Interleukin-10 Gene (*IL10*) Polymorphisms and Human Papillomavirus Clearance among Immunosuppressed Adolescents

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Abstract

Persistent infection with high-risk human papillomavirus (HPV) is a major risk factor for cervical cancer, and HPV clearance seems to be under host genetic influence. This study evaluated associations between three single nucleotide polymorphisms in the *IL10* promoter and clearance of low- or high-risk HPV infection in a cohort of 226 largely HIV-1–infected African-American adolescent females. Among immunosuppressed individuals (HIV-1 seropositive and $CD4^+ \leq 500$), the *GCC* haplotype in the *IL10* promoter was associated with reduced clearance of high-risk HPV16-like [relative hazard (RH), 0.46; 95% confidence interval (95% CI), 0.25-0.85; $P = 0.01$], HPV18-like (RH, 0.33; 95% CI, 0.16-0.67; $P = 0.002$), and any high-risk type (RH, 0.37; 95% CI, 0.20-0.68; $P = 0.002$) but not with low-risk HPV type (RH, 0.60; 95% CI, 0.29-1.25; $P = 0.17$). No associations were observed among immunocompetent individuals. The *IL10* GCC haplotype has been associated with production of relatively high levels of interleukin (IL)-10, which could (*a*) inhibit cytokines such as IL-2, TNF-α, IL-4, IL-6, and IL-12 that are involved in the T_H1-T_H2 immunoregulation; (*b*) down-regulate expression of MHC class I and class II molecules; or (*c*) induce the transcription of early promoter of HPV, all potentially contributing to duration of HPV infection among immunosuppressed individuals. These results support the hypothesis that *IL10* polymorphisms influence the clearance of infection with high-risk HPV types and warrant further studies of host genetic control of HPV pathogenesis and cervical cancer in the context of immunosuppression. (Cancer Epidemiol Biomarkers Prev 2007;16(8):1626–32)

Introduction

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection in the United States and the world (1, 2). Of the estimated 20 million infected persons in the United States, about half are between 15 and 24 years old, and another 6.2 million new cases (4.6 million ages 15-24) are diagnosed annually (3). An estimated 30% to 60% of all sexually active adults acquire HPV at some point in their lifetime (4, 5), and modeling studies suggest that up to 80% of sexually active women will have been exposed to HPV by age 50 (6). However, infection is usually transient, with 70% to 90% of infected individuals ''clearing'' the virus within 12 to 24 months (7, 8). Persistent HPV infection, along with environmental and genetic factors, predisposes individuals to cervical intraepithelial neoplasia and subsequent progression to cancer. Although the introduction of the Papanicolaou smear test in 1943 decreased the incidence and mortality rates of cervical cancer in the United States by >70% (9), half a century later more than a quarter of a million women were reported to have this disease. In 2006, an estimated 9,710 women were diagnosed and 3,700 women died with cervical cancer (10).

There is strong epidemiologic and virologic evidence that oncogenic HPV types are the primary causal agent of cervical cancer (11). More than 120 HPV types have been described and more are being identified based on variation in subgenomic amplicons (11, 12). Some of these HPV types may have different biological properties, such as host species specificity, preferential tissue (mucosal or cutaneous) tropism, and differential pathogenetic capability (13, 14). HPV DNA is present in virtually all human cervical carcinomas, with oncogenic HPV types 16, 18, 45, and 31 predominating (15-17). In a comprehensive review and meta-analysis, high-risk HPV types were strongly associated [relative risk, 17; 95% confidence interval (95% CI), 8.2-33] with invasive cervical carcinoma and carcinoma *in situ* (18).

Although most infected individuals naturally clear HPV viral infection, the virus persists in a subset of infected hosts. ''HPV viral persistence'' is often loosely defined as detection of the same HPV type on two or more occasions (19). However, persistence is inconsistently defined depending on the interval between test visits as reported. In several published studies, it has been defined as ranging from 2 months to 7 years, with a median of 6 months (19-24). With such variability, the shorter interval between visits, the more likely an infection would be considered persistent. Despite the differential HPV exposure assessment, several epidemiologic and laboratory studies have suggested that a persistent infection is required for the development of cervical neoplasia.

