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ORIGINAL RESEARCH

The -1082 A allele of the *interleukin-10* single nucleotide polymorphism -1082 G/A is associated with hepatitis virus co-infection in Indonesian Javanese HIV patients

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Objective: This study was conducted to determine the distribution of the single nucleotide polymorphism (SNP) at position -1082 of the proximal promoter region of the *interleukin* (*IL*)-10 gene and its association with hepatitis virus co-infection in Indonesian Javanese human immunodeficiency virus (HIV)-infected patients.

Methods: Blood samples were collected from 156 Indonesian Javanese HIV-infected patients; tested with serological and molecular assays for hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV); and subjected to SNP -1082 G/A polymorphism analysis.

Results: Hepatitis B surface antigen (HBsAg) (+)/HBV DNA (+), HBsAg (−)/HBV DNA (+), anti-HCV antibodies (+)/HCV RNA (+), and anti-HCV antibodies (−)/HCV RNA (+) were detected from all of HIV-infected individuals at rates of 3.8% (6/156), 0.6% (1/156), 16.0% (25/156), and 11.5% (18/156), respectively. The frequencies of -1082 GG, -1082 GA, and -1082 AA were 14.7% (23/156), 60.3% (94/156), and 25% (39/156), respectively. HBV co-infection was found only in -1082 A allele carriers, and these patients also showed higher rates of HCV co-infection (odds ratio: 2.24, 95% confidence interval: 1.22–4.10, P=0.009).

Conclusion: The -1082 A allele was associated with HBV and HCV co-infection in Indonesian Javanese HIV patients.

Keywords: *IL-10* -1082, HIV, HBV, HCV, Indonesia

Introduction

Human immunodeficiency virus (HIV) co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) has become a major concern worldwide. Approximately 10% of people infected with HIV are estimated to be co-infected with HBV, and 15%–30% are estimated to be co-infected with HCV.[1,2] In Indonesia, HIV/HBV co-infection rates reportedly range from 0% to 27.1%, while HIV/HCV rates range from 4% to 34.1%.[3–6] HIV, HBV, and HCV infections are persistent, and co-infection by these pathogens amplifies the burden of disease.[1,2,7]

The persistence of HIV, HBV, and HCV infections has been associated with immunosuppression during the initial immune response.[7] Interleukin (IL)-10, a cytokine capable of indirect repression of the T helper 1 (Th1) response, is a key player in the immunosuppression that directly leads to viral persistence.[8,9] IL-10 can be induced by pathogen or host factors, and the levels of IL-10 produced may vary among individuals.[10,11]

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A single nucleotide polymorphism (SNP) at position -1082 of the proximal promoter region of the *IL-10* gene (rs1800896) has been associated with differing levels of IL-10 production across three genotypes (-1082 GG, -1082 GA, and -1082 AA).[12] High production of IL-10 is associated with the -1082 GG genotype; low production of IL-10 is associated with the -1082 AA genotype; and IL-10 production in the -1082 GA genotype falls between the two extremes.[12] The -1082 AA genotype has also been associated with HIV type 1 (HIV-1) acquisition and cluster differentiation 4+ (CD4+) Th cell decline acceleration rates in late stages of the disease.[13,14] In the acute phase of HIV-1 infection, IL-10 levels may give way to viral replication by dampening the innate and adaptive immune responses, whereas in chronic HIV-1 infection, IL-10 may be protective by reducing immune activation and inhibiting HIV-1 replication in macrophages.[15] The *IL-10* SNP -1082 has also repeatedly been associated with HBV and HCV infections.[16–21] However, no study has been performed to assess the association of *IL-10* SNP -1082 with hepatitis virus co-infection in HIV-infected patients. Moreover, data on *IL-10* SNP -1082 allele frequencies in Indonesians are lacking.

