

Influence of Host Genetic Variation on Susceptibility to HIV Type 1 Infection

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For this review of genetic susceptibility to human immunodeficiency virus type 1 infection, far more information was available on factors involved in acquisition of the virus by an uninfected “recipient” than on propagation by the infected “donor.” Genetic variation presumably alters transmission from an infected host primarily by regulating the replication of virus and the concentration of particles circulating in blood and mucosal secretions of the potential donor. Thus, the effects of host genetic variation on transmission are inextricably bound to the well-established and powerful effects on virus load at different stages of infection. Teasing apart the effects in both donors and recipients has been and will continue to be quite difficult.

As a prelude to the discussion of host genetic determinants of susceptibility to HIV-1 infection, we briefly enumerate the nongenetic factors involved and the major issues that arise in designing and analyzing research on genetic variation. Subsequent sections emphasize the importance of evaluating genetically mediated predisposition to infection in the context of genetic influences on clinical responses in individuals who are already infected. Similarities and differences between these 2 types of effects may help distinguish between those factors more involved in initial viral penetration, those more involved in long-term host adaptation to established infection, and those equally important to both processes.

NONGENETIC INFLUENCES ON TRANSMISSION AND ACQUISITION

Biological factors. Viral and host biological characteristics are strong predictors of both transmission and acquisition of HIV-1 [1–3]. The infectivity of HIV-1 in a potential “donor” may differ from that in another because of differences in virus subtypes and the set of

virus quasi species that are more or less well adapted to the biological individuality of that donor. The envelope glycoprotein of HIV-1 is one major factor governing its *in vitro* tropism for certain host cell types [4], and differences in such properties as size, shape, and net charge of certain envelope motifs could alter the capacity of the virus to penetrate host cells. The duration of infection and the effectiveness of the immune response in the donor further dictate qualitative and quantitative characteristics of virus replication and the capacity to spread to susceptible “recipients.” In general, virus load during the acute and latter stages of infection is higher than during the long middle (“latent”) period, and higher donor virus load at those stages presumably increases the likelihood of transmission to a naive host. Another critical factor is the condition of immune activation in both donors and recipients, especially in areas of close contact; the absence of circumcision, ulceration, and other causes of mucosal disruption presumably increases access to or activates cells targeted by HIV-1 [5, 6]. The age of the recipient may be a surrogate for maturation or senescence in the host cellular immune processes involved in defending against viral penetration and integration [7]. Infection with herpes simplex viruses and, perhaps, other viral and bacterial agents may facilitate propagation of HIV-1 by activating cells or otherwise promoting virus replication and shedding [8–10]. Undoubtedly, other recipient immune defense mechanisms that can modulate the risk of infection are still undiscovered.

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Behavioral factors. Various behaviors determine the nature and intensity of the physical contact of virus-containing donor cells or secretions with tissues of the susceptible recipient. The route, nature, and frequency of potential exposure to the donor may affect the likelihood of transmission, but research aimed at separating the mode of transmission from other biological and behavioral factors can be especially difficult. Measures that counteract risk-enhancing behavior vary in their efficacy and in the degree of adherence achieved. Consistently used physical barriers (e.g., condoms) are the most widely evaluated and promoted means of prevention of sexual transmission [6, 11]. Locally applied chemical agents (e.g., virucides) have been receiving wide attention, but proof of effectiveness is still needed [12]. Antiretroviral treatment can decrease transmission by dramatically reducing virus load in potential donors, if behavioral lapses do not negate the pharmacotherapeutic benefit. Any combination of these factors could obscure the role of genetic variation in acquisition of infection and must be considered in the development, execution, and evaluation of immunogenetic research.

DESIGN AND ANALYTICAL ISSUES

The ideal investigation of genetic determinants of infection would include enough information about the aforementioned nongenetic factors to account and adjust for differences in distribution between the groups selected for comparison. In reality, research on genetic variation in both transmission and acquisition is seldom able to include the detail needed for such analytical precision. By definition, the subjects at highest risk (commercial sex workers, men who have sex with men, and injection drug users) have multiple contacts, of whom few, if any, would ordinarily be available to the study. Analyses usually have compared susceptible subjects, who often, but not always, are highly exposed, persistently seronegative (HEPS) individuals, with either subjects whose infection is of unknown duration or those with incident seroconversion. For these groups, whether the documentation of risk levels is comparable is difficult to determine, especially when the risk characteristics of donors are unavailable for analysis.

