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No Association of *IFNL4* Genotype With Opportunistic Infections and Cancers Among Men With Human Immunodeficiency Virus 1 Infection

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Background. *IFNL4* genetic variants that are strongly associated with clearance of hepatitis C virus have been linked to risk of certain opportunistic infections (OIs) and cancers, including Kaposi sarcoma, cytomegalovirus infection, and herpes simplex virus infection. As the interferon (IFN) λ family plays a role in response to viral, bacterial, and fungal infections, *IFNL4* genotype might affect risk for a wide range of OIs/cancers.

Methods. We examined associations between genotype for the functional *IFNL4* rs368234815 polymorphism and incidence of 16 OIs/cancers among 2310 men with human immunodeficiency virus (2038 white; 272 black) enrolled in the Multicenter AIDS Cohort Study during 1984–1990. Our primary analyses used Cox proportional hazards models adjusted for self-reported racial ancestry to estimate hazard ratios with 95% confidence intervals, comparing participants with the genotypes that generate IFN-λ4 and those with the genotype that abrogates IFN-λ4. We censored follow-up at the introduction of highly effective antiretroviral therapies.

Results. We found no statistically significant association between *IFNL4* genotype and the incidence of Kaposi sarcoma (hazard ratio, 0.92 [95% confidence interval, .76–1.11]), cytomegalovirus infection (0.94 [.71–1.24]), herpes simplex virus infection (1.37 [.68–2.93]), or any other OI/cancer. We observed consistent results using additive genetic models and after controlling for CD4 cell count through time-dependent adjustment or restriction to participants with a low CD4 cell count.

Conclusions. The absence of associations between *IFNL4* genotype and these OIs/cancers provides evidence that this gene does not affect the risk of disease from opportunistic pathogens.

Keywords. cytomegalovirus; genetics; herpes simplex virus; interferon λ; Kaposi sarcoma.

Variations in the human genome may influence susceptibility to infectious diseases [1–3]. Genotype for a dinucleotide frameshift variant (rs368234815) in the interferon (IFN) λ 4 gene (*IFNL4*) is a robust predictor of hepatitis C virus (HCV) clearance [4, 5]. The ancestral *IFNL4*-ΔG allele creates the open reading frame for full-length IFN-λ4, whereas the derived allele (*IFNL4*-TT) abrogates the protein [4]. Thus, IFN-λ4 is generated only by individuals who carry ≥1 copy of *IFNL4*-ΔG. There is evidence for strong evolutionary selection against *IFNL4*-ΔG, as the frequency of this allele varies markedly by ancestry; about 95% of Africans, about 54% of Europeans, and about 13% of Asians carry ≥1 copy of *IFNL4*-ΔG [4, 6, 7]. Given that HCV usually results in a chronic infection with limited impact on reproductive fitness, it is unlikely that HCV drove this selection [8].

IFN-λ proteins protect against infectious agents at tissue barriers [9–13]. IFN-λ–induced signaling leads to induction of numerous IFN-stimulated genes [14–16]. Animal models have shown a potential protective role of IFN-λ against viral [9–12, 17–21] and fungal infections [22]. Conversely, IFN-λ increases *Staphylococcus* and *Pseudomonas* levels in mice [23]. Thus, IFN-λ proteins may potentially protect against or promote infection with an array of agents. Knowledge regarding the range of expression of IFN-λ4 remains limited, and *IFNL4* rs368234815 does not abrogate expression of IFN-λ1-3; however, the strong genetic selection for *IFNL4*-TT supports the hypothesis that IFN-λ4 affects response to infectious agents other than HCV.

Immunocompromised individuals are at high risk of developing opportunistic infections (OIs) and certain virus-associated cancers. Most previous studies that examined

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the relationship between *IFNL4*-related variants and human immunodeficiency virus 1 type 1 (HIV-1) infection failed to detect an association with overall disease progression [24], but *IFNL4* genotype has been reported to be associated with certain HIV-1 related OIs/cancers. One group found that genotype for an *IFNL4* variant was associated with risk of developing Kaposi sarcoma (KS) [25]. Two groups reported associations between *IFNL4* variants and risk of cytomegalovirus disease [26, 27]. Reports for an association with herpes simplex virus (HSV) disease have yielded mixed results [28–30].