Materials and methods
Study population
Since 2009, our research group has conducted a molecular epidemiology study of human blood-borne viruses by collecting epidemiological data and blood samples from high-risk communities in the Central Java province, Indonesia. From November 2011 to February 2012, Indonesian Javanese adult HIV patients in the Voluntary Counseling and Testing Clinic at the Dr Moewardi General Hospital in Surakarta (n=156) were enrolled in the study. Blood samples collected from these patients were subjected to hematological and CD4+ T cells assays, fractionated, aliquoted, and kept frozen until analysis. Approval was obtained from the institutional ethical committee review boards of the Faculty of Medicine of Sebelas Maret University and Dr Moewardi General Hospital, Surakarta, Indonesia. Written informed consent was obtained from all individuals participating in the study. All procedures were conducted according to the principles of the Declaration of Helsinki.

Blood sample collection and screening for infection
Blood samples were obtained from each participant in ethylene diamine-tetra-acetic acid (EDTA) tubes. The blood samples were also screened for HBV, HCV, and hepatitis D virus (HDV) by serological assays, as described previously.[5]

Briefly, a SERATEC Hepatitis B Quick Test (Gesellschaft für Biotechnologie GmbH, Göttingen, Germany) was used to detect hepatitis B surface antigen (HBsAg). Ortho HCV PA II (Ortho Diagnostics, Tokyo, Japan) and HDV Ab ELISA kits (Diagnostic Automation, Calabasas, CA, USA) were used to detect anti-HCV and anti-HDV antibodies, respectively. All assays were performed according to the manufacturer's instructions. All samples were tested in duplicate at minimum.

Nucleic acid extraction and molecular detection
Viral nucleic acid extraction and molecular detection were performed as described previously.[5] Briefly, nucleic acid (DNA and RNA) was extracted from 200 µL of each plasma sample using the PureLink Viral RNA/DNA Kit (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. The nucleic acids were then aliquoted, and one aliquot was reverse-transcribed according to the Superscript III First-Strand cDNA Synthesis Supermix Kit protocol using random hexamers (Invitrogen). Molecular detection was performed by polymerase chain reaction (PCR) using the AmpliTaq Gold® 360 DNA Polymerase Kit (Invitrogen). A portion of the HIV *gag* gene encoding the *p24* region was amplified. A portion of the *HBsAg* gene was amplified by nested PCR. A portion of the *NS5B* region and a portion of the *E1–E2* region, including hyper variable region-1 of the HCV genome, were amplified by nested PCR. HDV RNA was detected by the amplification of a 400-nucleotide (nt)-long region of the HDV genome proposed for the classification of HDV genotypes. Internal amplification controls were included to exclude any false-negative results. The corresponding positive controls and one negative control (sterile water) were included for each group simultaneously. To prevent PCR contamination, the reagent preparation, sample processing, and nested PCR assays were performed in rooms separate from those where the amplified products were analyzed. Aerosol-resistant pipette tips were used throughout the assays. The PCR products were subjected to electrophoresis in 2% agarose gels, which were stained with ethidium bromide and visualized under ultraviolet illumination. The specificity was confirmed by sequencing the amplicons. All samples were tested in duplicate at minimum.

Detection of SNP -1082 G/A
Genomic DNA from each patient was isolated using the High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany). For SNP -1082 G/A polymorphism analysis, genomic samples were genotyped by PCR using the

FastStart HiFi PCR System dNTPack (Roche Diagnostics), with primer pairs previously described.[22] The PCR products were subjected to electrophoresis in 2% agarose, stained with ethidium bromide, and visualized under ultraviolet illumination. To avoid false negatives, an internal control primer, to amplify a 429-bp region of the *human growth hormone* (*HGH*) gene, was used for all PCR reactions.[22] All samples were tested twice at minimum.

IL-10 plasma measurements

The IL-10 levels in the plasma samples were measured using a Human IL-10 Immunoassay Quantikine ELISA (R&D Systems, Minneapolis, MN, USA). The cytokine concentration in the samples was calculated in pg/mL using recombinant human IL-10 (R&D Systems) as a standard. The absorbance was measured at 450 nm with an ELISA plate reader, and the reading at 540 nm was subtracted to correct for optical imperfections in the plate. All samples were tested in triplicate at minimum to calculate the mean level of IL-10 in each sample.

Statistical analysis

Statistical analysis was performed using SPSS version 20 software (SPSS, Chicago, IL, USA). A 95% confidence interval (CI) was used for all data analysis. Independent sample *t*-tests and Mann–Whitney *U* tests were used to compare the means of the data. Chi-square or Fisher's exact test, as indicated, was used to compare qualitative data. *P*-values less than 0.05 were considered significant.