In contrast, although more difficult to undertake and maintain, studies of heterosexual or homosexual partnerships (i.e., a single infected partner plus a single uninfected partner) have distinct advantages in settings where relatively high seroconversion rates reflect sufficiently intense exposure. The advantages of studies of such partnerships include the lower likelihood of ethnic heterogeneity, the ease of retrospective and prospective time-dependent assessment of donor and recipient risk, and the ability to determine whether viral isolates from recipients match those from donors (and other viral characteristics) [2, 13]. However, recall bias among infected or un-

infected partners and difficulty in following up with couples are potential threats to validity.

Inquiry into host genetic determinants of HIV-1 infection is at an early stage, with other potentially relevant genes yet to be discovered and examined [14]. When no specific hypothesis is under evaluation, numerous (often partially correlated) variables are exhaustively sifted for relationships. Associations arising from the multiplicity of comparisons invariably raise doubt about type I error. Investigators are often encouraged or compelled to “correct” estimates of statistical significance for the number of putatively tested variants. However, the number of tests actually performed is rarely equivalent to the number implied by the tabulated data, and treatment of all associations as equally unlikely and independent of each other also oversimplifies the analysis. This ostensibly conservative maneuver produces an assessment that is “safe” but also counter to the exploratory nature of many studies. Replication in separate populations, preferably by different investigators, is the most reliable approach to validating preliminary work, but second populations of similar size and composition often are not readily available. Other major considerations in the interpretation relationships among highly polymorphic markers (e.g., *HLA* genes) include measurement of frequency by chromosome or by individual, codominance, linkage disequilibrium, and intra- and intergenic (epistatic) interaction. Analytical tactics for coping with these phenomena are beyond the scope of this review.

GENETIC VARIATIONS WITH REPLICATED EFFECTS ON SUSCEPTIBILITY

Specific genetic polymorphisms associated with susceptibility to HIV-1 infection are, in our judgment, sufficiently strong and certain to merit highlighting (table 1). We accepted the effect of a genetic variant when the association was observed, by 2 independent investigative teams using established genotyping methods, in populations with at least 100 outcome events (e.g., seroconversion) and when the polymorphism is known to occur at a frequency of >1% of a major ethnic group. References have been selected accordingly. The same findings may not be universal for persons of all ages and ethnic backgrounds, for both sexes, or for every mode of transmission; however, very few instances were found in which study results, to date, would permit definitive comparisons of these variables.

By focusing on findings reproduced in at least 2 independent studies, we have highlighted and summarized information (table 1) for genetic polymorphisms that have been examined thoroughly enough to warrant comment about their role in susceptibility to HIV-1 infection. Our particular attention to genetic markers with known effects on the HIV-1 disease process increases the likelihood that they predict important but less thoroughly studied similarities or differences in susceptibility.

Table 1. Associations between human gene polymorphisms and susceptibility to HIV-1 infection.

Gene, marker or variant, transmission mode(s)	Ethnicity of subjects (location)	Predominant HIV-1 subtype	Effect on risk	Selected references
<i>CCR5</i>				
$\Delta 32$ (HHG*2) (homozygous and heterozygous) ^a				
MSM, IDU, heterosexual, and Tx	White (multiple)	B	Decrease	[15–22]
MTC	White (multiple)	B	None	
Promoter HHE (homozygous), P1/P1 ^b				
MSM, IDU, heterosexual	White, African American (United States)	B		[16, 23, 24]
MSM	White, African American (United States)	B	Increase	
MTC	White (Argentina) ^c	B		
<i>HLA</i>				
Concordance at <i>HLA</i> class I loci or at <i>HLA-B</i>				
MTC	African (Kenya)	A		[25–28]
Heterosexual	White (United Kingdom)	B	Increase	
MTC	African American (United States)	B		
Heterosexual	Zambian	C		
A2/6802 and A0205/6802 ^d				
MTC	African (Kenya)	A	Decrease	[29, 30]
MSM	White (United States)	B		

NOTE. Information is given for identical or biologically equivalent markers found to be associated with susceptibility to HIV-1 infection, by the same or different routes, in at least 2 independently reported studies of any ethnic group. IDU, injection drug use; MSM, men who have sex with men; MTC, mother-to-child; Tx, transfusion of blood product.

