frontiers | Frontiers in Virology

BRIEF RESEARCH REPORT
published: 13 June 2022
doi: 10.3389/fviro.2022.929053

Interferon Alpha-Inducible Protein 27 Expression Is Linked to Disease Severity in Chronic Infection of Both HIV-1 and HIV-2

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Specialty section:
This article was submitted to Translational Virology, a section of the journal Frontiers in Virology

Received: 26 April 2022
Accepted: 19 May 2022
Published: 13 June 2022

Citation:
Palm AA, Veerla S, Lindman J, Isberg P-E, Johansson E, Biague A, Månsson F, Norrgren H, Esbjörnsson J, Medstrand P and Jansson M (2022) Interferon Alpha-Inducible Protein 27 Expression Is Linked to Disease Severity in Chronic Infection of Both HIV-1 and HIV-2. Front. Virol. 2:929053. doi: 10.3389/fviro.2022.929053

Disease progression is slower in HIV-2, as compared with HIV-1 infection, in accordance with low or undetectable plasma viremia at viral setpoint. However, it is unclear why most HIV-2 infected individuals are still at risk of developing AIDS. To explore if specific host responses are linked to HIV disease severity, we have compared blood gene expression profiles between HIV seronegative and HIV-1, HIV-2 or dually HIV-1/HIV-2 infected individuals. In this study the gene encoding Interferon alpha-inducible protein 27 (IFI27) was found to be the most differentially expressed. Detailed expression analysis revealed significantly higher IFI27 expression in HIV infected individuals compared with seronegative individuals, irrespectively of HIV type. Moreover, IFI27 expression was higher in HIV-1 than in HIV-2 infected individuals. Multiple linear regression analysis, adjusting for age and sex, showed also that plasma viral load was the strongest predictor of IFI27 expression, followed by CD4% and HIV type. In line with this, IFI27 expression was found to be higher in HIV-2 viremic, compared with HIV-2 aviremic individuals. Still, HIV-2 aviremic individuals displayed elevated IFI27 expression compared with seronegative individuals. Furthermore, in HIV-2 infected individuals, IFI27 expression was also correlated with plasma markers previously linked to inflammation and disease progression in HIV infection. Taken together, our findings suggest that sustained elevation of type I interferon signaling, here reflected by elevated IFI27 expression in the chronic infection phase, is a key pathogenic feature of both HIV-1 and HIV-2.

Keywords: HIV-1, HIV-2, interferon-stimulated gene (ISG), viremia, chronic infection, disease severity, interferon alpha-inducible protein 27 (IFI27)

INTRODUCTION

Both HIV-1 and HIV-2 are causative agents of AIDS and are characterized by a progressive decline in $CD4^+$ T-cells (1). However, the $CD4^+$ T-cell decline and the rate of disease progression in untreated individuals is faster in HIV-1 than in HIV-2 infection (2, 3). In individuals that are dually infected with both HIV-1 and HIV-2 (HIV-D), it has also been shown that a preceeding HIV-2 infection delays disease progression (4, 5). The plasma viral load (pVL) at set point, and when adjusted for $CD4^+$ T-cell level, is higher in HIV-1 infected than in HIV-2 infected individuals (6–8). Accordingly, a large proportion of HIV-2 infected individuals will remain aviremic, i.e. with low or undetectable viremia, for extended periods of time (9). Still, disease progression occurs also in aviremic HIV-2 infected individuals (10–12), although the mechanisms behind this phenomenon are not clear.

HIV-1 disease progression is characterized by chronic immune activation and exhaustion (13). HIV-1 elite controllers, a group that in some aspects resembles HIV-2 aviremic individuals, presents with reduced immune activation and exhaustion compared to HIV-1 viremic individuals (6, 13). Less is known about the HIV-2 pathogenesis, but disease progression has been coupled to T-cell activation and exhaustion, and to the level of plasma inflammation markers (10–12, 14–19). Interestingly, also aviremic HIV-2 infected individuals have been suggested to harbor increased frequencies of activated and exhausted $CD4^+$ and $CD8^+$ T-cells compared to HIV seronegative individuals (10, 12).

