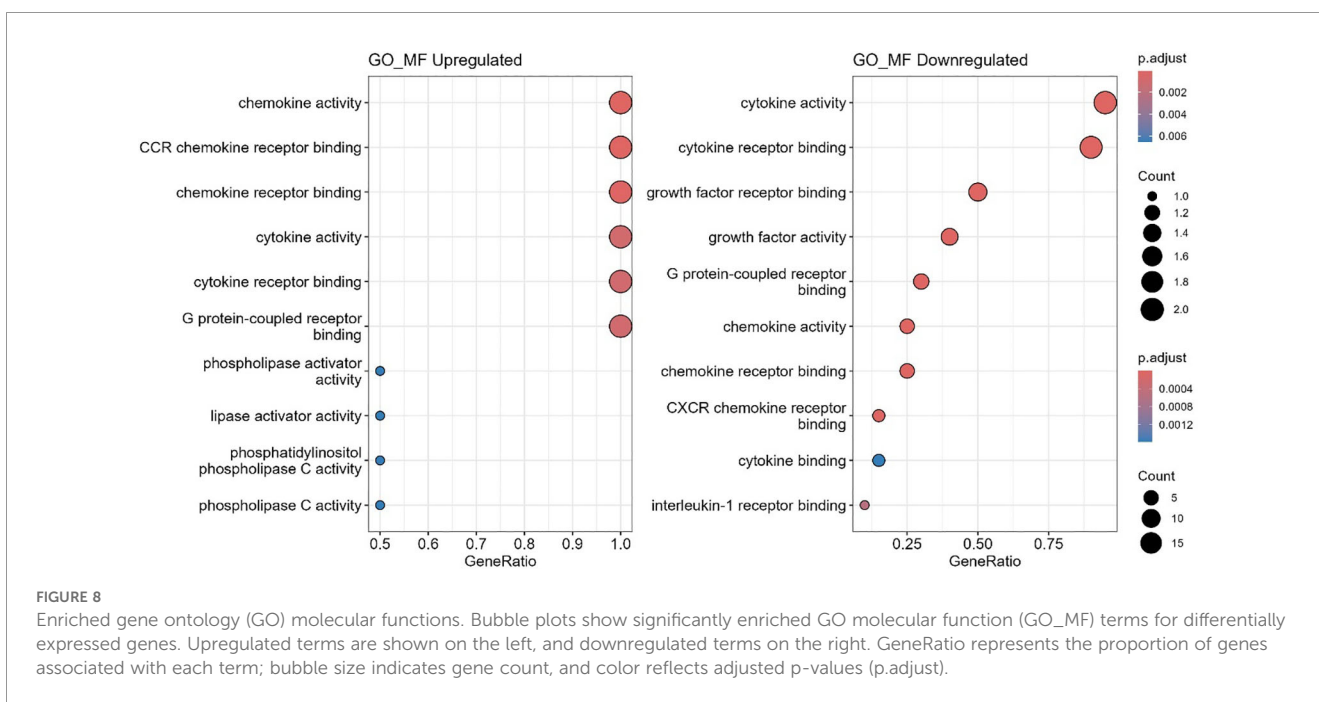


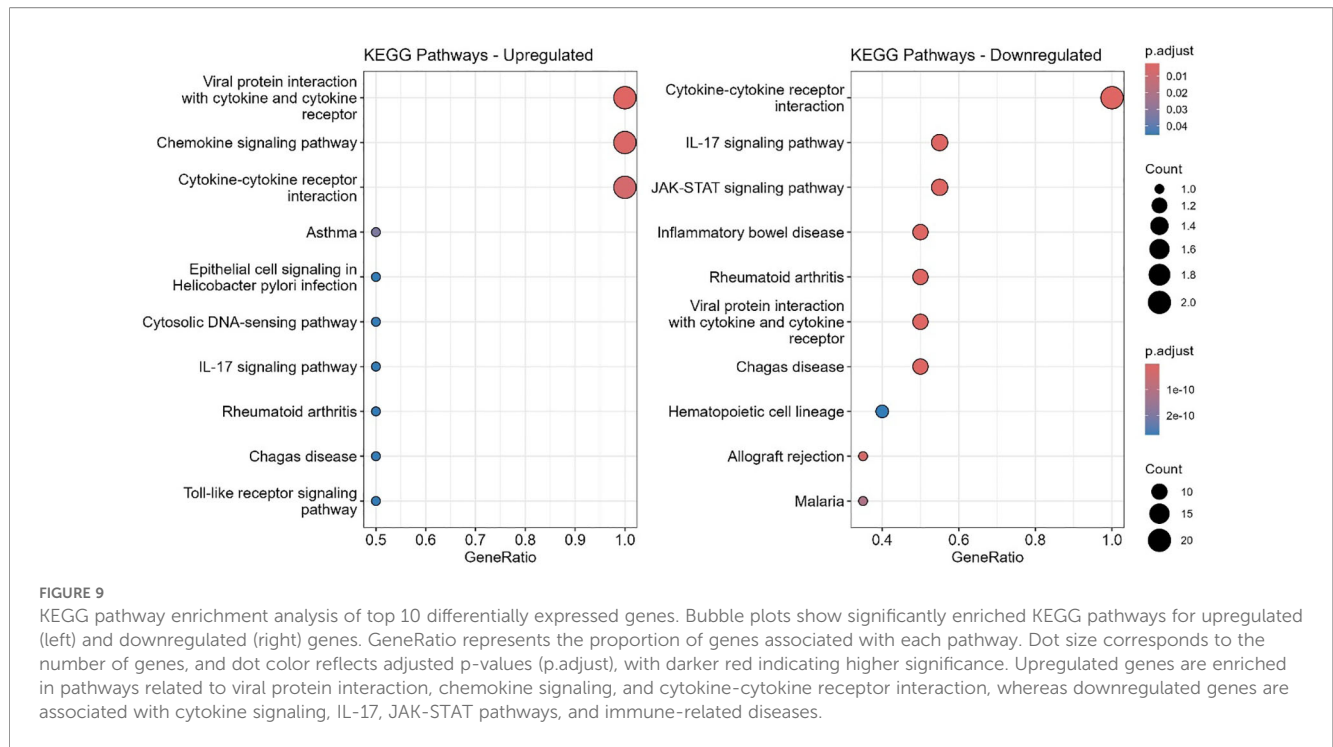
with prior reports (34, 35). Such impairment may perpetuate microbial translocation and chronic inflammation despite systemic viral suppression.

Specific cytokine associations were also observed. Lower IL-1 $\beta$  and IL-10 were associated with virologic control, suggesting that reduced expression supports a less inflammatory milieu favorable for viral suppression (36). Elevated GM-CSF was linked to unsuppressed viral load, consistent with its role in driving

myeloid activation and inflammatory responses that can promote viral replication and reservoir maintenance (37, 38). These findings highlight the prognostic potential of IL-1 $\beta$ , IL-10, and GM-CSF for stratifying patients prior to ART initiation.

Viral load correlations confirmed IP-10 as most strongly associated with viraemia, reinforcing its role in systemic inflammation and replication (39). IL-2R, IL-6, and MCP-1 also correlated positively, while RANTES displayed a negative





correlation, consistent with its competitive blockade of CCR5-mediated HIV entry (40, 41). Similarly, in East Africa, the REALITY trial found elevated IL-6 and IP-10 to be associated with increased all-cause mortality, whereas higher IL-23, IL-2, and RANTES were associated with reduced mortality (42).

Complementary machine learning analyses further identified RANTES and IP-10 as the most consistent predictors of HIV viral load across three independent modelling approaches. RANTES (CCL5) predicted lower viral load, consistent with its role as a CCR5 ligand that restricts HIV entry. In contrast, IP-10 predicted higher viral load, in line with its role as a marker of immune activation and disease progression as previously reported (43). IP-10 has also been reported to correlate with increasing viral loads in Southern Africa (44). The importance of IL-12/IL-23p40, IL-7, and IL-2R in the models additionally implicates dysregulated T-cell homeostasis and pro-inflammatory signaling in viral persistence. Notably, non-linear models (RF, GBM) captured threshold and saturation effects missed by LASSO, underscoring the value of machine learning in unravelling complex immune-viral dynamics.