^a The $\Delta 32$ variant (HHG*2) is a 32-bp deletion in the region coding for a portion of a transmembrane domain of the receptor. Homozygous subjects showed nearly complete protection, and heterozygous subjects showed slight protection.

^b *CCR5* haplotype nomenclature follows [23]. The homozygous human haplogroup or haplotype E (HHE) is a subset of the homozygous P1/P1 haplotype.

^c Includes both those treated and those not treated with zidovudine.

^d Designations are for *HLA-A* supertype, rather than alleles. Although associated markers were not identical in the 2 studies, comparable effects have been inferred.

Chemokine Receptor/Ligand System

Many types of inflammatory and immunoregulatory cells are strongly influenced by the interplay between secreted chemokines and receptors expressed on their surfaces. The functions of these receptors and ligands have received intense scrutiny because of their fundamental role in immunity in general and in cell penetration by HIV-1 in particular. Even though they are complex, passing familiarity with the biology of and the terminology for these receptors and ligands is necessary to understanding the role of the genes that govern their production.

Thus far, 2 receptor/ligand families have been found to be most prominent in HIV-1 infection (reviewed in [31–33]). Members of the C-C chemokine receptor (CCR) family, such as CCR2 and CCR5, are bound by CC-motif chemokine ligands (CCLs), including RANTES, macrophage inflammatory protein (MIP)-1 α , MIP-1 β , monocyte chemoattractant proteins, and others. Members of the C-X-C receptor (CXCR) family, such as CXCR4, are bound by ligands such as CXCL12, which encodes stromal cell-derived factor-1 (SDF-1).

The intricate role of these molecules in HIV-1 infection [34–36] was recognized more clearly when uninfected persons capable of suppressing replication of macrophage-tropic HIV-1 were found to have increased levels of RANTES, MIP-1 α , and MIP-1 β [37–40]. These chemokines are thought to diminish

virus propagation by competing with HIV-1 for its principal receptor or, less directly, by regulating receptor expression. Macrophage-tropic forms of HIV-1 that compete with CCLs mainly for CCR5 binding sites on macrophages have been designated “R5 viruses,” whereas T cell-tropic forms that compete with SDF-1 for the receptor CXCR4 have been designated “X4 viruses” [41]. Some viral isolates show tropism for both types of cells [4, 41, 42].

In the process of transmission and during the initial stages of HIV-1 infection, the non-syncytium-inducing, usually R5, phenotype in the virus population uses CCR5 as the preferred coreceptor [15, 43–46]. Although CXCR4-using X4 viruses also are present early during the course of infection, they are believed to dominate later. They are transmissible from infected to uninfected individuals but, for reasons not yet clear, seldom account for new infections. Additional detail on these aspects can be found in previous reviews [47, 48].

Considerable attention has been given to variation in the *CCR* and *CXCR* genes, which are distributed mostly along chromosomes 2 and 3 [49–54]. The 2 CCLs that, thus far, have been found to be most relevant to susceptibility are MIP-1 α and RANTES, which are encoded by genes on chromosomes 4 and 17 (in particular, *CCL3[SCYA3]* and *CCL5[SCYA5]*, respectively) [55–61]. The *CXCL12* gene on chromosome 10 en-

codes SDF-1. Despite clear recognition of the clinical and epidemiological impact of the more common inherited sequence variations (i.e., polymorphisms) in these genes, the mechanistic effects of their altered formation, production, and function have not been fully elucidated [62–64].

CCR2 and CCR5 variants. Variation in the genes for these 2 adjacent members of the CCR family has been the most thoroughly studied. In assessing the studies, however, the reader should be alert to the multiplicity of genes and variants and the earlier use of several different designations, which may have accentuated certain reported effects or obscured others. Recent approaches to simplification of typing and standardization of nomenclature should improve the interpretation of population research on the influence of these genes and variants in HIV-1 infection [16, 23, 31, 65].