Upon virus encounter, the innate immune response provides the first line of defence, including production of type I interferons (IFN-I) (20). This in turn results in the transcription of interferon-stimulated genes (ISGs), which, for example, inhibits viral transcription, translation and replication, thereby contributing to viral control during acute infections (20, 21). However, persistent up-regulation of ISGs during chronic infections, is associated with chronic and generalized immune activation, which is a key feature of $CD4^+$ T-cell depletion and disease progression in pathogenic HIV-1 and SIV infection (22–25). By contrast, nonpathogenic chronic SIV infection is associated with lower levels of ISG expression and immune activation during the chronic infection phase, compared with pathogenic SIV and HIV-1 infection (22–24). Although associations between IFN-I and ISG expression and disease severity have been investigated for HIV-1 infection and both pathogenic and nonpathogenic SIV infection (22–25), such studies have not included HIV-2, a virus strain originating from nonpathogenic SIV_{sm} (26).

In this study, gene expression in whole blood was compared between individuals infected with HIV-1, HIV-2 or HIV-D, and HIV seronegative individuals. Results showed that the ISG encoding the Interferon alpha-inducible protein 27 (IFI27), was significantly linked to disease severity in both HIV-1 and HIV-2 infection.

MATERIALS AND METHODS

Study Participants

The individuals included in this study were part of a well-defined occupational cohort of police officers in Guinea-Bissau (27, 28). In this study, 39 HIV-1, 43 HIV-2, and 14 HIV-D infected individuals and 35 HIV seronegative individuals were enrolled (**Table 1**). All individuals were treatment naïve or unsuccessfully treated [defined by a pVL above 1000 RNA copies/ml plasma (29)]. We also included nine HIV-1 infected individuals that were successfully treated, i.e. with a pVL < 1000 copies/ml. The HIV-2 infected individuals were further subdivided according to level of pVL, where 13 had a pVL ≥ 75 copies/ml, and were referred to as viremic, and 30 had a pVL < 75 copies/ml and were referred to as aviremic (**Table 1**). Among the aviremic HIV-2 infected individuals 16 had pVL that was detected below the technical quantification threshold (above 0 but below 75 copies/ml). Informed consent was obtained from all the study participants, and the study was approved by the National Ethical Committee, Ministry of Public Health in Guinea-Bissau, and the Ethical Committee at Lund University.

$CD4^+$ T-Cell Level and Plasma Viral Load Determination

HIV status, $CD4^+$ T-cell levels and pVL were determined as previously described (10). We used CD4% instead of absolute $CD4^+$ T-cell counts for analysis, as CD4% has been shown to be a more stable marker in settings with high pathogenic burden (30). The technical pVL quantification threshold was 75 copies/ml plasma for HIV-1 or HIV-2 single-infected, and 135 copies/ml plasma for HIV-D infected individuals (31).

Blood Collection and RNA Isolation

Whole blood (2.5 ml) was collected from study participants in PAXgene tubes (PreAnalytiX). Sample tubes were stored frozen until use. The tubes were thawed at room temperature overnight, before proceeding with total RNA extraction using the

TABLE 1 | Characteristics of study participants included in the qPCR analysis.

Characteristic	Negative	HIV-1	HIV-2	*HIV-2 viremic*[b]	*HIV-2 aviremic*[c]	HIV-D
Individuals (females)	35 (14)	39 (16)	43 (11)	*13 (1)*	*30 (10)*	14 (3)
Age in years[a]	52 (44-58)	47 (39-53)	54 (48-58)	*56 (49-59)*	*54 (48-58)*	45 (41-51)
CD4%[a]	41.6 (35.5-47.5)	10.7 (6.7-19.6)	25.1 (15.8-35.9)	*14.9 (14.2-19.7)*	*29.2 (23.0-38.7)*	12.7 (11.0-21.2)
Viral load[a]	N/A	12496 (4463-37322)	15 (0-660)	*1656 (732-6142)*	*5 (0-25)*	4396 (995-19556)

[a]*Median (interquartile range).*

[b]*HIV-2 infected viremic individuals either naïve to treatment (plasma VL>75 RNA copies/ml) or receiving suboptimal ART (VL>1000 RNA copies/ml)*

[c]*HIV-2 infected aviremic individuals naïve to treatment (plasma VL<75 RNA copies/ml)*

N/A: not applicable

PAXgene Blood RNA kit (Qiagen) according to the manufacturer's instructions.