Results

General characteristics of the study population

This study included 156 Indonesian Javanese HIV-infected patients, whose general characteristics are tabulated in Table 1. The samples were derived from 86 males (55.1%) and 70 females (44.9%). The mean age of the patients was 36.9±8.7 years, ranging from 19 years to 72 years. Most of the patients received combination of zidovudine, lamivudine, and nevirapine as standard regimen of antiretroviral therapy (ART) in the Voluntary Counseling and Testing Clinic at the Dr Moewardi General Hospital in Surakarta. Twenty of patients (8 males, 12 females) reported that they had not started ART. The levels of IL-10 were not significantly different between the antiretroviral-treated and untreated patients (*P*=0.782). Eosinophilia was found predominantly in male patients (odds ratio [OR]: 2.49, 95% CI: 1.30–4.76, *P*=0.006). Unless otherwise stated, no statistical associations could be drawn.

HIV and hepatitis co-infection in patients

HIV RNA was detected in 26.3% (41/156) of the samples (Table 2), more frequent (70.0%, 14/20) in

Table 1 Hematological characteristics of the patients

Hematological characteristics	Sex		*IL-10* SNP -1082			Total
	Male	**Female**	**-1082 GG**	**-1082 GA**	**-1082 AA**	
Elevated IL-10	25.6 (22/86)	20.0 (14/70)	13.0 (3/23)	25.5 (24/94)	23.1 (9/39)	23.1 (36/156)
Anemia	50.0 (43/86)	50.0 (35/70)	56.5 (13/23)	48.9 (46/94)	48.7 (19/39)	50.0 (78/156)
Leukocytopenia	37.2 (32/86)	48.6 (34/70)	34.8 (8/23)	36.2 (34/94)	61.5 (24/39)	42.3 (66/156)
Leukocytosis	1.2 (1/86)	1.4 (1/70)	0.0 (0/23)	2.1 (2/94)	0.0 (0/39)	1.3 (2/156)
Eosinophilia	65.1 (56/86)	42.9 (30/70)	56.5 (13/23)	57.4 (54/94)	48.7 (19/39)	55.1 (86/156)
Basophilia	1.2 (1/86)	0 (0/70)	0.0 (0/23)	1.1 (1/94)	0.0 (0/39)	0.6 (1/156)
Neutropenia	51.2 (44/86)	44.3 (31/70)	65.2 (15/23)	47.9 (45/94)	38.5 (15/39)	48.1 (75/156)
Neutrophilia	1.2 (1/86)	4.3 (3/70)	4.3 (1/23)	1.1 (1/94)	5.1 (2/39)	2.6 (4/156)
Lymphocytopenia	36.0 (31/86)	30.0 (21/70)	26.1 (6/23)	34.0 (32/94)	35.9 (14/39)	33.3 (52/156)
Lymphocytosis	16.3 (14/86)	17.1 (12/70)	26.1 (6/23)	14.9 (14/94)	15.4 (6/39)	16.7 (26/156)
Thrombocytopenia	1.2 (1/86)	4.3 (3/70)	0.0 (0/23)	4.3 (4/94)	0.0 (0/39)	2.6 (4/156)
Thrombocytosis	16.3 (14/86)	12.9 (9/70)	21.7 (5/23)	12.8 (12/94)	15.4 (6/39)	14.7 (23/156)
CD4+ T helper						
≤21%	67.4 (58/86)	57.1 (40/70)	73.9 (17/23)	56.4 (53/94)	71.8 (28/39)	62.8 (98/156)
>21%	32.6 (28/86)	42.9 (30/70)	26.1 (6/23)	43.6 (41/94)	28.2 (11/39)	37.2 (58/156)
CD4+ T helper count						
≤350 cells/mm³	68.6 (59/86)	58.6 (41/70)	78.3 (18/23)	57.4 (54/94)	69.2 (27/39)	63.5 (99/156)
>350 cells/mm³	31.4 (27/86)	41.4 (29/70)	21.7 (5/23)	42.6 (40/94)	30.8 (12/39)	36.5 (57/156)

Notes: Values are presented as percents (n/total). Normal ranges for the hematologic parameters elaborated in the table are as follows: IL-10, 0–9.9 pg/mL; non-anemia hemoglobin, male ≥13 g/dL, female ≥12 g/dL; leukocytes, 4,500–11,000 cells/μL; eosinophils, 0%–4%; basophils, 0%–2%; neutrophils, 55%–80%; lymphocytes, 22%–44%; thrombocytes, 140,000–450,000.
Abbreviations: CD4+, cluster differentiation 4+; *IL-10*, interleukin-10; SNP, single nucleotide polymorphism.