Variations in the promoter and coding regions of *CCR5* have been found to alter the ease of HIV-1 acquisition in several populations. Most attention has been given to the 32-bp deletion ($\Delta 32$) in the region coding for a portion of 1 transmembrane domain of the receptor; this deletion occurs at an allele frequency of ~9% and a carriage frequency of 15%–18%, among white European individuals, but the frequencies in other major racial groups are negligible [17, 23, 66]. Several well-designed and well-executed studies and numerous case reports have now confirmed virtually complete protection against homosexual and heterosexual transmission of HIV-1 infection in persons carrying 2 copies of the deletion [15, 17–21]. Although infection with X4 viruses that do not require *CCR5* for penetration has been reported for several individuals homozygous for *CCR5* $\Delta 32$, the nearly complete protection of homozygous individuals is quite striking, compared with that of individuals carrying 2 intact copies of *CCR5*. The impact at the population level is far less dramatic, however, because only 1%–2% of the white population and virtually none of other racial groups are homozygous. On the other hand, these studies have demonstrated that the absence of the receptor is quite compatible with apparently normal health and have suggested intervention strategies for infected persons and perhaps for uninfected persons.

A single copy of $\Delta 32$ usually confers modest protection against virus replication and development of disease, as has been measured in cohort studies of seroconversion in white homosexual individuals and others [16–18, 23, 67]. At hazard ratios ranging from 0.5 to 0.8, the effect on disease is not always strong and may be less consistent in different risk groups or at different stages of infection [21, 68–70]. In the Multicenter AIDS Cohort Study (MACS), comparisons of HEPS individuals with individuals who seroconverted [16], as well as analysis of horizontal and vertical transmission in other populations [22, 71–73], have documented more-subtle degrees of protection against initial HIV-1 infection among individuals heterozygous for $\Delta 32$. Not surprisingly, with smaller populations and with

groups of subjects less well selected in terms of exposure, detection of this relationship has been even more difficult.

In *CCR2*, a valine-to-isoleucine (I) mutation at position 64 in the coding region has been associated with favorable prognosis, among heterozygous HIV-1-infected individuals [16, 67, 74–76]. The effect appeared to be even stronger in conjunction with the $\Delta 32$ variant, among the small fraction of white individuals who carried both variants [16, 67]. Although some variation in the lineage containing the 64I substitution does seem to delay deterioration among some infected patients, the effect has been somewhat inconsistent between white patients and those of African descent in particular [23, 75, 77]. The role of the *CCR2* single-nucleotide polymorphism (SNP) in preventing infection also is somewhat ambiguous. A protective effect of the 64I-bearing genotypes, comparable to that seen for disease progression, has been observed for perinatal transmission [76], but evidence for a role in decreased susceptibility in the context of sexual transmission is mostly lacking [16, 21, 78].

Extensive research on polymorphisms in the *CCR5* promoter region has been highly informative. In several studies, certain patterns of SNPs distributed along the promoter sequence appear to be involved in the occurrence of HIV-1 infection and disease. One important set of SNPs has been found in a composite haplotype called “P1” [79] and in a single subgroup of these SNPs, designated human haplogroup or haplotype E (HHE) [16, 23, 24, 77]. In white individuals, the homozygous genotype (HHE/HHE) has been associated with both increased likelihood and an accelerated course of infection, including perinatal infection [24]. One other study of acquisition has suggested a relationship in Thai HEPS individuals [80] that was compatible with the primary effect of HHE in white individuals. Homozygosity for a haplotype designated “HHD” [23], which is found more commonly in ethnic African individuals, has been reported to be associated with increased perinatal infection [81] and with more-rapid progression [82], but the relationship has not been confirmed for transmission by any other mode.

CCL5 (encoding RANTES). Recent work suggests that polymorphisms in *CCL5* alter the likelihood and the course of infection. Variations at 2 promoter SNPs (at –403 and –28) and at 2 other downstream sites form haplotypes that differentially modulate RANTES expression and its interference with virus replication. Two haplotypes marked by –403A and –28C or by one of the other shared SNPs have shown some but not complete consistency in their disadvantage to exposed uninfected individuals, as well as to infected individuals [65, 83]. Conversely, the –28G variant, which is found much more frequently in Asian individuals, seemed to contribute favorably to the prognosis for infected persons, whereas carriers of 28G showed no predisposition to infection, in Japanese populations [84]. Further assessment of this SNP in populations of European and African origin will be difficult. In short, *CCL5* poly-

morphisms may be added to table 1 in the near future, but interpretation of the findings to date is difficult in view of differences in the extent of genetic typing and the populations examined.