Microarray Analysis

An exploratory microarray gene expression analysis was performed on samples from HIV seronegative (n = 8), HIV-1 (n = 8), HIV-2 (n = 7) and HIV-D (n = 8) infected individuals to identify candidate genes for further analyses. HIV infected individuals were matched on CD4% to allow identification of virus specific differences in gene expression. Total RNA was depleted of globins using GLOBINclear kit (ThermoFisher Scientific) according to manufacturer's instructions. RNA quantity and integrity were analyzed using NanoDrop Spectrophotometry and the Agilent 2100 Bioanalyzer (Agilent). Gene expression data were generated using the Illumina HT12 v4 BeadChip (Illumina) which provides genome-wide transcriptional coverage of well-characterized genes, gene candidates, and splice variants. It targets more than 25,000 annoted genes with more than 48,000 probes. Of note, IFI27 is targeted by a single probe. Expression data were initially pre-processed and normalized using Quantile Normalization method (32). These analyses were performed using GenomeStudio software V2011.1. Non-annotated probe sets and probe sets with signal intensities below the median of the negative control intensities in 80% of the samples that did not belong to one condition were excluded. Following this the remaining probe set comprised of 20595, 20819, 20562 and 20689 probes for the comparisons of gene expression between HIV seronegative individuals and HIV infection groups combined (i.e. HIV-1, HIV-2 and HIV-D), HIV-1, HIV-2 and HIV-D infected individuals, respectively. Raw and processed data have been deposited in the Gene Expression Omnibus (GSE200606).

qPCR Analysis

Total RNA was quantified using a NanoDrop 2000 Spectrophotometer (ThermoFisher Scientific). cDNA synthesis was performed on 500 ng total RNA using Superscript IV (ThermoFisher Scientific) with random hexamers (Invitrogen) according to manufacturer's instructions, in a total reaction volume of 20 µl. IFI27 and GAPDH (used as internal control) were amplified using the Hs00271467_m1 and Hs03929097_g1 TaqMan gene expression assays, respectively, with TaqMan Fast Advanced Master Mix (all from ThermoFisher Scientific). Reactions were set up according to manufacturer's instructions, using 2 µl of cDNA as input, and analyzed on a StepOnePlus instrument (Applied Biosystems). The fold change in gene expression was calculated using the 2^-ΔΔCt method (33) and geometric means with confidence intervals are presented.

Plasma Inflammation Markers

For HIV-2 infected individuals, plasma concentrations of interferon gamma-induced protein 10 (IP-10, also known as CXCL10), soluble CD14 (sCD14), and beta-2-microglobulin (b2m) were analyzed using the Magnetic Luminex assay (R&D Systems Inc.) on the Bio-Plex 200 platform (Bio-Rad Laboratories Inc.) according to manufacturer's instructions. Plasma was diluted 1:2, 1:600 and 1:4000 for quantification of IP-10, sCD14 and b2m, respectively.

Statistical Analysis

Statistical analyses of differentially expressed genes were performed in R by student's t-test with Benjamini-Hochberg *post-hoc* correction for multiple comparisons. Differentially expressed genes were considered when the fold change was above 1.5 and the adjusted p-value was below 0.05. All other statistical analyses were performed using GraphPad Prism 9.2.0 (GraphPad software, La Jolla, California). To achieve normal distribution, the following variables were log10-transformed prior to statistical analysis: IFI27 fold change, CD4%, pVL, b2m, sCD14 and IP-10. Differences between study participants were analyzed using t-test, comparing two groups, and One-way ANOVA with Tukey's *post-hoc* test, comparing more than two groups. Pearson correlation analysis was used to assess correlations between IFI27 and CD4%, pVL and plasma inflammation markers. Multiple linear regression analysis was used to identify significant predictors of IFI27 expression.

RESULTS

IFI27 Differentiates HIV Infected From HIV Seronegative Individuals

We performed an exploratory array expression analysis to identify genes that were differentially expressed in HIV infected [HIV-1 (n = 8), HIV-2 (n = 7) or HIV-D (n = 8)] and HIV seronegative (n = 8) individuals (**Table S1**), where the HIV infected individuals were matched on CD4%. IFI27 was found to be the most strongly upregulated gene, with a 16.7-fold higher expression in HIV infected individuals compared with seronegative controls (adjusted p-value = 0.004, **Figure S1**).