Table 2 Distribution of serological and virological markers for HIV progression, HIV/HBV, and HIV/HCV co-infection among -1082 GG, -1082 GA, and -1082 AA genotypes

Serological and virological markers	IL-10 SNP -1082			Total
	GG (n=23)	GA (n=94)	AA (n=39)	
HIV RNA (+)	4.3 (1/23)	28.7 (27/94)	33.3 (13/39)	26.3 (41/156)
HBsAg (+)	0 (0/23)	4.3 (4/94)	7.7 (3/39)	4.5 (7/156)
HBV DNA (+)	0 (0/23)	4.3 (4/94)	7.7 (3/39)	4.5 (7/156)
Anti-HCV antibodies (+)	4.3 (1/23)	21.3 (20/94)	38.5 (15/39)	23.1 (36/156)
HCV RNA (+)	4.3 (1/23)	20.2 (19/94)	59.0 (23/39)	27.6 (43/156)
HBsAg (+) + HBV DNA (+)	0 (0/23)	3.2 (3/94)	7.7 (3/39)	3.8 (6/156)
HBsAg (−) + HBV DNA (+)	0 (0/23)	1.1 (1/94)	0 (0/39)	0.6 (1/156)
Anti-HCV antibodies (+) + HCV RNA (+)	0 (0/23)	13.8 (13/94)	30.8 (12/39)	16.0 (25/156)
Anti-HCV antibodies (−) + HCV RNA (+)	4.3 (1/23)	10.6 (10/94)	17.9 (7/39)	11.5 (18/156)
HIV RNA (+) + HBsAg (+)	0 (0/23)	1.1 (1/94)	5.1 (2/39)	1.9 (3/156)
HIV RNA (+) + HBV DNA (+)	0 (0/23)	1.1 (1/94)	5.1 (2/39)	1.9 (3/156)
HIV RNA (+) + HBsAg (+) + HBV DNA (+)	0 (0/23)	1.1 (1/94)	5.1 (2/39)	1.9 (3/156)
HIV RNA (+) + anti-HCV antibodies (+)	0 (0/23)	2.1 (2/94)	7.7 (3/39)	3.2 (5/156)
HIV RNA (+) + HCV RNA (+)	0 (0/23)	1.1 (1/94)	5.1 (2/39)	1.9 (3/156)
HIV RNA (+) + anti-HCV antibodies (+) + HCV RNA (+)	0 (0/23)	1.1 (1/94)	2.6 (1/39)	1.3 (2/156)

Note: Values are presented as percents (n/total).
Abbreviations: DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL-10, interleukin-10; SNP -1082, single nucleotide polymorphism -1082; RNA, ribonucleic acid.

antiretroviral-untreated patients (OR: 9.42, 95% CI: 3.31–26.79, $P<0.001$), or in antiretroviral-treated for 2 years or less (26.3%, 25/95, OR: 6.96, 95% CI: 1.57–30.98, $P=0.011$) (Table 3). HBsAg (+)/HBV DNA (+) and HBsAg (−)/HBV DNA (+) results were detected in 3.8% (6/156) and 0.6% (1/156) of the samples, respectively (Table 2). The anti-HCV antibody positive rate was 23.1% (36/156), and this finding was significantly more predominant in male patients (OR: 2.20, 95% CI: 0.99–4.87, $P=0.049$). The HCV RNA positive rate was 27.6% (43/156) and also occurred more frequently in male patients (OR: 1.54, 95% CI: 0.75–3.17, $P=0.235$). Patients with elevated IL-10 were more likely to present with HCV co-infection, indicated by

the presence of HCV RNA (OR: 2.76, 95% CI: 1.26–6.04, $P=0.010$). HDV was not detected in any patient.