The Multicenter AIDS Cohort Study (MACS), which is now part of the MACS/Women's Interagency HIV Study (WIHS) Combined Cohort Study, is a study of men at risk for or infected with HIV-1. The study was begun in 1984, before the availability of highly effective antiretroviral therapy (ART), and its participants had a high incidence of KS and OIs caused by a wide range of pathogens. Here we examine the association between *IFNL4* genotype and the development of OIs/cancers in men with HIV-1 infection enrolled in MACS, seeking to replicate previous findings and assess whether the *IFNL4* genotype is associated with the risk of other OIs/cancers.

METHODS

Study Population

MACS is a prospective study of men who have sex with men enrolled at 4 US sites (Baltimore, Maryland; Chicago, Illinois; Pittsburgh, Pennsylvania; and Los Angeles, California) [31]. After an initial (baseline) study visit, participants are seen every 6 months. Each visit involves administration of questionnaires, a physical examination, and collection of a blood sample. Diagnoses of OIs and cancers are recorded, and the CD4 lymphocyte count is measured at each visit. In addition to study visits, information is also collected through other methods, such as telephone calls or a mailed questionnaire to determine vital status and new diagnoses. If a participant can no longer be reached, attempts are made to acquire information from contacts named by the participant, AIDS registries, the National Death Index, and other sources [32]. Medical records are reviewed to confirm reported diagnoses. An institutional review board at each study site has approved the MACS. Written informed consent was obtained from all participants before enrollment.

For the present analysis, we examined data from 2310 participants with HIV-1 infection who enrolled during the first 2 waves of the study (1984–1985 or 1987–1990), including those who were infected with HIV-1 at study entry (seroprevalent; 80.3%) and those who acquired the virus after enrollment (seroconverter; 19.7%). The analysis was restricted to men for whom an *IFNL4* genotype result was available and whose self-reported race was either white or black, including those of Hispanic ethnicity (Supplementary Figure 1). Individuals of other racial/ethnic groups were too few for meaningful analysis.

OIs and Cancers

We examined 16 outcomes. The primary analysis considered 10 OI/cancer diagnoses selected a priori based on estimated statistical power (minimal detectable hazard ratio [HR] ≥3.0 at 90% power) and biological plausibility. Those diagnoses were KS, cytomegalovirus disease (including retinitis), non-Hodgkin lymphoma, chronic mucocutaneous herpes simplex, *Pneumocystis* pneumonia, *Candida* esophagitis, cryptococcal infection (neuroinvasive), toxoplasmosis, cryptosporidiosis, and atypical mycobacteria. We also performed exploratory analyses for 6 conditions with either low statistical power (progressive multifocal leukoencephalopathy, recurrent pneumonia, pulmonary tuberculosis, and histoplasmosis) or no clear infectious cause other than HIV-1 infection (wasting syndrome and dementia).

Laboratory Methods

Genotypes for the *IFNL4* rs368234815 and rs117648444 variants were determined using the Illumina Infinium BeadChips version 1 Multi-Ethnic Global Array (MEGA) with genotypes imputed to the TopMed reference panel by using minimac4 on the Michigan Imputation server. Genotyping was performed using Illumina GenomeStudio and PLINK (version 1.90) in the laboratory of Steven Wolinsky of Northwestern University (database of Genotypes and Phenotypes [dbGaP] study accession no. phs002226.v1.p1).

Statistical Methods

We first examined the overall distribution of *IFNL4* genotypes, stratified by race, examining whether the genotype proportions were inconsistent with Hardy-Weinberg equilibrium (HardyWeinberg package; R 4.1.0 software) [33]. We used χ^2 tests to determine whether the frequency of ever having a CD4 cell count <200/μL differed by genotype.

We calculated the unadjusted incidence rate for the first occurrence of each OI/cancer, by *IFNL4* genotype and overall. Follow-up started at enrollment for seroprevalent participants and at HIV-1 diagnosis for men who became infected after study entry. Incidence rates for the first occurrence of each specific OI/cancer were calculated as the number of observed incident events divided by the number of person-years of follow-up without regard to the occurrence of other OIs/cancers. To eliminate the potential confounding effect of ART, which became available in 1996, we censored follow-up for all cohort members on 31 December 1995. Participants who remained alive but were no longer available for study center visits continued to be followed up for outcomes [32]. For participants in whom the outcome of interest occurred, follow-up ended on the date of diagnosis of that outcome. For participants without the outcome of interest, the end of follow-up was defined as follows: for participants dying on or before 31 December 1995, date of death; for those who remained in active follow-up

through 31 December 1995, that date; for those who were alive but not in active follow-up on 31 December 1995, the later of the last visit date or the last OI/cancer diagnosis date, on or before 31 December 1995.

