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# Influence of Human Leukocyte Antigen–B22 Alleles on the Course of Human Immunodeficiency Virus Type 1 Infection in 3 Cohorts of White Men

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The human leukocyte antigen (HLA)–B22 serogroup—which consists of the alleles *B\*54*, *B\*55*, and *B\*56*—has been associated with rapidly progressive disease in white patients with human immunodeficiency virus (HIV) infection. Subjects from 3 cohorts of men who have sex with men ( $N = 671$ ), all of whom experienced HIV-1 seroconversion at roughly the same time, were molecularly typed at *HLA-A*, *-B*, and *-C* loci. Mean HIV RNA loads during early HIV infection were higher in B22-positive men than in B22-negative men (difference, 0.481 log<sub>10</sub> HIV RNA copies/mL; 95% confidence interval [CI], 0.156–0.806 log<sub>10</sub> HIV RNA copies/mL;  $P = .004$ ). Independent of accepted markers of progression, time-to-AIDS was shorter in B22-positive seroconverters (adjusted hazard ratio, 1.98; 95% CI, 1.27–3.10;  $P = .003$ ). White B22 serogroup alleles (*B\*55* and *\*56*) appear to predispose to unfavorable outcome of HIV infection as strongly as some or all *B\*35* and *B\*53* alleles. This finding may have greater implications for Asians, because the marker frequency for B22 is higher among Asians than among whites (~10% vs. ~4%).

Host genetic variation influences the outcome of human immunodeficiency virus (HIV) type 1 infection [1–3]. The effect of HLA class I loci appears to be stronger than those of other known genetic influences on the disease process at the population level [4–7]. Homozygosity at HLA class I loci increases the likelihood of more-rapid disease progression [5, 8, 9]. Specific *HLA-B* alleles have been repeatedly associated with

either faster or slower disease progression [4, 5, 9–15], and effects of that allelic variation also have been seen at early stages of infection [6, 7, 16, 17].

Although some of these genetic effects undoubtedly differ by race, virus subtype, route of transmission, and other factors, replication of findings from one cohort to another provides reassurance of their validity, as well as their generalizability. Individual *HLA-B* alleles showing the most consistent relationships with clinical outcome of HIV infection usually have population frequencies >5%. However, lower allele frequencies in study cohorts of limited size would likely preclude recognition of modest allele-specific effects. The association of poor prognosis with the serologically defined HLA-B22 serogroup [13] is an example of a heretofore unconfirmed association with a relatively infrequent allele group.

Our access to 3 long-standing cohorts of white, HIV-1-infected, men who have sex with men offered sufficient statistical power to reexamine the deleterious effect of the *HLA-B22* serogroup. Here, we report that *HLA-B22* is associated with unequivocally higher early

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HIV-1 load and faster progression to AIDS in HIV-1-infected white men. Although those findings would be important in their own right, they are of particular interest, because the B22 cluster (representing a total of 18 alleles of *B\*54*, *B\*55*, and *B\*56* [18]) belongs to the *HLA-B7* supertypic group, which also contains the *HLA-B\*35* and *B\*53* alleles that are known for their unfavorable influence. The B22, *B\*35*, and *B\*53* allele groups share affinity for cytotoxic T lymphocyte peptide binding motifs containing proline at anchor residue position 2; however, unlike the *B\*3502*, *B\*3503*, and *B\*53* alleles, those in the B22 group may show less restriction in their position 9 residue repertoire than that reported to account for the *B\*35/53* association with more-rapid progression to AIDS [19].

## SUBJECTS AND METHODS

**Subject selection and outcome measurement.** We studied 671 white men from the Multicenter AIDS Cohort Study (MACS;  $n = 438$ ), the DC Gay cohort (DCG;  $n = 93$ ), and the Amsterdam Cohort Study (ACS;  $n = 140$ ), all of whom experienced HIV-1 seroconversion at roughly the same time ( $\pm 12$  months for  $>90\%$  of subjects) and who had molecular *HLA* and *CCR2-5* typing data and follow-up data available for up to 13 years before the censoring date (1 January 1996), before the widespread use of highly active antiretroviral therapy. For 305 MACS and 39 DCG participants, at least 1 measurement of plasma HIV-1 RNA load was taken within the first 42 months after seroconversion. Those men did not differ meaningfully from the remaining MACS and DCG study populations with regard to median person-years of follow-up, proportions with other contributory genetic markers (see below), median time to AIDS, or AIDS-defining condition. For all 3 groups of seroconverters (SCs), the clinical end point was AIDS, as defined by 1987 Centers for Disease Control and Prevention criteria [20].