To validate the array results, we determined IFI27 gene expression using qPCR in 39 HIV-1, 43 HIV-2, and 14 HIV-D infected individuals, and 35 HIV seronegative controls (**Table 1**). Among these study participants HIV-2 infected individuals had lower pVL levels compared to HIV-1 ($p < 0.001$) and HIV-D infected individuals ($p < 0.001$). Moreover, the CD4% was higher in HIV-2 infected compared with HIV-1 ($p < 0.001$) and HIV-D ($p = 0.040$) infected individuals. Seronegative individuals also had higher CD4% compared with HIV-1 ($p < 0.001$), HIV-2 ($p < 0.001$) and HIV-D ($p < 0.001$) infected individuals. HIV-2 infected individuals were older, as compared to HIV-1 and HIV-D infected individuals ($p = 0.001$ and $p = 0.009$, respectively).

IFI27 expression was found to be 42.2 ($p < 0.001$), 5.5 ($p < 0.001$) and 24.5 ($p < 0.001$) fold higher in HIV-1, HIV-2 and HIV-D infected as compared with seronegative individuals, respectively (**Figure 1**). Furthermore, the IFI27 expression was 7.7 fold higher in HIV-1 compared with HIV-2 infected individuals ($p < 0.001$, **Figure 1**).

IFI27 Is Linked to Disease Severity in Both HIV-1 and HIV-2 Infections

Next, we investigated if IFI27 expression correlated with CD4% and pVL in HIV infected individuals (**Table S2**). IFI27 was negatively correlated with CD4% in both HIV-1 ($r = -0.559$, $p < 0.001$) and HIV-2 infection ($r = -0.592$, $p < 0.001$), and positively

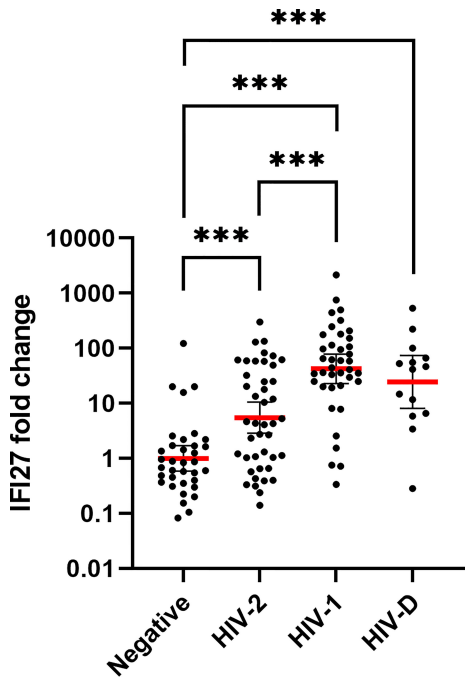

FIGURE 1 | IFI27 gene expression by HIV infection status. The relative IFI27 fold change gene expression, compared to HIV seronegative controls, was quantified and calculated by qPCR and the 2^-ΔΔCT method, in whole blood of HIV seronegative (n = 35), HIV-2 (n = 43), HIV-1 (n = 39) and HIV-D (n = 14) infected individuals. The red line illustrates the geometric mean with confidence interval as error bars. IFI27 expression was log10-transformed prior to statistical comparison between groups using One-way ANOVA with Tukey's *post-hoc* test. ***p < 0.001.

correlated with pVL in both HIV-1 (r = 0.717, p < 0.001) and HIV-2 (r = 0.676 and p < 0.001) infection. In HIV-D infection, we did not observe any correlations between IFI27 expression and pVL or CD4% (**Table S2**) and further analyses within this group were not considered.