Data from immunodeficient patients, including HIV-1–infected individuals and immunomanipulated animal models, indicate that cellular immune defects are associated with persistence or clearance of HPV (5, 25). A previous study with the Reaching for Excellence in Adolescent Care and Health (REACH) cohort suggested that the frequency of HPV persistence varied inversely with $CD4^+$ cell count ($CD4^+$; ref. 26). Other studies have shown that HPV infection and high-grade squamous intraepithelial lesions are more

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freqeuent among HIV-1–seropositive women with lower $CD4^+$ (27, 28). It has also been reported that HPV-associated cancers occur frequently in HIV/acquired immunodeficiency syndrome patients (29). HPV can persist for a long period even in some immunocompetent individuals, evading the host immune system before it is activated.

Although the reasons for HPV persistence and associated diseases are not fully understood, several immune evasion mechanisms have been suggested (5, 30), including genetically mediated determinants of host immune response that specifically result in the dysregulation of immunostimulatory cervical cytokine signals (31). Recent studies have focused on the family of cytokines involved in T_H1 (cellular) and T_H2 (humoral) immunoregulation with a mucosal shift from T_H1-type to T_H2-type responses in women with HPV infection (32, 33). A similar shift has been described with the development of cervical pathology among HIV-1–coinfected and HPV-coinfected women (34). One of the critical modulators of this balance is interleukin (IL)-10, which stimulates functions of innate and T_H2-related immunity but suppresses T_H1-related immune responses. IL-10 also stimulates $CD8^+$ T cells and immunoglobulin production by B cells; both of which are immunologically very significant. Several investigators have reported high expression levels of IL-10 associated with the development of HPV-associated diseases (32, 35) and with protective HPV vaccination. Models using pathogens in mice have shown that IL-10 plays an important role in balancing the protective and pathologic immune responses in the absence of $CD4^+$ T cells (36, 37); the cytokine may thus play a role in the immune clearance of HPV in patients with persistent infection. Here, our aim was to identify host genetic variants in the *IL10* gene proximal promoter region associated with time to clearance of type-specific HPV infection among adolescent females with varying degrees of HIV-1–induced CD4 immunosuppression. We report our findings for three common polymorphisms and the functionally distinct haplotypes in *IL10*, which have been known to vary the production profiles of the cytokine.

Materials and Methods

Study Population. Between 1996 and 2000, adolescents (ages 12-19 years) were recruited into multifaceted REACH study at 15 clinical sites in 13 U.S. cities (38). Of the 548 enrolled, we examined 301 (55%) African-American females. Those enrolled had acquired HIV-1 infection through sexual activity or injection drug use or remained HIV-1 seronegative despite high-risk behavior (sexual activity and illegal substance abuse). Methods for quarterly follow-up, sample collection, HIV-1 and HPV testing, and immunophenotyping of $CD4^+$ cell counts have been described in detail elsewhere (39, 40). The parent study and this substudy conformed to the procedures for informed consent approved by institutional review boards at all sponsoring organizations and to human experimentation guidelines set forth by the U.S. Department of Health and Human Services.

HPV DNA Detection. At enrollment and every 6 months thereafter, cervical lavage samples were tested for HPV. Briefly, viral DNA fragments from the samples were amplified using consensus primers MY09/11 and HMB01 and hybridized for a consensus probe and for 32 different HPV types using a chemiluminescent dot blot format (41). PCR-based HPV data were classified as follows: negative; positive for the specific types; or ''positive, type unknown'' if the sample was positive for the generic probe but not for specific HPV type. PCR amplification of human β-globin gene segment was used as an internal control for DNA quality, and samples negative for this assay were excluded from analysis. For analytic purposes, HPV types were categorized according to phylogenetic patterns (26, 42) into (*a*) high risk (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, and 82), (*b*) low risk (6, 11, 42, 44, 54, 40, 13, 32, 62, 72, 2, 57, and 55), (*c*) HPV16 and HPV16-like (16, 31, 33, 35, 52, 58, and 67), and (*d*) HPV18 and HPV18-like (18, 39, 45, 59, 68, 70, 26, 69, and 51).