We fit Cox proportional hazards models to estimate HRs and 95% confidence intervals (CIs) for associations between *IFNL4* genotype and each OI/cancer, using Firth's correction [34] to lessen the impact of potential small sample bias on HR estimates for some outcomes. In other models, we examined the relationship of *IFNL4* genotype with any OI/cancer, any OI/cancer or death, AIDS-related death, or all-cause death. Our primary analysis used a dominant genetic model with *IFNL4* categorized based on the genetic capacity to produce IFN-λ4 (ΔG/TT + ΔG/ΔG compared with TT/TT). These models were adjusted for self-reported race alone. We also examined genotype in additive models based on the number of copies of the *IFNL4*-ΔG allele and models that were adjusted for race, age at enrollment, study site of enrollment, and CD4 cell count, where this count was treated as an ordinal time-dependent variable (categorized as ≥500/μL, 499–200/μL, 199–100/μL, or <100/μL). In sensitivity analyses restricted to men experiencing immunodeficiency, follow-up began when the participant's CD4 cell count dropped below 500/μL or 200/μL and ended as described above.

To replicate methods of previous studies, we created additional models for KS and cytomegalovirus disease. For KS, we examined the genotype for *IFNL4* rs368234815 combined with the *IFNL4* rs117648444 variant, which modifies IFN-λ4 into proteins that strongly (P70) or more weakly (S70) impair HCV clearance [25, 35]. For cytomegalovirus, we compared the *IFNL4*-ΔG/ΔG genotype group with a reference group consisting of the TT/TT and ΔG/TT genotypes combined [27]. In addition, we performed analyses of KS restricted to men who had a positive test result for human herpesvirus 8 (HHV-8) antibody, as previously determined by an indirect immunofluorescent assay [36]. For *Pneumocystis* pneumonia, we fitted another set of models with follow-up censured when aerosolized pentamidine was approved for primary prevention of *Pneumocystis* pneumonia (16 June 1989) [37].

Analyses were performed using SAS software, version 9.4 (SAS Institute). Cox models were fit using the PHREG procedure. A 95% CI that excluded an HR of 1.0 was considered equivalent to a *P* value <.05 and statistically significant.

RESULTS

Among the 2310 men included in this analysis, the median age at enrollment was 32 years (Table 1). The vast majority self-reported as white (non-Hispanic, 82.1% of total; Hispanic, 6.1%) and 11.8% were black (non-Hispanic, 11.1% of total; Hispanic, 0.7%). Most participants (85.6%) enrolled in 1984–1985 during the first wave of recruitment. The distribution by study site was as follows: Baltimore, 22.3%; Chicago, 24.4%; Pittsburgh, 17.4%; and Los Angeles, 35.9%. About 80% of participants were infected with HIV-1 at study entry. During the follow-up period for our analysis, 48.7% of participants developed ≥1 OI/cancer and 54.3% had a CD4 cell count <200/μL. The most common outcomes were *Pneumocystis* pneumonia (24.5%) and KS (18.7%).

As expected, *IFNL4* genotype frequencies differed markedly by race. Among white participants, 45.2% were homozygous for the TT allele and therefore could not produce the IFN-λ4 protein, whereas the TT/TT genotype was present in 18.0% of black participants (Table 2). The genotype proportions in these populations did not deviate from expectations under Hardy-Weinberg equilibrium. Consistent with previous reports, we found no association between *IFNL4* genotype and a lowest CD4 cell count <200/μL (Supplementary Table 1). There was no evidence for an association between *IFNL4* and either overall mortality rate (HR, 1.00 [95% CI: .91–1.11]) or AIDS-related deaths (1.00 [.90–1.11]). Analyses of mortality that treated *IFNL4* genotype as an additive variable or adjusted for confounding variables yielded similar results (data not shown).