To determine the relative contribution of HIV type (HIV-1 or HIV-2), sex, age, pVL, and CD4% on IFI27 gene expression, we performed multiple linear regression. The overall regression was significant (p < 0.001, r^2 = 0.621) and IFI27 was found to be significantly predicted by HIV type (p = 0.019), CD4% (p = 0.008) and pVL (p < 0.001) when adjusting for age and sex (**Table S3**). Next, we investigated the interaction between HIV type and CD4%, and pVL, by multiple linear regression. At undetectable pVL levels, the level of IFI27 expression was found to be significantly higher in HIV-2 infected individuals compared with expression levels extrapolated for the HIV-1 infected individuals, both in the crude analysis (p = 0.036, **Figure 2A** and **Table S3**), and when adjusting for age and sex (p = 0.015, **Table S3**). No significant interaction was observed between HIV type and pVL (i.e. the slope of the regression line did not differ between the groups) in either crude (p = 0.148) or adjusted analysis (p = 0.108). For CD4%, there was no significant difference in level of IFI27 expression between the groups in either crude analysis (p = 0.126, **Figure 2B** and **Table S3**) or when adjusting for age and sex (p = 0.170, **Table S3**). Instead, the rate of IFI27 increase with CD4% decline was higher for HIV-2 as compared with HIV-1 infected individuals in crude analysis (p = 0.048, **Figure 2B** and **Table S3**), while this difference was lost when adjusting for age and sex (p = 0.094).

IFI27 Expression Is Increased in Both Viremic and Aviremic HIV-2 Infected Individuals

To further dissect the relationship between IFI27 expression and disease severity in HIV-2 infected individuals, we stratified this group by level of pVL. We compared the IFI27 expression in HIV-2 aviremic (pVL < 75 copies/ml, n = 30) and HIV-2 viremic individuals (pVL ≥ 75 copies/ml, n = 13) and found that aviremic individuals had 19.8 fold lower levels of IFI27 (p < 0.001, **Figure 3A**). However, even in the absence of quantifiable pVL, the IFI27 expression was still 2.2 fold higher in aviremic individuals compared to HIV seronegative individuals (n = 35, p = 0.049, **Figure 3B**). Next, we investigated if the IFI27 expression differed in HIV-2 aviremic individuals, i.e. individuals that naturally controlled their infection, and HIV-1 successfully treated individuals, i.e. individuals with a treatment-induced control of viremia. Here, we did not observe any significant difference in IFI27 expression between natural HIV-2 and treatment-induced HIV-1 control of viremia (p = 0.245, **Figure 3C**).

Finally, we set out to determine if IFI27 expression was correlated with plasma markers previously linked to immune activation and inflammation, viremia and disease progression, i.e. beta-2-microglobulin (b2m), soluble CD14 (sCD14), and IP-10 (also known as CXCL10) (17–19). Results showed that IFI27 was positively correlated with b2m, sCD14 and IP-10, (r = 0.724, p < 0.001; r = 0.710, p < 0.001; and r = 0.663, p < 0.001, respectively) in the studied HIV-2 infected individuals (**Figure S2** and **Table S2**).

DISCUSSION

In this study, comparing gene expression profiles of whole blood sampled from HIV seronegative and HIV-1, HIV-2 or dually HIV-1/HIV-2 infected individuals, IFI27, an IFN-I induced gene, was found to be the most differentially expressed. IFI27 was significantly upregulated in HIV-2, and even more so in HIV-1, chronically infected individuals as compared with HIV seronegative controls. Our exploration of variables associated with IFI27 expression levels, revealed that the IFI27 expression was associated with both pVL and CD4%, with the strongest association to pVL, when adjusting for HIV infection type, sex and age.

Importantly, individuals with aviremic HIV-2 infection also displayed elevated IFI27 expression levels, as compared with HIV seronegative individuals. Thus, despite the lack of viremia above 75 copies/ml, this group of aviremic HIV-2 infected individuals also presented with chronic innate immune activation, in our study reflected by elevated IFI27 expression. This observation is in line with our previous reports on elevated