Genotyping. Three common single nucleotide polymorphisms (SNPs) in the proximal promoter region of *IL10*, known to influence the expression of the gene (Table 1), were typed by the PCR SNP-specific primer method using procedures recommended by the manufacturer (Department of Transplantation Immunology, University of Heidelberg, Heidelberg, Germany and Pel-Freez Clinical Systems, Brown Deer, WI). The PCR SNP-specific primer method links neighboring SNPs from opposing directions to yield haplotype-specific amplicons as described previously (43).

Statistical Analyses. Female adolescents were eligible if they completed two or more study visits and tested HPV DNA positive at one or more visits. Results are presented for combined ''prevalent'' (HPV positive at baseline) and ''incident'' (HPV negative at baseline) infections. HPV infection clearance time was defined as the time between the estimated start date and end date of infection as follows: For individuals with prevalent infection, 90 days (half of the time between scheduled 6-month visits) were added to the observed duration of HPV infection beginning at baseline; for those with incident infection, the midpoint between the last visit where HPV DNA was not detected using PCR and the first HPV DNA-positive visit date was taken as infection incident date. Likewise, when follow-up ended with a HPV-positive visit, 90 days were added to the observed duration of infection to ensure comparability of assumptions about clearance for censored and noncensored observations. Analyses with or without additional 90 days did not appreciably change the results.

Even with PCR-based HPV typing, it was not possible to distinguish continuous infection from reinfection. We assumed that a single HPV-negative visit between two visits positive for the same HPV type was a continuous infection and not a reinfection. In these circumstances, we assume that the individual was still infected but with HPV DNA levels below the level of detection. However, we considered an individual who was HPV negative for two visits between two positive visits to be reinfected after clearance for 1 year and excluded that individual from the study. When two consecutive HPV-negative visits followed a positive visit, the midpoint between the last HPV-positive and first HPV-negative visit was considered the date of clearance. Two or more HPV-positive visits followed by a single HPV-negative visit and no further follow-up were censored at the HPV-negative visit. For analytic simplicity, we excluded 75 females from the study: 24 who were not HPV infected during the study, 27 who had HPV test result from only a single visit, 19 who had inadequate follow-up (i.e., less than two visits) or missing HPV infection data after a positive diagnosis visit, 2 who became HIV-1 seropositive during the study, and 3 individuals reinfected with the same HPV type after two consecutive visits with missing or negative results. For those with data missing at any single visit, we assigned the HPV status at the closest adjacent visit. The unit of analysis was type-specific HPV infection rather than an individual, so an individual could be counted more than once if she was infected with and/or cleared multiple HPV types in different visit periods. Individuals coinfected with HPV types in different groups at the same visit or at different visits during the study period were analyzed separately by HPV types.

Our analyses focused on the effect of common genetic polymorphisms and the haplotypes in *IL10* gene promoter on time to HPV type-specific clearance according to HIV-1 serostatus and $CD4^+$ cell count ($CD4^+$). Because there were very few HIV-1–seropositive individuals with $CD4^+$ of <200 at

Table 1. Polymorphisms examined in the *IL10* gene proximal promoter region

Gene	Chromosomal map	Polymorphisms*/haplotypes	NCBI ID	MAF (n = 228)	Haplotype frequency	P_{HWE}†
IL10		Promoter −1082 (A/G)	rs1800896	0.33		0.39
	1q31-q32	Promoter −819 (C/T)	rs1800871	0.42		0.93
		Promoter −592 (C/A)	rs1800872	0.42		0.93
		GCC			0.33	
		ATA			0.42	
		ACC			0.25	

Abbreviations: NCBI, National Center for Biotechnology Information; MAF, minor allele frequency.
*Second allele is the minor allele.
†P values based on Hardy-Weinberg equilibrium; Pearson χ^2 (1 degree of freedom) among all HPV-infected individuals.