Genotypic distribution and hematologic findings for IL-10 SNP -1082

In our study population, the frequency of the -1082 GA genotype was the highest (60.3%, 94/156), followed by that of the -1082 AA (25%, 39/156) and -1082 GG genotypes (14.7%, 23/156), respectively, which defied Hardy–Weinberg equilibrium ($P=0.007$). Leukocytopenia (OR: 1.38, 95% CI: 0.83–2.30, $P=0.215$), lymphocytopenia (OR: 1.10, 95% CI: 0.65–1.86, $P=0.725$), a CD4+ Th cell frequency >21% (OR: 1.05, 95% CI: 0.63–1.74, $P=0.862$), and a CD4+

Table 3 ART and co-infection status among -1082 GG, -1082 GA, and -1082 AA genotypes

IL-10 SNP -1082	ART status	CD4+ T helper		HIV RNA (+)	Co-infection status			
		≤21%	≤350 cells/mm³		HBsAg (+)	HBV DNA (+)	Anti-HCV antibodies (+)	HCV RNA (+)
GG (n=23)	≤2 years (n=95)	15.3 (15/98)	17.2 (17/99)	2.4 (1/41)	0.0 (0/7)	0.0 (0/7)	2.8 (1/36)	2.3 (1/43)
	>2 years (n=41)	2.0 (2/98)	1.0 (1/99)	0.0 (0/41)	0.0 (0/7)	0.0 (0/7)	0.0 (0/36)	0.0 (0/43)
	Untreated (n=20)	0.0 (0/98)	0.0 (0/99)	0.0 (0/41)	0.0 (0/7)	0.0 (0/7)	0.0 (0/36)	0.0 (0/43)
GA (n=94)	≤2 years (n=95)	35.7 (35/98)	36.4 (36/99)	34.1 (14/41)	28.6 (2/7)	28.6 (2/7)	27.8 (10/36)	16.3 (7/43)
	>2 years (n=41)	13.3 (13/98)	15.2 (15/99)	4.9 (2/41)	28.6 (2/7)	28.6 (2/7)	16.7 (6/36)	18.6 (8/43)
	Untreated (n=20)	5.1 (5/98)	3.0 (3/99)	26.8 (11/41)	0 (0/7)	0 (0/7)	11.1 (4/36)	9.3 (4/43)
AA (n=39)	≤2 years (n=95)	17.3 (17/98)	18.2 (18/99)	24.4 (10/41)	28.6 (2/7)	28.6 (2/7)	19.4 (7/36)	23.3 (10/43)
	>2 years (n=41)	9.2 (9/98)	7.1 (7/99)	0.0 (0/41)	14.3 (1/7)	14.3 (1/7)	22.2 (8/36)	25.6 (11/43)
	Untreated (n=20)	2.0 (2/98)	2.0 (2/99)	7.3 (3/41)	0.0 (0/7)	0.0 (0/7)	0.0 (0/36)	4.7 (2/43)

Note: Values are presented as percents (n/total).
Abbreviations: ART, antiretroviral therapy; CD4+, cluster differentiation 4+; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL-10, interleukin-10; RNA, ribonucleic acid; SNP, single nucleotide polymorphism.

Th cell count >350 cells/mm^3 (OR: 1.03, 95% CI: 0.62–1.71, *P*=0.918) were frequently found in the -1082 A allele carriers. The mean percentage and absolute counts of CD4+ Th cells in patients with the -1082 GG genotype (14.6%, standard deviation 7.7; 262.0 cells/mm^3, standard deviation 154.6) were lower (*P*<0.001) compared with that in the other genotypes. IL-10 plasma levels were not associated with the genotype variations of *IL-10* SNP -1082.