Cytokine network analysis provides important insights into the immune signaling dynamics underlying HIV pathogenesis. IL-1Ra emerged as a central regulatory node with the highest betweenness centrality, consistent with its role in modulating immune responses and mitigating excessive inflammation (31). GM-CSF, TNF- $\alpha$ , IL-1 $\beta$ , and MIP-1 $\alpha$  exhibited high degree centrality, highlighting their roles in sustaining chronic inflammation. GM-CSF promotes M1 macrophage activation, creating a pro-inflammatory environment that supports viral persistence (38, 45). Similarly, TNF- $\alpha$  and IL-1 $\beta$  are potent drivers of systemic inflammation and neurotoxicity,

contributing to HIV-associated neurocognitive impairment and immune dysregulation (46). Chemokines such as MCP-1, MIG, and IP-10 occupied highly connected regions, consistent with their roles in recruiting CCR2<sup>+</sup> and CXCR3<sup>+</sup> immune cells to infection sites and exacerbating viral dissemination and chronic immune activation (39). Collectively, these findings suggest that cytokines with high network centrality are not merely bystanders but active drivers of HIV pathogenesis.

Functional enrichment analyses provided additional context. Gene Ontology (GO) revealed upregulation of chemotaxis-related processes, including granulocyte and eosinophil migration, supporting ongoing inflammation despite ART (47, 48). Conversely, pathways regulating leukocyte activation and differentiation, including JAK-STAT signaling, were downregulated (49, 50), suggesting impaired adaptive immune coordination. Molecular function analysis showed upregulation of chemokine receptor binding, cytokine activity, and G protein-coupled receptor (GPCR) signaling but downregulation of interleukin-1-receptor activity and CXCR binding, pointing to robust inflammatory signaling but reduced immune responsiveness (39, 51, 52). At the cellular component level, downregulation of plasma membrane receptor complexes suggests impaired immune recognition of infected cells (53).

KEGG pathway analysis confirmed enrichment of inflammatory pathways, including chemokine signaling and cytokine-receptor interactions (26). Downregulation of JAK-STAT, IL-17, and hematopoietic cell lineage pathways highlights persistent immune exhaustion and impaired hematopoiesis, consistent with previous reports (54-57).

## Conclusion

ART initiation reduces circulating virus, thereby reducing immune activation. Thus, there is a concomitant reduction in systemic inflammation and a partial restoration of immune function in PLWH. However, recovery remains incomplete and functionally dysregulated. Persistent chemotactic signaling sustains immune cell trafficking, while downregulation of activation and differentiation pathways limits antigen-specific responses. This creates a paradox of numerical immune recovery but functional compromise, contributing to viral non-suppression despite ART.

Key cytokines—IL-1 $\beta$ , IL-10, GM-CSF, RANTES, and IP-10 emerge as potential prognostic markers of disease progression. Targeted interventions could include restoring mucosal immunity through IL-17 modulation, reducing immune activation via IP-10 inhibition, and enhancing RANTES activity to block HIV entry. Together, these findings highlight cytokine signatures as critical determinants of HIV persistence and immune recovery and support their use in risk stratification and therapeutic development.

## Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by Ethics Committee for the Basic and Applied Sciences (ECBA 016/22–23) and the Ghana Health Service Ethics Review Committee (GHS-ERC-011/03/20). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

MA: Validation, Project administration, Writing – review & editing, Formal analysis, Conceptualization, Data curation, Software, Writing – original draft, Methodology, Investigation. EM: Validation, Writing – review & editing, Methodology, Writing – original draft, Investigation, Data curation, Formal analysis. NA: Investigation, Writing – review & editing, Writing – original draft, Data curation, Validation, Formal analysis, Methodology. KK: Writing – review & editing, Writing – original draft, Formal analysis, Methodology, Data curation, Validation, Investigation. KT: Data curation, Writing – original draft, Investigation, Methodology, Writing – review & editing, Formal analysis. CO: Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Methodology. JAA: Investigation, Software, Writing – review &

editing, Formal analysis. SN: Formal analysis, Investigation, Writing – review & editing, Software. RB-D: Investigation, Writing – review & editing, Methodology, Writing – original draft. SF: Writing – review & editing, Methodology, Writing – original draft, Investigation. SQ: Writing – review & editing, Investigation, Methodology. SE-Q: Writing – review & editing, Investigation, Methodology. FB: Methodology, Writing – review & editing, Investigation. FN: Writing – review & editing, Resources, Writing – original draft, Methodology, Investigation. JA: Writing – review & editing, Investigation, Resources, Methodology. GA: Data curation, Project administration, Validation, Formal analysis, Resources, Methodology, Conceptualization, Writing – review & editing, Investigation, Supervision. EB: Methodology, Project administration, Validation, Supervision, Formal analysis, Software, Data curation, Visualization, Resources, Writing – review & editing, Investigation, Conceptualization. PQ: Software, Methodology, Writing – original draft, Conceptualization, Data curation, Investigation, Visualization, Supervision, Resources, Validation, Funding acquisition, Writing – review & editing, Project administration, Formal analysis.