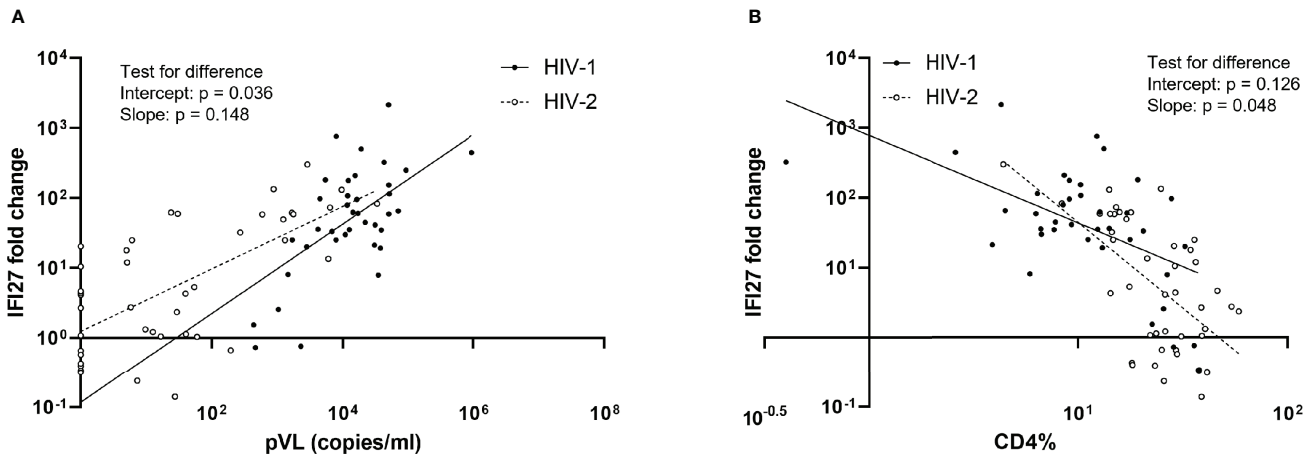

FIGURE 2 | Associations between IFI27 expression and plasma viral load (pVL) **(A)** and CD4% **(B)**. The relative IFI27 fold change gene expression, compared to HIV seronegative controls, was quantified and calculated by qPCR and the 2^-ΔΔCT method. IFI27 fold change, pVL and CD4% were log10-transformed prior to analysis. P-values for difference between HIV-1 (n = 39 for pVL and 38 for CD4%) and HIV-2 (n = 43 for both pVL and CD4%) in intercept and slope (i.e. the interaction between IFI27 and pVL or CD4%) were calculated by crude multiple linear regression analysis, without adjustment for sex and age. Additional results from these analyses are provided in **Table S3**.