Associations between *IL-10* SNP -1082 genotypes and HIV/HBV and HIV/HCV co-infections

HIV RNA was detected more frequent in -1082 A allele carriers (-1082 GA and AA) (OR: 1.37, 95% CI: 0.78–2.40, *P*=0.277, Table 2). HBV co-infection was only found in -1082 A allele carriers. One patient with the -1082 GA genotype was HBsAg-negative but HBV DNA-positive. Anti-HCV antibodies (OR: 1.63, 95% CI: 0.89–3.00, *P*=0.115) and HCV RNA (OR: 2.24, 95% CI: 1.22–4.10, *P*=0.009) were also predominantly found in -1082 A allele carriers. Anti-HCV antibody (+)/HCV RNA (+) results were detected only in -1082 A allele carriers. To confirm the present finding, we tested the Indonesian Javanese "hepatitis virus positive only" samples collected from our previous study.[4,5] In those samples, HBsAg positive (n=23) and HBV DNA (n=20) were only found in -1082 allele carriers. Anti-HCV antibodies (53.2%, 149/280) and HCV RNA (19.6%, 55/280) were also predominantly found in -1082 A allele carriers (OR: 1.61, 95% CI: 1.11–2.34, *P*=0.012 and OR: 2.14, 95% CI: 1.17–3.91, *P*=0.014, respectively) in those samples.

Discussion

In our study, the -1082 GA genotype was found in the highest frequency, followed by -1082 AA and GA, which defied Hardy–Weinberg equilibrium. This finding also differs from a previous study involving a Thai population, in which -1082 AA was found in the highest frequency (87.3%).[23] Moreover, the -1082 AA genotype frequency was reported to be extremely high in Japanese (92.4%) and Chinese populations (92.3%).[17,21] Ethnic differences between study populations may be one of the reasons for these distinctive results. However, our results contribute additional information regarding the distribution of SNP -1082 alleles in Asia, particularly Southeast Asia, as data on the distribution of SNP -1082 genotypes across ethnic groups in this region remain extremely limited.

The *IL-10* SNP -1082 polymorphism was analyzed for its association with the most common biomarker of disease progression, CD4+ Th cell levels. The mean CD4+ Th cell percentages in patients with the -1082 GG genotype were significantly lower than those in -1082 A allele carriers (-1082 GA and -1082 AA), consistent with a prior study.[24] Thus, the *IL-10* SNP -1082 may have underlying but as-yet-undetermined epigenetic or environment modulatory factors, or this SNP may be in linkage disequilibrium (LD) with other genes, with a modulatory effect on attenuating CD4+ T cell decline.[24]

The levels of plasma IL-10 were not associated with the -1082 SNP genotypes (GG, GA, and AA), consistent with a previous study.[25] However, the elevation of IL-10 was associated with HIV/HCV co-infection, indicated by the presence of HCV RNA, and is also consistent with a previous study.[26] Upregulation of IL-10 expression has been associated with the interaction between the HCV core protein and Toll-like receptor-2 and has been shown to be induced by non-structural protein 3 in macrophages and dendritic cells.[26,27] Moreover, IL-10 was significantly associated with preserved levels of CD4 T cells in HIV patients, indicating that HCV co-infection may be contributing to unbalanced persistent inflammation.[28]

Previously, the -1082 GG genotype was reported as a host genetic factor in the susceptibility to HBV infection in the Egyptian population.[29] However, in a meta-analysis performed by Lu et al, the G allele of the *IL-10* SNP -1082 was not associated with HBV infection in the Asian population.[30] In the present study, all HBV co-infections were found only in -1082 A allele carriers (-1082 AA and -1082 GA), suggesting that the -1082 A allele is associated with HBV infection, as reported previously in non-HIV-infected patients.[17,31,32] This same polymorphism may play a different role in disease susceptibility in different ethnic populations, as different populations often have different LD patterns.[29] However, HCV co-infections were also found to be predominant in -1082 A allele carriers, consistent with previous studies performed in HCV-mono-infected Chinese populations,[33,34] suggesting a potential role for the -1082 allele in hepatitis virus susceptibility in Indonesian Javanese patients.

Conclusion

In summary, -1082 A allele carriers (-1082 GA and AA), particularly Indonesian Javanese patients, showed increased rates of HIV/HBV and HIV/HCV co-infections. Although this study focused on a relatively small number of individuals, these findings contribute to evidence of the presence of genetic variants important for predicting host susceptibility to hepatitis virus co-infection in HIV patients.

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Disclosure

The authors report no conflicts of interest in this work.

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