CXCL12 (encoding SDF-1). In investigations reported thus far, the effects on disease progression of the single variant 3'A at position 801 in the untranslated region of *CXCL12*, in either the homozygous or the heterozygous state, have been less consistent than those observed for the *CCR* and *CCL* polymorphisms [67, 85, 86]. The few studies of this variant marker of susceptibility to infection are even more difficult to interpret: none have definitively implicated it as a predisposing or protective factor in susceptible individuals [87, 88].

HLA and the Antigen-Presenting System

The central importance, to HIV-1 pathogenesis, of the major histocompatibility complex (MHC) class I antigen-processing and -presenting system is no longer in doubt [77, 89–92]. Class I alleles differentially bind peptides, restrict generation of CD8⁺ cytotoxic T lymphocytes (CTLs), and govern response to viral antigens. CTLs destroy infected cells in HIV-1–positive individuals by targeting HIV-1 peptides bound to class I molecules on infected cells and, presumably, by establishing a dynamic equilibrium between evolving virus and the HLA-restricted adaptive arm of host immunity [93–98]. HLA class I molecules also interact with NK cells through their complex set of activating and inhibiting receptors [99, 100], although NK cell response in HIV-1 infection has been less intensively investigated than CTL activity [101–104]. Thus, the HLA class I system heavily regulates 2 crucial, intertwined mechanisms for controlling the virus.

Both CTL and NK cell activity also are considered to be highly likely to promote or impede the initial establishment of infection. In HEPS individuals, HIV-1–specific CTL responses to viral products—if not to replicative virus—have been reported [105–109], but demonstrating that the CTLs are actively protecting against infection, rather than simply circulating in the wake of virus exposure, has not been easy. In addition, sufficient data have not been found for NK cell activation in seronegative individuals that would support a prominent role for interaction with that class I–mediated pathway as a mechanism of protection. Although the belief that class I variation accounts for the differential likelihood of acquiring HIV-1 infection may have been tempered by the uncertainty about protective CTL or NK cell responses, certain phenomena of class I polymorphism have been increasingly implicated as risk modifiers.

Class I homozygosity. Although homozygosity at class I loci has been found to be strongly associated with poor control of and relatively rapid disease progression, in cohorts of populations of white individuals and those of African ancestry [110–112], this lack of diversity at class I loci has not proved to be

disadvantageous for seronegative individuals susceptible to initial acquisition of infection. No disadvantage has been reported either for the same MACS comparison groups (HEPS individuals vs. those who seroconverted) that yielded relationships for both *CCR* and *HLA* polymorphisms [16, 29] or for HIV-discordant couples in Zambia who displayed other effects of class I polymorphism (see below).

HLA class I allele sharing. In contrast, there is intriguing evidence that identity of HLA class I alleles between potential virus donors and recipients increases the susceptibility of the latter. In the absence of antiretroviral therapy, sharing of the same alleles at class I loci (with or without sharing at class II loci) between infected pregnant women and their infants increased the likelihood of mother-to-child (MTC) transmission [25, 26]. If verified, the phenomenon suggests increased maternal alloreactivity to and destruction of nonidentical infant cells. Among heterosexual partners, modest efforts have been inconsistent in reproducing an analogous effect on susceptibility resulting from sexual contact [27, 108], whereas investigation of HIV-discordant, cohabiting couples in Zambia has documented highly significant enhancement of susceptibility associated with concordance at the *HLA-B* locus but not at the *HLA-A* or *HLA-C* locus [28].

The likely increase in susceptibility in an exposed individual who shares the same alleles at class I loci with a potential donor may offer particularly useful biological insight. Donor-recipient concordance at ≥ 1 class I locus may strongly favor penetration of donor viruses or infected cells conditioned by the shared alleles. By displaying a molecular profile resembling that of the recipient (i.e., “self”), divergent donor viruses may partially circumvent the protection conferred on the larger proportion of recipients who carry a distinctive allele profile (i.e., “foreign”).