## Funding

The author(s) declared that financial support was received for this work and/or its publication. This work was funded in part by the Crick African Network (CAN/A00004/1 and CAN/F00009/1 to PQ), which receives funding from the UK's Global Challenges Research Fund (MR/P028071/1), and by the Francis Crick Institute, which receives core funding from Cancer Research UK (FC1001647), the UK Medical Research Council (FC1001647) and the Wellcome Trust (FC1001647). This publication was partially based on research funded by the Bill & Melinda Gates Foundation (INV-036307 to PQ). MA is supported by a Ghana Educational Trust Fund Scholarship (GETFund) and Ghana National Petroleum Commission (GNPC) Foundation Scholarship. EM is supported by a WACCBIP-World Bank ACE PhD fellowship (WACCBIP+NCDs: Awandare).

## Acknowledgments

We gratefully thank all study participants and the contributions of the various clinical teams. Clinical teams included Frances Odofuorkor Lawson, Abigail Dede Teye, Irene Atswei Adjetey, John Blankson, Emelia Bedford Smith, and Stephanie Osei-Poku from the Greater Accra Regional Hospital (Accra); Maxwell Pappoe, Franklina Aboagye, and Samuel Gyedu from the University Hospital, Legon; Daniel Vitor, Gify Osa, Nii Affotey Odai, and Solomon Adjei from Tema General Hospital; Florence Bosomtwe, Nora Blevi, and Precious Dompey from Ho Municipal Hospital; the nurses at the ART clinic of the Upper East Regional Hospital (Bolgatanga); and the nurses at the ART clinic of the War Memorial Hospital (Navrongo). Their dedication to patient care, data collection, and study implementation was invaluable in strengthening this research.

## Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References

- Delgado E, Ampofo WK, Sierra M, Torpey K, Pérez-Alvarez L, Bonney EY, et al. High prevalence of unique recombinant forms of HIV-1 in Ghana: molecular epidemiology from an antiretroviral resistance study. *J Acquir Immune Defic Syndr*. (2008) 48:599–606. doi: 10.1097/QAI.0b013e3181806c0e
- Giovanetti M, Ciccozzi M, Parolin C, Borsetti A. Molecular epidemiology of HIV-1 in african countries: A comprehensive overview. *Pathogens*. (2020) 9. doi: 10.3390/pathogens9121072
- Ansa GA, Walley JD, Siddiqi K, Wei X. Assessing the impact of TB/HIV services integration on TB treatment outcomes and their relevance in TB/HIV monitoring in Ghana. *Infect Dis Poverty*. (2012) 1:13. doi: 10.1186/2049-9957-1-13
- Oguntibeju O. Quality of life of people living with HIV and AIDS and antiretroviral therapy. *HIV/AIDS - Res Palliative Care*. (2012) 117–124. doi: 10.2147/hiv.s32321
- Wainberg MA. Two standards of care for HIV: Why are Africans being short-changed? *Retrovirology*. (2009) 6:109. doi: 10.1186/1742-4690-6-109
- Appiedu-Addo SNA, Appeaning M, Magomere E, Ansa GA, Bonney EY, Quashie PK. The urgent need for newer drugs in routine HIV treatment in Africa: the case of Ghana. *Front Epidemiol*. (2025) 5:1523109. doi: 10.3389/fepid.2025.1523109
- Danforth K, Granich R, Wiedeman D, Baxi S, Padian N. Global mortality and morbidity of HIV/AIDS. In: Holmes KK, Bertozzi S, Bloom BR, Jha P, editors. *Major infectious diseases*. Washington DC: The International Bank for Reconstruction and Development / The World Bank (2017). doi: 10.1596/978-1-4648-0524-0\_ch2
- Boasso A, Shearer GM, Choungnet C. Immune dysregulation in human immunodeficiency virus infection: know it, fix it, prevent it? *J Internal Med*. (2009) 265:78–96. doi: 10.1111/j.1365-2796.2008.02043.x
- Appeaning M, Magomere E, Abotsi AM, Amoako NAY, Kouffie KE, Tetteh BE, et al. Slow virologic control but strong immune and metabolic recovery with dolutegravir-anchored therapy in an HIV cohort in Ghana. *Virol J*. (2025) 22:247. doi: 10.1186/s12985-025-02873-w
- Mosha IH, Nyondo GG, Munishi CG, Njiro BJ, Bwire GM. Prevalence and factors associated with viral non-suppression in people living with HIV receiving antiretroviral therapy in sub-Saharan Africa: A systematic review and meta-analysis. *Rev Med Virol*. (2024) 34:e2540. doi: 10.1002/rmv.2540
- Nyongesa MK, Mwatasa MH, Kagonya VA, Mwambingu G, Ngetsa C, Newton CRJC, et al. HIV virological non-suppression is highly prevalent among 18- to 24-year-old youths on antiretroviral therapy at the Kenyan coast. *BMC Infect Dis*. (2022) 22:449. doi: 10.1186/s12879-022-07428-w
- Quaker AS, Shirima LJ, Msuya SE. Trend and factors associated with non-suppression of viral load among adolescents on ART in Tanzania: 2018–2021. *Front Reprod Health*. (2024) 6:1309740. doi: 10.3389/frph.2024.1309740
- Naif HM. Pathogenesis of HIV infection. *Infect Dis Rep*. (2013) 5:e6. doi: 10.4081/idr.2013.s1.e6
- Tapela K, Oyawoye FO, Olwal CO, Oporum PC, Amponsah JA, Segbedzi KAL, et al. Probing SARS-CoV-2-positive plasma to identify potential factors correlating with mild COVID-19 in Ghana, West Africa. *BMC Med*. (2022) 20. doi: 10.1186/s12916-022-02571-2
- Therneau T. A package for survival analysis in S. R package version. New York, Springer. (2015) 2:2014. doi: 10.32614/CRAN.package.survival
- Boldini D, Grisoni F, Kuhn D, Friedrich L, Sieber SA. Practical guidelines for the use of gradient boosting for molecular property prediction. *J Cheminformatics*. (2023) 15. doi: 10.1186/s13321-023-00743-7
- Clark RRS, Hou J. Three machine learning algorithms and their utility in exploring risk factors associated with primary cesarean section in low-risk women: A methods paper. *Res Nurs Health*. (2021) 44:559–70. doi: 10.1002/nur.22122
- Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein–protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res*. (2023) 51:D638–46. doi: 10.1093/nar/gkac1000
- Csardi G, Nepusz T. The igraph software. *Complex Syst*. (2006) 1695:1–9. Available online at: <https://igraph.org>
- Yu G, Wang LG, Han Y, He QY. clusterProfiler: an R package for comparing biological themes among gene clusters. *Omic*s. (2012) 16:284–7. doi: 10.1089/omi.2011.0118
- Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, et al. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat Genet*. (2000) 25:25–9. doi: 10.1038/75556

## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fimmu.2026.1753475/full#supplementary-material>

### SUPPLEMENTARY FIGURE 1

Cytokine hazard ratios for HIV progression. Forest plot of hazard ratios (HRs) for individual cytokines derived from a Cox proportional hazards model. HRs >1 indicate an increased risk of viral non-suppression, whereas HRs <1 suggest virologic control. Horizontal lines represent 95% confidence intervals (CIs), and statistical significance is denoted by \*\*\*.

### SUPPLEMENTARY FIGURE 2

Model performance (predicted vs. observed). Scatterplots of predicted versus observed log viral load ( $\log_{10}$  copies/mL) for the test set using LASSO regression, Random Forest (RF), and Gradient Boosting Machine (GBM). Each point represents an individual sample. The fitted regression line (blue) with 95% confidence band (gray) indicates model calibration.

### SUPPLEMENTARY FIGURE 3

Partial dependence of top cytokines. Partial dependence plots (PDPs) for the top 10 cytokines identified across models, shown separately for RF (blue) and GBM (orange). Each panel depicts the marginal effect of one cytokine on predicted log viral load, holding other variables constant. Non-linear associations and threshold effects are evident.

### SUPPLEMENTARY FIGURE 4

Enriched cellular components. GO cellular component (GO\_CC) enrichment analysis of downregulated genes shows enrichment in membrane-associated components, particularly the external side of the plasma membrane and the plasma membrane signalling receptor complex. Dot size indicates gene count, and color represents adjusted p-values.

22. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res.* (2000) 28:27–30. doi: 10.1093/nar/28.1.27
23. The UniProt Consortium. UniProt: the universal protein knowledgebase in 2023. *Nucleic Acids Res.* (2023) 51:D523–d531. doi: 10.1093/nar/gkac1052
24. Catalfamo M, Le Saout C, Lane HC. The role of cytokines in the pathogenesis and treatment of HIV infection. *Cytokine Growth Factor Rev.* (2012) 23:207–14. doi: 10.1016/j.cytogfr.2012.05.007
25. Ngcobo S, Molatlhegi RP, Osman F, Ngcapu S, Samsunder N, Garrett NJ, et al. Pre-infection plasma cytokines and chemokines as predictors of HIV disease progression. *Sci Rep.* (2022) 12. doi: 10.1038/s41598-022-06532-w
26. Reuter MA, Pombo C, Betts MR. Cytokine production and dysregulation in HIV pathogenesis: Lessons for development of therapeutics and vaccines. *Cytokine Growth Factor Rev.* (2012) 23:181–91. doi: 10.1016/j.cytogfr.2012.05.005
27. Miedema F, Hazenberg MD, Tessalear K, Van Baarle D, De Boer RJ, Borghans JAM. Immune activation and collateral damage in AIDS pathogenesis. *Front Immunol.* (2013) 4:298. doi: 10.3389/fimmu.2013.00298
28. Vidya Vijayan KK, Karthigeyan KP, Tripathi SP, Hanna LE. Pathophysiology of CD4+ T-cell depletion in HIV-1 and HIV-2 infections. *Front Immunol.* (2017) 8:580. doi: 10.3389/fimmu.2017.00580
29. Yi JS, Cox MA, Zajac AJ. T-cell exhaustion: characteristics, causes and conversion. *Immunology.* (2010) 129:474–81. doi: 10.1111/j.1365-2567.2010.03255.x
30. Guo H, Gao J, Taxman DJ, Ting JPY, Su L. HIV-1 infection induces interleukin-1 $\beta$  Production via TLR8 protein-dependent and NLRP3 inflammasome mechanisms in human monocytes. *J Biol Chem.* (2014) 289:21716–26. doi: 10.1074/jbc.M114.566620
31. Al-Qahtani AA, Alhamlan FS, Al-Qahtani AA. Pro-inflammatory and anti-inflammatory interleukins in infectious diseases: A comprehensive review. *Trop Med Infect Dis.* (2024) 9:13. doi: 10.3390/tropicalmed9010013
32. Bordoni V, Sacchi A, Casetti R, Cimini E, Tartaglia E, Pinnetti C, et al. Impact of ART on dynamics of growth factors and cytokines in primary HIV infection. *Cytokine.* (2020) 125:154839. doi: 10.1016/j.cyto.2019.154839
33. Hileman CO, Funderburg NT. Inflammation, immune activation, and antiretroviral therapy in HIV. *Curr HIV/AIDS Rep.* (2017) 14:93–100. doi: 10.1007/s11904-017-0356-x
34. Bixler SL, Mattapallil JJ. Loss and dysregulation of Th17 cells during HIV infection. *Clin Dev Immunol.* (2013) 2013:852418. doi: 10.1155/2013/852418
35. Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, et al. CD4+ T Cell Depletion during all Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract. *J Exp Med.* (2004) 200:749–59. doi: 10.1084/jem.20040874
36. Villacres MC, Kono N, Mack WJ, Nowicki MJ, Anastos K, Augenbraun M, et al. Interleukin 10 responses are associated with sustained CD4 T-cell counts in treated HIV infection. *J Infect Dis.* (2012) 206:780–9. doi: 10.1093/infdis/jis380
37. Bouzeineddine NZ, Philippi A, Gee K, Basta S. Granulocyte macrophage colony stimulating factor in virus-host interactions and its implication for immunotherapy. *Cytokine Growth Factor Rev.* (2025) 81:54–63. doi: 10.1016/j.cytogfr.2024.12.002
38. Petrina M, Martin J, Basta S. Granulocyte macrophage colony-stimulating factor has come of age: From a vaccine adjuvant to antiviral immunotherapy. *Cytokine Growth Factor Rev.* (2021) 59:101–10. doi: 10.1016/j.cytogfr.2021.01.001