**Genetic typing.** *HLA* class I genes were typed initially by polymerase chain reaction (PCR) with sequence-specific primers (SSP), either according to published protocols [21] or by using a commercially available typing kit (Pel-Freez Clinical Systems), which defined alleles largely as 2-digit specificities. Individuals with apparent homozygosity at any *HLA* class I locus were either typed by sequencing, using the ALFexpress automated sequencer (Amersham Pharmacia Biotech) [22], or were analyzed by reference strand conformation analyses (Pel-Freez Clinical Systems). PCR-SSP-based *CCR2* and *CCR5* typing was performed as described elsewhere [23, 24].

**Statistical methods.** In the cohorts treated separately and in aggregate, men who carried an allele in the B22 serogroup (*B\*54*, *\*55*, and *\*56*) were compared with those who did not. Longitudinal analysis for correlated virus load measurements at baseline ( $<6$  months), 6–18 months, 19–30 months, and 31–42 months was performed to compare B22-positive subjects to

others, adjusted for the effects of *HLA* class I homozygosity; *B\*27*, *\*35*, *\*53*, *\*57*, and *CCR2-CCR5* haplotypes [24, 25]; and the time effect through mixed models (SAS MIXED procedure [26]). Mixed models were also used to assess the effects of markers on viral dynamics during the 40-month period for the correlated virus load measurements. Times from seroconversion to AIDS were analyzed as Kaplan-Meier plots, with differences assessed by log-rank tests of significance. By use of stratified Cox proportional hazards models, we estimated hazard ratios (HRs) of AIDS for B22, adjusting for the effects of the above-mentioned genetic markers and for the cohort effect. Adjusted results were verified by repeating comparisons in the aggregated cohorts with subjects restricted to participants carrying none of those other markers. HIV RNA load measurements (values transformed to  $\log_{10}$ ) and survival analyses were censored at 1 January 1996. All analyses were performed with statistical routines in SAS software (version 8.02; SAS Institute).

**Linkage disequilibrium (LD) analysis.** Patterns of LD at *HLA* class I loci were determined for 313 subjects in the MACS cohort typed at *HLA-A*, *-B*, *-Cw*, and *-DRB1* loci, using Francis Yeh's PopGene software (version 1.32; available at: <http://www.ualberta.ca/~fyeh>). Hardy-Weinberg equilibrium in the 3 *HLA* class I loci also was examined using the same software. LD was quantified by the  $\Delta$  value, which represents the difference between observed and expected frequency.

## RESULTS

**Cohort characteristics.** Overall age and median AIDS-free times were comparable for the SCs from the MACS, DCG, and ACS (table 1). Frequencies of contributing *HLA* class I alleles, including those of the B22 serogroup, and contributing *CCR* haplotype frequencies did not differ substantially among the cohorts. All loci analyzed were in Hardy-Weinberg equilibrium.

**Virus load.** Overall, mean  $\log_{10}$  HIV RNA loads were higher in the B22-positive than in B22-negative MACS and DCG participants (table 2) in each of the 4 intervals during the 42 months after seroconversion (figure 1). The differences ranged from 0.34 to 0.63  $\log_{10}$  HIV RNA copies/mL and were independent of other major genetic markers of progression ( $P = .004-.19$ ). Comparing B22-positive and -negative men for the entire 42-month period, the overall adjusted difference was significantly different ( $P = .004$ ).

**Individual B22 alleles.** The mean HIV RNA loads (table 2) for each individual B22 allele were increased. However, no subjects with virus load data available carried *B\*54*, and the numbers of subjects with *B\*55* and *B\*56* were insufficient to establish equivalence in the magnitude of their separate effects.

**Time-to-AIDS.** Kaplan-Meier plots of data from the 3 cohorts analyzed jointly and separately demonstrated significantly more rapid progression among B22-positive SCs than

among other SCs (figure 2). In the combined cohorts, the HR of AIDS conferred by B22 was 1.97 (95% confidence interval [CI], 1.26–3.06;  $P = .003$ ) before and 1.76 (95% CI, 1.11–2.79;  $P = .017$ ) after adjustment for the other genetic markers of progression (including HLA-Cw\*0303; see below), again indicating the independence of the B22 effect from other known HLA and CCR effects (tables 3 and 4). The 3 cohorts were comparable with respect to time-to-AIDS, as measured by the homogeneity of survival curves by log-rank test ( $P = .38$ ).