Individual HLA class I alleles. Certain specific groups of class I alleles have profound effects on the outcome of infection. Two (*HLA-B*27* and **57*) have been consistently associated with a favorable prognosis, mostly by influencing early viral equilibration [77, 111, 113–119]. *HLA-B*57* confers a favorable effect irrespective of differences in ethnicity, virus clade, and risk group [118–121]. These 2 consistently favorable *HLA* allele groups also have promoted more-frequent CTL responses to canarypox-HIV vaccine in uninfected volunteers [92]. Frequent detection of immunodominant CTL responses to conserved HIV-1 epitopes may account for the epidemiological findings [118, 122, 123]. Similar CTL responses have been detected in chimpanzees with analogous *HLA* alleles [124]. In striking contrast, no study of susceptibility has uncovered even moderate protection by either of the 2 groups of class I alleles [28, 29, 125–128]. Because *HLA-B*27* alleles are less frequent in most populations and quite uncommon in individuals of African ancestry, detection of their role, if any, in facilitating acquisition could be difficult. For the more common *HLA-B*57* alleles, the

lack of protection against HIV-1 infection seems particularly surprising, in view of the selectively strong CTL response generated by HIV-1 vaccine constructs administered to uninfected individuals [92].

At the other extreme, several allele groups (the B22 serogroup, *HLA-B*35*, and *HLA-B*53*) have been rather convincingly associated with unfavorable prognosis or higher viral RNA levels in infected persons [77, 110, 114, 116, 129–131]. According to a proposed hypothesis, the often-observed deleterious effect of *HLA-B*35* alleles is confined largely to *HLA-B*3502* and **3503*, in which the preferred peptide motifs consist of a proline at anchor position 2 and a nontyrosine residue at position 9 [132]. *HLA-B*53* very closely resembles these 2 alleles in its motif preference. In contrast, the tyrosine-preferring *HLA-B*3501* may influence prognosis very little. On the other hand, motif data for the former 2 *HLA-B*35* alleles are sparse, and studies of Zambian HIV-1 subtype C–infected subjects with ample frequency of *HLA-B*53* alleles have not supported such a distinction [119]. Other members of the B7 supertype allele group (e.g., *HLA-B*07* and the B22 serogroup) also preferentially bind motifs with a proline at position 2 but a greater variety of residues at position 9; only the latter group also has been clearly associated with an unfavorable outcome [116, 131]. No other single *HLA-B* allele has been shown to exert influence on the course of infection at a similar magnitude and statistical significance, and no associations between *HLA-A* or *HLA-C* alleles and disease control have been convincingly documented. With regard to infection, a report from the MACS has recently demonstrated a comparable disadvantage for *HLA-B*3502* and **3503* [29], but any indication of a similar effect due to any other *HLA-B* allele has not yet been found.

Although no clear prognostic effect has yet been established for any *HLA-A* allele in infected persons, 1 group of *HLA-A* alleles has been reported to protect against initiation of infection, in some but not all populations. An earlier indication that members of the *HLA-A2/A6802* supertype protected Kenyan women from HIV-1 subtype A infection [126] was followed by a report that these alleles also diminished MTC transmission, among the infants of these women (sex workers) [30]. More recently, the subset of alleles in the *HLA-A0205/A6802* cluster in the same *HLA-A2/A6802* supertype was observed more frequently among HEPS individuals than among those with HIV-1 subtype B seroconversion, in the MACS [29]. However, *HLA-A*6802*–seronegative partners among a large number of Zambian couples discordant for HIV-1 subtype C infection unequivocally showed, if anything, a predisposition to seroconversion (R.A.K., unpublished data). Whether this apparent disparity is due primarily to virus subtype or other differences will be important to learn. No association between any other allele and the occurrence of infection has been consistent enough to recognize as confirmed [80, 125–128, 133, 134].

CONCLUSION

As with disease prognosis for HIV-1–infected individuals, evidence is persuasive that the risk of acquiring infection is modulated by genetic polymorphisms in the chemokine receptor/ligand and the antigen-processing/presentation systems. Effects of variations in other gene systems also have been suggested (e.g., *HLA-DR/DQ* and *IL10*) [26, 135–137], and more will undoubtedly be discovered. To date, research has established both reassuring consistencies across populations and clear inconsistencies due to differential distribution, by ethnicity, of specific variants. Methodological obstacles to studying the genetics of acquisition in uninfected individuals will continue to limit the reproducibility of each new finding. However, unequivocal differences between the effects of markers on acquisition and their effects on disease progression should yield valuable insight into the contributions of genetic variation to the timing, as well as the nature, of host genetic contributions to HIV infection and AIDS.

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