39. Yin X, Wang Z, Wu T, Ma M, Zhang Z, Chu Z, et al. The combination of CXCL9, CXCL10 and CXCL11 levels during primary HIV infection predicts HIV disease progression. *J Trans Med.* (2019) 17. doi: 10.1186/s12967-019-02172-3
40. Coffey MJ, Woffendin C, Phare SM, Strieter RM, Markovitz DM. RANTES inhibits HIV-1 replication in human peripheral blood monocytes and alveolar macrophages. *Am J Physiol.* (1997) 272:L1025–1029. doi: 10.1152/ajplung.1997.272.5.L1025
41. Favre N, Verollet C, Dumas F. The chemokine receptor CCR5: multi-faceted hook for HIV-1. *Retrovirology.* (2024) 21. doi: 10.1186/s12977-024-00634-1
42. Riitho V, Connon R, Gwela A, Namusanje J, Nhema R, Siika A, et al. Biomarkers of mortality in adults and adolescents with advanced HIV in sub-Saharan Africa. *Nat Commun.* (2024) 15:5492. doi: 10.1038/s41467-024-49317-7
43. Ruhanya V, Jacobs GB, Naidoo S, Paul RH, Joska JA, Seedat S, et al. Impact of plasma IP-10/CXCL10 and RANTES/CCL5 levels on neurocognitive function in HIV treatment-naïve patients. *AIDS Res Hum Retroviruses.* (2021) 37:657–65. doi: 10.1089/aid.2020.0203
44. Streeck H, Maestri A, Habermann D, Crowell TA, Esber AL, Son G, et al. Dissecting drivers of immune activation in chronic HIV-1 infection. *EBioMedicine.* (2022) 83:104182. doi: 10.1016/j.ebiom.2022.104182
45. Ushach I, Zlotnik A. Biological role of granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) on cells of the myeloid lineage. *J Leukoc Biol.* (2016) 100:481–9. doi: 10.1189/jlb.3RU0316-144R
46. Brabers NA, Nottet HS. Role of the pro-inflammatory cytokines TNF-alpha and IL-1beta in HIV-associated dementia. *Eur J Clin Invest.* (2006) 36:447–58. doi: 10.1111/j.1365-2362.2006.01657.x
47. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity.* (2013) 39:633–45. doi: 10.1016/j.immuni.2013.10.001
48. Obeagu EI. Influence of cytokines on the recovery trajectory of HIV patients on antiretroviral therapy: A review. *Medicine.* (2025) 104. doi: 10.1097/MD.00000000000041222
49. Hu Q, Bian Q, Rong D, Wang L, Song J, Huang H-S, et al. JAK/STAT pathway: Extracellular signals, diseases, immunity, and therapeutic regimens. *Front Bioengineering Biotechnol.* (2023) 11:1110765. doi: 10.3389/fbioe.2023.1110765
50. Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. *Signal Transduction Targeted Ther.* (2021) 6. doi: 10.1038/s41392-021-00791-1
51. Alkhatib G. The biology of CCR5 and CXCR4. *Curr Opin HIV AIDS.* (2009) 4:96–103. doi: 10.1097/coh.0b013e328324bbec
52. Sodhi A, Montaner S, Gutkind JS. Viral hijacking of G-protein-coupled-receptor signalling networks. *Nat Rev Mol Cell Biol.* (2004) 5:998–1012. doi: 10.1038/nrm1529
53. Abbas W, Herbein G. Plasma membrane signaling in HIV-1 infection. *Biochim Biophys Acta (BBA) - Biomembranes.* (2014) 1838:1132–42. doi: 10.1016/j.bbame.2013.06.020
54. Cai CW, Sereti I. Residual immune dysfunction under antiretroviral therapy. *Semin Immunol.* (2021) 51:101471. doi: 10.1016/j.smim.2021.101471
55. Fenwick C, Joo V, Jacquier P, Noto A, Banga R, Perreau M, et al. T-cell exhaustion in HIV infection. *Immunol Rev.* (2019) 292:149–63. doi: 10.1111/imr.12823
56. Tsukamoto T. Hematopoietic stem/progenitor cells and the pathogenesis of HIV/AIDS. *Front Cell Infect Microbiol.* (2020) 10:60. doi: 10.3389/fcimb.2020.00060
57. Usman A, Balogun O, Shuaib BI, Musa BOP, Yusuf AA, Ajayi EIO. Prevalence of cytopenia and its correlation with immunosuppression in naïve HIV-1 infected patients initiating first-line antiretroviral therapy: A pilot study. *Infection Chemotherapy.* (2023) 55:479. doi: 10.3947/ic.2023.0080