the first HPV-positive visit during the study period, subjects were divided into two groups based on CD4$^+$ (CD4$^+$ > 500 versus CD4$^+$ ≤ 500). Deviation from Hardy-Weinberg equilibrium was examined for all three loci using the Pearson χ^2 test. Kaplan-Meier and Cox proportional hazards regression models were used separately in the HIV-1–seronegative and two HIV-1–seropositive groups to evaluate associations between *IL10* promoter haplotype and time to HPV type-specific clearance. Differences among nonparametric estimates of survival curves were assessed using Wilcoxon and log-rank tests for time-to-event univariate analysis between carriers and noncarriers of individual *IL10* promoter haplotypes (44). Separate analyses were carried out for clearance of type-specific HPV16-like, HPV18-like, high-risk, and low-risk infections. All analyses were done with SAS/SAS Genetics version 9.2 (SAS Institute).

Results

The mean age at enrollment of the 301 African-American adolescent females (203 HIV-1 seropositive and 98 HIV-1 seronegative) was 16.7 years (median, 17.0). Their mean duration of follow-up was 2.6 years (median, 2.8; range, 0.5-4.7) with an average of 6.07 visits (median, 6; range, 2-11). Of these, only 226 individuals were infected with at least one type of high-risk HPV type and 83 of them were coinfected with at least one of each of the HPV16-like, HPV18-like, and low-risk HPV type at the same visit or different visits during the study period; thus, those 83 were included in three different analyses (Fig. 1). Four individuals were infected with other high-risk HPV but not coinfected with HPV16-like or HPV18-like types. Thus, among these participants, 226 (165 HIV-1 seropositive and 61 HIV-1 seronegative) met the inclusion criteria for high-risk HPV persistence, 178 (132 HIV-1 seropositive and 46 HIV-1 seronegative) for HPV16-like HPV persistence, 169 (123 HIV-1 seropositive and 46 HIV-1 seronegative) for HPV18-like HPV persistence, and 131 (106 HIV-1 seropositive and 25 HIV-1 seronegative) for low-risk persistence (Table 2). The overall observed median time to clearance of infection was 601, 594, 691, and 440 days for HPV16-like, HPV18-like, high-risk, and low-risk HPV type infections, respectively. However, the duration of HPV infection in different risk groups varied by HIV-1 status and CD4$^+$ (Table 2), with a trend of longer median duration time as CD4$^+$ decreased.

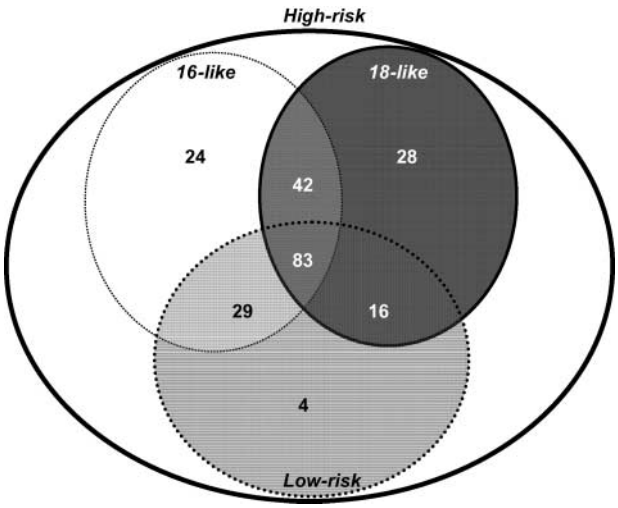

Figure 1. Distribution of coinfection by HPV type among African-American adolescents participating in the REACH cohort.

Kaplan-Meier curves and the log-rank test for clearance of high-risk HPV infection over time indicated a statistically significant difference between HIV-1–seropositive and HIV-1–seronegative individuals (P = 0.01). Figure 2A shows that the time to 50% clearance of high-risk HPV was shorter for HIV-1–seronegative (641 days) than HIV-1–seropositive individuals with CD4$^+$ of >500 (811 days) and CD4$^+$ of ≤500 (1,011 days). High-risk HPV cleared significantly more slowly among HIV-1–seropositive patients with CD4$^+$ of >500 [relative hazard (RH), 0.63; 95% CI, 0.41-0.97; P = 0.04] or CD4$^+$ of ≤500 (RH, 0.61; 95% CI, 0.39-0.94; P = 0.03) than HIV-1–seronegative individuals (similar results for other HPV risk groups not shown).