Table 1. Population Characteristics of White and Black Human Immunodeficiency Virus–Infected Participants in the Multicenter AIDS Cohort Study With an *IFNL4* Genotype Result (n = 2310)

Characteristic	Study Participants, No. (%)[a]
Age at enrollment, median (IQR)	32 (28–37)
Race/ethnicity	
White non-Hispanic	1897 (82.1)
White Hispanic	141 (6.1)
Black non-Hispanic	256 (11.1)
Black Hispanic	16 (0.7)
Enrollment year	
1984–1985	1978 (85.6)
1987–1990	332 (14.4)
Study site	
Los Angeles, California	830 (35.9)
Chicago, Illinois	563 (24.4)
Baltimore, Maryland	514 (22.3)
Pittsburgh, Pennsylvania	403 (17.4)
HIV seroprevalence at baseline/infection status	
Seroprevalent	1856 (80.3)
Seroconverter	454 (19.7)
Lowest CD4 cell count	
<200 cells/μL	1255 (54.3)
≥200 cells/μL	1055 (45.7)
Any AIDS OI or cancer	
Yes	1126 (48.7)
No or data missing	1184 (51.3)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; OI, opportunistic infection.

[a]Data are through 31 December 1995 and represent no. (%) of participants unless otherwise specified.

Table 2. *IFNL4* Genotype for White and Black Human Immunodeficiency Virus–Infected Participants in the Multicenter AIDS Cohort Study[a]

	Study Participants, No. (%)	
IFNL4 Genotype	White	Black
TT/TT	922 (45.2)	49 (18.0)
TT/ΔG	911 (44.7)	129 (47.4)
ΔG/ΔG	205 (10.1)	94 (34.6)

[a]Test for Hardy-Weinberg equilibrium: White men, $p = .38$; Black men, $p = .75$).

Table 3 shows incidence rates and race-adjusted HRs for all outcomes. Previous studies reported associations of *IFNL4* genotype with KS, and with disseminated cytomegalovirus and HSV infections. Regarding KS, we found incidence rates (per 100 person years) of 1.54 for those with the *IFNL4*-ΔG/ΔG genotype, 2.64 for *IFNL4*-ΔG/TT and 2.73 for *IFNL4*-TT/TT. The dominant model produced an HR of 0.92 (95% CI: .76–1.11), while the additive model for the development of KS produced a borderline protective association (HR, 0.87 per *IFNL4*-ΔG copy [.75–1.00]). A previous publication reported that, compared with individuals unable to produce IFN-λ4 (ie, *IFNL4*-TT/TT genotype), those with *IFNL4* genotypes that generate the stronger P70 form of IFN-λ4 had a higher incidence of KS; no difference was found for those with the weaker IFN-λ4 S70 protein [25]. We attempted to replicate those findings but found no difference between those who could generate IFN-λ4 P70 and those who could not generate IFN-λ4 (HR, 0.86 [95% CI: .70–1.06]). Comparing those who could generate IFN-λ4 S70 with those incapable of generating IFN-λ4 also showed no difference (HR, 1.10 [95% CI: .82–1.45]).

We also performed an analysis restricted to participants with a positive result for antibodies to HHV-8. Among the 2310 men in the analytic cohort, 1413 tested positive for HHV-8 in a sample collected on or before 31 December 1995, 10 tested positive for HHV-8 after that date, 52 had an indeterminate test result, 452 had a negative result, and 383 had no HHV-8 antibody test result. Among the 1413 men with a positive result during the analytic period, the HR was 0.95 (95% CI: .77–1.17) in the dominant genetic model and 0.89 per *IFNL4*-ΔG copy (.76–1.04) in the additive model.

For cytomegalovirus disease, the dominant model produced an HR of 0.94 (95% CI: .71–1.24), and the additive model an HR of 0.95 per *IFNL4*-ΔG copy (.77–1.17). We also performed an analysis to replicate the methods from a previous report on cytomegalovirus disease [27], by comparing those with the *IFNL4*-ΔG/ΔG genotype with the ΔG/TT and TT/TT groups combined. That analysis yielded no association (HR, .95 [95% CI: .59–1.44]). We also found no associations between *IFNL4* genotype and chronic mucocutaneous HSV infection (HR for dominant model, 1.37 [95% CI: .68–2.93]; HR for additive model, 1.09 [.65–1.80]).