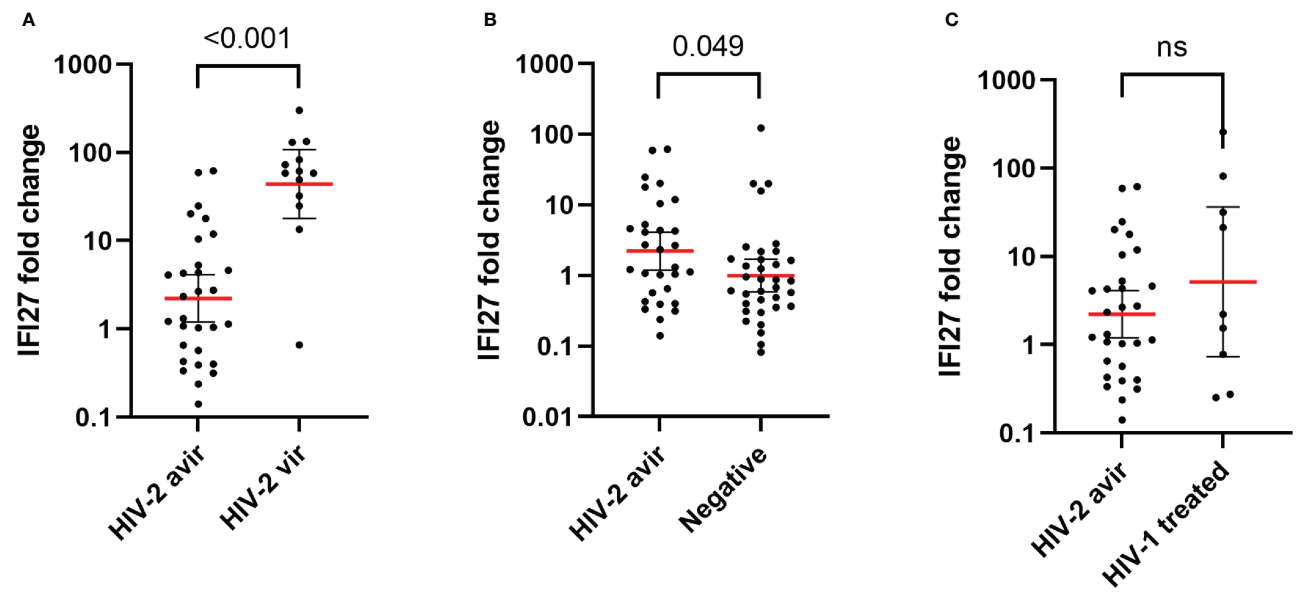

FIGURE 3 | IFI27 fold change expression in HIV-2 aviremic (n = 30) vs HIV-2 viremic (n = 13) **(A)**, HIV seronegative (n = 35) **(B)**, and HIV-1 successfully treated **(C)** (n = 9) individuals. The relative IFI27 fold change gene expression, compared to HIV seronegative controls, was quantified and calculated by qPCR and the 2^-ΔΔCT method. The red line illustrates the geometric mean with confidence interval as error bars. IFI27 expression was log10-transformed prior to statistical comparison between groups using t-test. ns = non significant.

frequencies of $CD4^+$ and $CD8^+$ T-cells expressing markers of immune activation and exhaustion in aviremic HIV-2 infected individuals (10, 12). Moreover, the strong associations between IFI27 expression and plasma inflammation markers, b2m, sCD14 and IP-10, suggest that IFI27 is part of a larger inflammatory network linked to disease in HIV-2 infection. Accordingly, this further supports that although level of viremia contributes significantly to the expression of IFI27,

other factors, such as infection duration, may be involved. Indeed, our multivariate analysis showed that, at undetectable pVL levels, the IFI27 expression level was higher in HIV-2 than extrapolated for HIV-1 infected individuals. Furthermore, in aviremic HIV-2 infected individuals we did not observe a difference in IFI27 expression between individuals supgrouped according to undetectable or unquantifiable pVL (data not shown). It has also been reported that HIV-1 viremic nonprogressors have lower levels of ISGs compared with rapid progressors (34). Further, it was recently demonstrated that ART treated HIV-1 infected immunological non-responders, (i.e. individuals under treatment with successfully suppressed pVL but whose $CD4^+$ T-cell count do not recover) had higher IFI27 levels as compared with immunological responders (35).

It has been suggested that the $CD4^+$ T-cell recovery upon treatment is lower in HIV-2 infected individuals compared to HIV-1 infected individuals (36). Clinical follow-up of treatment outcome based on $CD4^+$ T-cell count may therefore not be sufficient in HIV-2 infection. Since the HIV-2 aviremic individuals cannot be monitored by viral load measurements it would be valuable to identify other potential markers of disease progression and treatment outcome. Our data suggests that IFI27 could be such potential suitable marker to further explore in larger cohorts, both during disease progression and treatment.

In a study based on single-cell RNA sequencing, it was recently shown that IFI27, and other ISGs, were upregulated in the acute phase of HIV-1 infection (37). Of note, during SARS-CoV-2 infection, the ISG levels have been shown to be important determinants for the outcome in Covid-19, such that mild acute infections are characterized by a strong and transient expression of ISGs, whereas severe Covid-19 is characterized by a lower and sustained ISG expression (38). Such detailed description of how acute IFI27 levels translates to subsequent HIV-1 or HIV-2 disease progression is yet to be presented. Previous studies have shown that the upregulated expression of IFN-I is maintained during chronic HIV-1 infection (25). However, despite an expected antiviral effect of IFN-I and ISGs, chronic IFN-I expression has a seemingly limited impact on viral load and instead contributes to the systemic immune activation (25). Data from animal studies have shown that expression of various ISGs is upregulated in the chronic phase of nonpathogenic SIV infection, but to a lower level as compared to in pathogenic SIV infections (22–24). Our data demonstrates that HIV-2, an infection that presents as an intermediate between pathogenic and nonpathogenic HIV-1/SIV infections (6, 23), is also associated with upregulated IFI27 expression, but to a lower level than in HIV-1 infection. Thus, we speculate that the inability of the adaptive immune responses to durably control virus replication in HIV infection permits ongoing innate immune activation, in turn driving the disease progression in infected individuals. We have previously shown that HIV-2 delays HIV-1 disease progression in dually infected individuals and that this effect appears to be established during early infection (4, 5). Thus, it would have been interesting to study if IFN-I signaling is linked to this observation. However, this merits a separate investigation and could not be addressed in the current study comprised of a limited number of HIV-D infected individuals sampled during the chronic infection phase.