No deviation from Hardy-Weinberg equilibrium was observed in the three *IL10* promoter SNPs (Table 1). As described previously (45), two SNPs (rs1800871 and rs1800872) showed complete linkage disequilibrium. In our genotyping scheme, inclusion of both of these SNPs did not enhance the resolution of local haplotypes but they were useful for intercohort and interpopulation comparisons. Slower rate of clearance (RH, 0.56; 95% CI, 0.37-0.86; P = 0.007; Fig. 2B) was observed overall with individuals carrying the *IL10* GCC haplotype (heterozygotes and homozygotes). In a stratified analysis, among HIV-1–seronegative and HIV-1–seropositive subjects with CD4$^+$ of >500, the estimated survival curves for HPV infection clearance for HPV16-like, HPV18-like, high-risk, and low-risk HPV type infection all showed no association with the functionally distinct *IL10* promoter haplotypes (Table 3). In contrast, among the HIV-1–seropositive subjects with CD4$^+$ of ≤500, clearance time differed significantly for HPV16-like (P = 0.01), HPV18-like (P = 0.002), and all high-risk HPV group (P = 0.002) in carriers of *IL10* GCC haplotype (Fig. 2C-E). The time to 50% clearance of HPV16-like, HPV18-like, and all high-risk HPV groups was longer among individuals carrying GCC haplotype than those without the haplotype (HPV16-like, 819 versus 457 days; HPV18-like, 1,095 versus 355 days; and high risk, 1,493 versus 597 days). The association of *IL10* promoter haplotype and reduced clearance was statistically significant for all high-risk type groups (HPV16-like: RH, 0.46; 95% CI, 0.25-0.85; P = 0.01; HPV18-like: RH, 0.33; 95% CI, 0.16-0.67; P = 0.002; and high risk: RH, 0.37; 95% CI, 0.20-0.68; P = 0.002; Table 3; Fig. 2C-E).

Table 2. Median infection clearance time of HPV16-like, HPV18-like, high-risk, and low-risk types among HIV-1–seropositive and HIV-1–seronegative individuals

HPV type	HIV-1 seropositive				HIV-1 seronegative	
	$CD4^+ \leq 500$		$CD4^+ > 500$			
	n	Clearance (d), median (IQR)	*n*	Clearance (d), median (IQR)	*n*	Clearance (d), median (IQR)
HPV16-like	66	694 (348-1,180)	66	625 (360-1,076)	46	482 (330-727)
HPV18-like	58	607 (319-1,078)	65	433 (287-811)	46	368 (277-589)
High risk	81	803 (455-1,293)	84	666 (388-1,191)	61	525 (309-814)
Low risk	50	459 (348-686)	56	442 (283-733)	25	295 (265-454)

Abbreviation: IQR, interquartile range.

Separate analyses adjusting for age at enrollment did not appreciably change these associations. The association with the low-risk type showed the same pattern but the difference was not statistically significant (RH, 0.60; 95% CI, 0.29-1.25; $P = 0.17$; Fig. 2F).

Discussion

Our findings indicate that polymorphisms in *IL10* promoter influence the high-risk HPV infection clearance among immunosuppressed individuals (HIV-1 seropositive with $CD4^+ \leq 500$). IL-10 is a pluripotential cytokine controlling inflammatory and immunoregulatory response to different pathogen (46, 47). It is produced primarily by the T_H2 subset of $CD4^+$ cells along with monocytes, macrophages, and activated T and B cells, but in certain homeostatic conditions, it may be produced by some T_H1 cells and even nonhematopoietic sources, such as keratinocytes. IL-10 is usually secreted later than other immunoregulatory cytokines (48, 49) and often protects host tissues from damage due to secondary hyperinflammation. In other circumstances, this cytokine may suppress $CD4^+$ T cells and antigen-presenting cells or inhibit the production and secretion of other cytokines and chemokines, including IL-1, IL-2, IL-4, IL-6, IL-8, IL-12, tumor necrosis factor-α, macrophage colony-stimulating factor, macrophage inflammatory protein-1α, macrophage inflammatory protein-1β, RANTES, and IL-10 itself (50-52). Thus, IL-10 seems to have an important function as a down-regulator of inflammation and cellular immunity.