Regarding the other outcomes included in our primary analysis (Table 3), for *Pneumocystis* pneumonia, the dominant genetic model yielded a HR of 1.03 (95% CI: .87–1.22); censoring follow-up to account for the introduction of primary prophylaxis against *Pneumocystis carinii* yielded similar results (HR, 1.08 [95% CI: .84–1.39]). We found no associations of *IFNL4* genotype with the other 6 primary outcomes. In most cases, the 95% CI was statistically inconsistent with a 2-fold change in the HR.

For the 6 outcomes included as exploratory analyses, we observed no differences in HRs for either genetic model (Table 3). Because none of those associations were statistically significant at the nominal .05 *P* value cutoff, we did not adjust for multiple testing. We also found no association for *IFNL4* genotype with either of the composite end points (any OI/cancer or any OI/cancer or death; Table 3).

Because the risk of developing an HIV-1-related OI/cancer depends on the degree of immunodeficiency, we created a series of models that considered the longitudinally measured CD4 cell count values for each participant, as well as race, study site, and age at enrollment (Supplementary Table 2). Those analyses yielded results similar to those obtained models adjusted for race alone. Sensitivity analyses in which follow-up time began only with evidence of immunodeficiency (CD4 cell count <500/μL or <200/μL) (Supplementary Table 3) also yielded similar results. Results from models restricted to white participants were similar to those in the overall study population. Models restricted to black participants had low statistical power for most outcomes, owing to the small number of individuals in that group (Supplementary Table 4).

DISCUSSION

We investigated the association between the *IFNL4* genotype and the development of 16 OIs/cancers among men with HIV-1 infection enrolled in a long-term cohort study. Whereas some prior studies reported associations between *IFNL4* genotype and some of these outcomes, we found no statistically significant associations, and our results rule out a strong association for most of the outcomes we examined. Therefore, despite evidence that the IFN-λ family plays an important role in a range of infections, we found no evidence that the functional genetic polymorphism that eliminates generation of IFN-λ4 affects the risk of disease from pathogens that cause HIV-related OIs/cancers.

Our findings regarding the relationship between *IFNL4* genotype and KS contradict those from the Swiss HIV Cohort Study [25]. In that analysis among men who have sex with men, investigators found the KS incidence to be increased in those with IFN-λ4 P70 (HR, 1.42 [95% CI: 1.06–1.89]). In contrast, we found no such association. In our analyses based on the *IFNL4* rs368234815 variant alone, there was no association

Table 3. Incidence Rates and Hazard Ratios Among White and Black Human Immunodeficiency Virus–Infected Participants in the Multicenter AIDS Cohort Study, by *IFNL4* Genotype and Genetic Model

Class	Outcome	Participants, No.	Incidence Rate[a]			Dominant[b]		Additive[b]	
			ΔG/ΔG	ΔG/TT	TT/TT	HR	95% CI	HR	95% CI
Primary analysis									
Viral and virus-associated cancers	Kaposi sarcoma	431	1.54	2.64	2.73	0.92	.76–1.11	0.87	.75–1.00
	Cytomegalovirus disease	199	0.98	1.11	1.22	0.94	.71–1.24	0.95	.77–1.17
	Non-Hodgkin lymphoma (no CNS involvement)	72	0.18	0.42	0.47	0.83	.52–1.32	0.78	.54–1.12
	Chronic mucocutaneous herpes simplex	32	0.13	0.23	0.15	1.37	.68–2.93	1.09	.65–1.80
Fungal	*Pneumocystis* pneumonia	565	2.67	3.54	3.38	1.03	.87–1.22	0.98	.86–1.11
	Candida esophagitis	176	0.94	0.99	1.05	0.91	.68–1.23	0.92	.73–1.14
	Cryptococcal infection (neuroinvasive)	50	0.18	0.38	0.21	1.60	.90–2.97	1.17	.77–1.74
Parasitic	Toxoplasmosis	69	0.27	0.42	0.40	0.97	.60–1.57	0.90	.62–1.28
	Cryptosporidiosis	69	0.35	0.42	0.37	1.18	.74–1.93	1.12	.78–1.57
Bacterial	Atypical mycobacterial	27	0.27	0.11	0.16	0.92	.43–1.99	1.17	.67–2.01
Exploratory analysis									
Other	Wasting syndrome	168	0.94	0.95	0.98	1.03	.76–1.40	1.04	.83–1.30
	Dementia	97	0.58	0.61	0.50	1.19	.79–1.81	1.10	.82–1.46
Viral	Progressive multifocal leukoencephalopathy	22	0.18	0.13	0.11	1.40	.61–3.42	1.42	.78–2.56
Bacterial	Recurrent pneumonia	15	0.09	0.05	0.12	0.45	.15–1.24	0.63	.27–1.34
	Pulmonary tuberculosis	11	0.09	0.04	0.08	0.69	.21–2.18	0.99	.39–2.29
Fungal	Histoplasmosis	12	0.04	0.08	0.07	1.13	.38–3.60	1.06	.44–2.35
Composite end points									
	Any OI/cancer	1126	5.40	7.36	7.46	0.97	.86,1.09	0.930	.85,1.01
	Any OI/cancer or death	1418	7.52	9.27	9.18	1.00	.90,1.11	0.960	.89,1.04