Both HIV-1 and HIV-2 infection results in the loss and dysregulation of $CD4^+$ T cell (1). However, other target cells, including $CD4^+$ plasmacytoid dendritic cells (pDCs), have also been shown to be dysregulated (39–41). Moreover, in both SIV and HIV infections, pDCs have been shown to be the major source of IFN-alpha (a type I IFN) (23). Still, it has been reported that HIV-2, in contrast to HIV-1, favors pDC to develop into a antigen presenting phenotype, rather than becoming excessive IFN-alpha producers (42). It has also been suggested that HIV-2, *via* the expression of vpx may contribute to productive infection of DCs *via* blockade of the SAMHD1 (43, 44). Thus, it is tempting to speculate that the early and productive infection of pDCs in acute HIV-2 infection results in a balanced IFN-alpha response, combined with efficient antigen presentation, subsequently contributing to a less pathogenic chronic infection. Furthermore, gene expression analysis of monocytes from chronically HIV-1 infected individuals identified IFN-alpha as the main driver of the monocyte gene expression profile (45). Interestingly, IFI27 was found to be the most upregulated gene, especially in the HIV-1 infected individuals with high pVL (45). Monocytes in chronic HIV-1 and HIV-2 infection have also been shown to display an activated phenotype (45, 46) and to be desensitized to TLR-stimulation (45). These findings are in line with data previously reported by us showing a defective TLR responsiveness of cells in whole blood from both HIV-1 and HIV-2 infected individuals (47). Taken together these studies point to an important role of myeloid cells in the regulatory network between HIV and IFN-I. However, this network is complex, and the beneficial or detrimental effects of IFN-I signaling is likely determined by numerous factors, including timing, i.e. acute vs chronic infection phase. While both administration of IFN-I and inhibition of its signaling pathways has been therapeutically pursued, the clinical impact has so far been limited (48).

In conclusion, our current findings suggest a scenario in which the level of IFN-I signaling, here reflected by IFI27 expression, is a key feature in determining the pathogenesis of both HIV-1 and HIV-2 infections. We believe that a better understanding of the factors involved in shaping the IFN-I signaling in response to both HIV-1 and HIV-2 infections could unravel new therapeutics and treatment monitoring approaches.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.ncbi.nlm.nih.gov/geo/, GSE200606.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The National Ethics Committee, Ministry of Public Health in Guinea-Bissau and the Ethical Committee at Lund university. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AP designed and conducted the RNA extractions and qPCR analyses, interpreted the data, and drafted the manuscript. SV designed, conducted, and summarized the bioinformatics analyses. EJ conducted the Luminex analyses. P-EI contributed substantially to the statistical analyses. JL, FM, and HN coordinated the study cohort. JL, FM, JE, HN, PM, and MJ contributed to the study design and results interpretation, and critically reviewed the manuscript. AB was medically responsible for the study participants. MJ contributed to the study design, interpreted data, revised and critically reviewed the manuscript. AP, PM, and MJ conceptualized the study. All authors read and approved the submitted version.

FUNDING

This research was funded by grants given to MJ from the Swedish Research Council (grant number 2016-02285, 2019-01439) and The Swedish Fund for Research without Animal Experiments (N2019-0009, F2021-0010). PM was supported by the Swedish Research Council (grant numbers 2019-05235 and 2020-02344) and Österlund Foundation. JE received funding from the Swedish Research Council (grant number 2020-06262).

ACKNOWLEDGMENTS

We thank SCIBLU Genomics Center at Lund University for technical support concerning the microarray. The listed authors and the members of the Sweden Guinea-Bissau Cohort Research (SWEGUB CORE) group, including Babetida N'Buna, Antonio Biague, Ansu Biai, Cidia Camara, Zacarias Jose da Silva, Joakim Esbjörnsson, Marianne Jansson, Emil Johansson, Sara Karlson, Jacob Lopatko Lindman, Patrik Medstrand, Fredrik Månsson, Hans Norrgren, Angelica A. Palm, Gülsen Özkaya Sahin and Sten Wilhelmson are indebted to the staff of the Police Clinics and the National Public Health Laboratory (LNSP) in Bissau, Guinea-Bissau.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fviro.2022.929053/full#supplementary-material

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