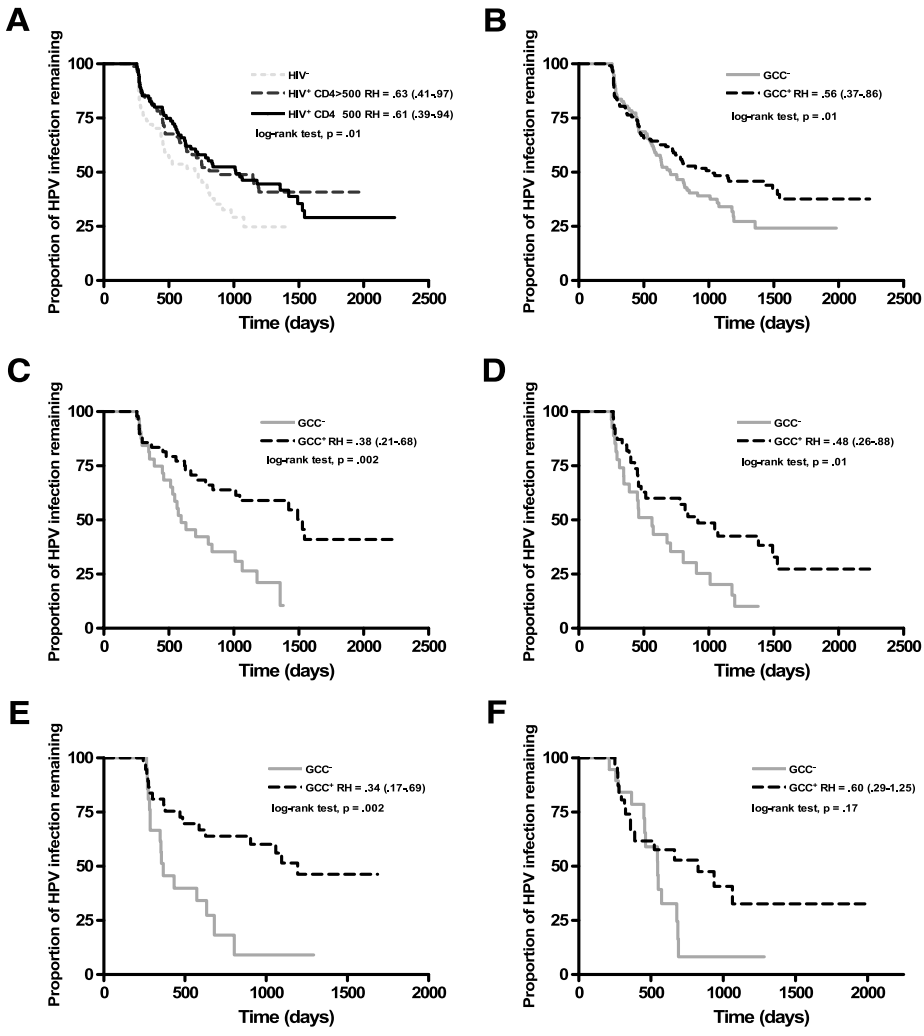

Figure 2. Kaplan-Meier survival curves show the effect of **A.** HIV-1 infection and $CD4^+$ count on high-risk HPV infection clearance time (*n*/event = 226/169); **B.** *IL10* GCC haplotype on high-risk HPV infection clearance time (*n*/event = 226/169); **C.** *IL10* GCC haplotype on high-risk HPV infection clearance time among HIV-1–seropositive individuals with $CD4^+ \leq 500$ (*n*/event = 81/47); **D.** *IL10* GCC haplotype on HPV16-like HPV infection clearance time among HIV-1–seropositive individuals with $CD4^+$ of ≤500 (*n*/event = 66/46); **E.** *IL10* GCC haplotype on HPV18-like HPV infection clearance time among HIV-1–seropositive individuals with $CD4^+ \leq 500$ (*n*/event = 58/33); **F.** *IL10* GCC haplotype on low-risk HPV infection clearance time among HIV-1–seropositive individuals with $CD4^+ \leq 500$ (*n*/event = 50/30). Number of individuals (*n*), number who cleared (event), RH with 95% CI, and statistical *P* value (*P*) based on Cox proportional hazard models are shown.