Abbreviations: CI, confidence interval; CNS, central nervous system; HR, hazard ratio; OI, opportunistic infection.

[a]Incidence rate per 100 person-years .

[b]HRs were adjusted for race. The dominant genetic model is based on the genetic capacity to produce interferon λ4 (*IFNL4* ΔG/TT + *IFNL4* ΔG/ΔG compared with *IFNL4* TT/TT).

for a dominant genetic model and a borderline protective association (ie, opposite the direction in the Swiss study) in an additive genetic model.

Three previous studies examined potential associations between *IFNL4* variants and cytomegalovirus disease, although the results from those reports were inconsistent (Supplementary Table 5). In the Swiss HIV cohort, cytomegalovirus retinitis was more frequent in individuals with the *IFNL4*-ΔG/ΔG genotype than those with either the *IFNL4*-ΔG/TT or the *IFNL4*-TT/TT genotype [27]. On the other hand, a protective association was observed between the *IFNL4* rs12979860-T allele, which is in linkage disequilibrium with *IFNL4*-ΔG, and cytomegalovirus disease after cessation of prophylaxis in liver transplant recipients [26]. Among solid organ transplant recipients, there was no association between genotype for the *IFNL4*-ΔG/TT (rs368234815) variant and cytomegalovirus disease [38]. In the current study, we found no association in either direction between the *IFNL4* genotype and the risk of disease caused by cytomegalovirus (HR, 0.94), and the 95% CI for that analysis (.71–1.24) was inconsistent with a large effect in either direction. Together, available studies fail to provide consistent evidence that *the IFNL4* genotype affects the risk of cytomegalovirus disease.

Studies of *IFNL4* genotypes and HSV infection have produced inconsistent results. In a case-control analysis of 56 Italian subjects, the rs12979860-T allele was associated with more frequent and more severe oral HSV episodes [30]. However, in patients with a history of recurrent herpes simplex labialis, the *IFNL4* rs12979860 CC genotype, which is in strong linkage with the loss of function *IFNL4*-TT/TT genotype, was associated with an increased risk of recurrent herpes simplex keratitis [29]. Previously, our group found no association between the functional *IFNL4* rs368234815 genotype and HSV-related outcomes, including episodes of oral or genital herpes, in a cohort of HIV-infected women [28]. In the current study, we observed no association with chronic mucocutaneous HSV infection among HIV-infected men.

Some participants in the present analysis were included in an earlier study that found no association between genotype for the *IFNL4* rs12979860 variant and risk of AIDS or death [24]. Similarly, we saw no association between *IFNL4* rs368234815 genotype and those outcomes or development of a low CD4 cell count.

Strengths of our study include a large well-defined cohort with long-term follow-up, enrollment more than a decade before the availability of ART, and genetic data for the primary functional *IFNL4* variant rather than a proxy polymorphism. Our study was limited by incomplete data for HHV-8 antibody results in the analysis of KS and lack of any information on underlying coinfections for other outcomes. Statistical power was low for some outcomes, especially those designated as exploratory. Another limitation of our analysis is that the study population did not include women, and we therefore could not examine the relationship between *IFNL4* genotype and invasive cervical cancer, which is considered an HIV-related cancer.

The reason for evolutionary selection against the *IFNL4*-ΔG allele and the functional role of IFN-λ4 remains unclear; however, there is evidence that *IFNL4*-ΔG impairs clearance of enteric and respiratory viruses [39, 40]. Future studies might focus on the association of *IFNL4* with acute infections that affect the gastrointestinal or respiratory epithelial tissues.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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