Although certain features of the study might have led to spurious results with the *IL10* polymorphisms, we doubt that they accounted for the associations. First, we might have underestimated the duration of HPV infection by left censoring prevalent infection and right censoring persistent infection. Prevalence of HPV infection was higher among African-Americans than other ethnic groups in the REACH cohort (26). We observed only 24 incident high-risk HPV cases (versus 202 HPV prevalent cases), and some were still HPV-positive at the end of the study. However, left censoring is less likely to be an important factor for two reasons. Adolescent participants were unlikely to have been infected for long periods before their enrollment in the study. In addition, although the CD4$^+$ was measured simultaneously with the first detection of HPV (i.e., cross-sectionally), similarity in proportions of incident and prevalent cases with low or high CD4$^+$ (P = 0.21) suggested that CD4$^+$ at the first HPV-positive visit is a valid surrogate of immunosuppression status. Second, here as in the earlier REACH study of HPV (26), both HIV-1 status and CD4$^+$ influenced the natural history of HPV infection among African-Americans, and we appropriately stratified for those potential determinants. Third, to avoid stratification by ethnicity that can potentially confound genetic analyses, we confined our analysis to African-Americans.

The modulating influence of *IL10* polymorphisms in our analysis was CD4$^+$ dependent occurring only in immunocompromised HIV-1–seropositive individuals. A previous study showed that HPV infection was associated with increased IL-10 levels in HIV-1–seropositive women but with decreased IL-10 levels in HIV-1–seronegative women (34). In our study, we observed reduced clearance of high-risk HPV with the *IL10* GCC haplotype, which is believed to encode for higher IL-10 level. However, an opposite albeit nonsignificant association was seen with this haplotype among HIV-1 seronegatives, suggesting a trend in association that decreases with declining CD4$^+$ (Table 3). CD4$^+$-dependent host response to IL-10 has been found in knockout mouse models of other pathogen clearance (36, 37). Qureshi et al. (36) reported that *IL10* knockout mice were better protected from *Pneumocystis carinii* infection than wild-type mice; however, when the *IL10* knockout mice were depleted of CD4$^+$ T cells, their immunity to the infection failed and their lung injury was significantly worse than in CD4$^+$ T-cell–depleted wild-type mice (36). Consistent results were observed in *IL10* knockout mice with *Toxoplasma gondii* (37).

The association between *IL10* polymorphisms and the clearance of low-risk HPV was not significant. One explanation is that *IL10* polymorphisms have less effect on the low-risk HPV type among immunosuppressed individuals. Alternatively, as indicated in Fig. 1, this could reflect (*a*) confounding in all low-risk HPV carriers by carriage of high-risk HPV, which have a longer clearance time [median, 803 (interquartile range, 455-1,293) versus 459 (interquartile range, 348-686); Table 2], and (*b*) the relatively smaller sample size of the low-risk group (n = 50) compared with the other groups.

Many participants had an infection with more than one HPV16-like, HPV18-like, high-risk, and low-risk HPV group at the same or a later visit. We considered the natural history of HPV infection with each HPV group independently of a coinfection with HPV of a different group, and an individual with multiple infections could belong to different groups. However, if an individual was infected with the HPV type from the same group, only the most persistent type was included in the analysis. That approach had some disadvantages, but most individuals were infected with multiple HPV types (Fig. 1). Our assay was able to detect most of the high-risk types; some of the low-risk types that might have been missed are rare and would have had little effect on our findings. Our study was restricted to a maximum follow-up period of 4 years for HPV clearance; however, the design was more powerful than previous case-control studies, in which persistence was defined as the presence of the same HPV type in two or three consecutive visits spanning variable times.

By any of several mechanisms, IL-10 might enhance persistence and progression of HPV infection. IL-10 down-regulates expression of MHC class I and class II molecules, and increased IL-10 production may decrease CD4$^+$ immune recognition of class II molecules bearing HPV and associated tumor antigens (53, 54). In the context of HIV-1 infection, HPV antigen presentation may be impaired by a CD4$^+$-MHC class II molecular imbalance. Thus, the combination of CD4$^+$ cell depletion due to HIV-1 and class II suppression by higher IL-10 concentrations may make it even easier for HPV to evade an otherwise effective immune response. Increased IL-10 concentration may also disrupt the pattern of T_H1 cytokine function (55, 56) so as to obscure any associations that would otherwise have been observed with polymorphisms in T_H1 cytokines and HPV clearance. Furthermore, beyond regulating immunity, IL-10 seems to induce the transcription of an early promoter of HPV type 16 in a significant and dose-dependent manner (57).

Polymorphisms in the *IL10* proximal promoter region are known to influence the production of IL-10 (58, 59) and have been examined extensively for associations with natural history of pathogens, such as Epstein-Barr, herpes zoster, HIV, and hepatitis C (60-62). The GCC haplotype produces high levels of IL-10, the ACC haplotype produces medium levels, and the ATA produces low levels (58, 59) The effect of GCC haplotype has mostly been evaluated in a dominant model (GCC carriers). Our study was too small to evaluate the dose effect of the *IL10* haplotype combinations (GCC/GCC versus other haplotype combinations). IL-10 production might suppress the effects of other cytokines within the T_H1-T_H2 pathway and in a CD4$^+$-dependent manner. That could explain why the association of *IL10* haplotypes with clearance of high-risk HPV groups (Table 3) was seen only in individuals with HIV-1–induced lymphopenia. Although the three SNPs in the proximal region of the *IL10* promoter that we examined are the most studied variants associated with IL-10 production, certain of the >40 other SNPs and microsatellites in the gene region

Table 3. Clearance of HPV infection by HPV type among HIV-1–seropositive (CD4$^+$ > 500 and CD4$^+$ ≤ 500) and HIV-1–seronegative individuals with *IL10* GCC haplotype

HPV type	HIV-1 seropositive						HIV-1 seronegative		
	CD4$^+$ ≤ 500			CD4$^+$ > 500					
	n/event*	RH (95% CI)	P	n/event*	RH (95% CI)	P	n/event*	RH (95% CI)	P
HPV16-like	66/46	0.48 (0.26-0.88)	0.01	66/37	0.81 (0.422-1.54)	0.51	46/32	1.68 (0.82-3.44)	0.15
HPV18-like	58/33	0.34 (0.17-0.69)	0.002	65/40	0.67 (0.36-1.24)	0.20	46/33	1.21 (0.61-2.40)	0.58
High risk	81/47	0.38 (0.21-0.68)	0.002	84/43	0.74 (0.40-1.34)	0.32	61/39	1.78 (0.94-3.38)	0.08
Low risk	50/30	0.60 (0.29-1.25)	0.17	56/36	1.80 (0.91-3.56)	0.09	25/21	0.98 (0.41-2.30)	0.95

*n = total number of individuals; event = total individuals who cleared.

have also been shown to be associated with the cytokine production and expression (60, 63). A comprehensive study including these additional polymorphisms in *IL10*, along with other genes in the T_H1-T_H2 pathway, would more fully elucidate the immunoregulation of HPV infection and clearance.

Recently, two highly efficacious vaccines have been approved for use in immunocompetent humans to prevent infection with the most common high-risk HPV types (16 and 18), and one vaccine also protects against types 6 and 11 (64, 65). How well these vaccines will protect against infection with other oncogenic types or in immunosuppressed hosts is unknown. Because many vaccines confer immunity by simulating a natural infection, polymorphisms in genes that play a role in the natural history and pathogenesis of the infection (e.g., *IL10*) could also regulate vaccine response. Such genetic information might therefore be used to improve treatment and vaccine efficacy and effectiveness, expand the target population to include HIV-1–infected individuals, and ultimately contribute to the realization of personalized therapy and vaccination.

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