**LD.** We searched in the largest of the 3 cohorts (MACS), which had complete high-resolution typing of HLA-A, -B, and -Cw alleles, for LD as a possible explanation for the B22 effect. No HLA-A allele was in sufficiently strong LD to contribute. The most common Cw allele found in a B22 haplotype was Cw\*0303; LD between the 2 was significant ( $P = .001$ ;  $\Delta$ [LD parameter], 0.0049). Although participants with Cw\*0303 (in the absence of B22) had higher mean virus load ( $4.45 \pm 0.40 \log_{10}$  HIV RNA copies/mL; table 2) and increased HR (1.68; 95% CI, 1.19–2.36;  $P = .003$ ), the entire group of B22-positive SCs showed the strongest relationships (tables 2 and 4). Conversely, the B22 effect was evident in the absence of Cw\*0303: mean virus load was still high ( $4.78 \pm 0.50 \log_{10}$  HIV RNA

copies/mL) in the 11 SCs who were positive for B22 but negative for Cw\*0303 (table 2). In 642 subjects who were HLA-B22 negative, the effect of HLA-Cw\*0303 on time-to-AIDS was sought in the presence of the same covariates. It showed a significant risk effect in the “absence” of B22 (HR, 1.51; 95% CI, 1.08–2.11;  $P = .017$ ), but its effect was somewhat weaker in the presence of HLA-B22 (table 4). Cw\*0303 occurred in stronger LD with B\*1501 ( $P < .0001$ ;  $\Delta$ , 0.0128), but the HLA-Cw\*0303-B\*1501 haplotype was not associated with higher HIV RNA load ( $P = .19$ –.98) or rapid disease progression ( $P = .14$ ). There is no known strong LD of B22 with any DRB1 alleles in white subjects.

**Possible alternative explanations.** Two other possible explanations were considered. Homozygosity at HLA class I loci could not account for the B22 effect. Only 1 subject was homozygous for B22 (B\*5501/\*5601); 20.7% of B22-positive and 22.3% of B22-negative SCs were homozygous for A and/or Cw alleles. Likewise, the B22 serogroup did not exert its effect through an association with any specific AIDS outcome because the frequencies of presenting AIDS diagnoses were quite similar among HLA-B22-positive and -negative subjects in the MACS.

**Table 1. Characteristics of the genetically typed human immunodeficiency virus type 1-positive subjects in the Multicenter AIDS Cohort Study (MACS), DC Gay (DCG), and Amsterdam Cohort Study (ACS) populations and frequency distribution of HLA-B and CCR allele and genotypes associated with progression to AIDS and/or virus load.**

Characteristic	MACS (n = 438)	DCG (n = 93)	ACS (n = 140)
Age, mean years	34.7	35.3	35.1
Time to AIDS, median years (95% CI)	8.51 (8.00–9.46)	8.89 (7.12–9.46)	8.37 (7.16–9.60)
Allele <sup>a</sup>			
HLA-B*08	11.2 (18.9)	11.1 (21.5)	13.2 (24.3)
HLA (B22) <sup>b</sup>	<b>2.0 (3.7)</b>	<b>4.8 (9.7)</b>	2.1 (4.3)
HLA-B*54	<b>0.0</b>	<b>0.5 (1.1)</b>	0.0
HLA-B*55	<b>1.4 (2.7)</b>	<b>3.7 (7.5)</b>	1.4 (2.9)
HLA-B*56	<b>0.6 (1.1)</b>	<b>0.5 (1.1)</b>	0.7 (1.4)
HLA-B*27	4.2 (8.2)	6.3 (11.8)	3.9 (7.9)
HLA-B*35	9.3 (16.7)	11.1 (20.4)	12.1 (22.9)
HLA-B*53	0.9 (1.8)	0.0	0.0
HLA-B*57	4.6 (8.7)	6.3 (10.8)	3.2 (6.4)
CCR5*G2 <sup>c</sup>	8.6 (17.1)	8.6 (17.2)	7.9 (15.7)
CCR2*F2 <sup>c</sup>	9.8 (18.3)	7.5 (15.1)	8.9 (15.0)
CCR*E/E (genotype) <sup>d</sup>	11.9	9.7	10.0

**NOTE.** B22 frequencies are in bold type. CI, confidence interval.

<sup>a</sup> Allele frequencies are based on chromosome nos. (2N); marker frequencies (prevalence) shown in parentheses are based on no. of individuals (N).

<sup>b</sup> The B22 serogroup includes B\*54, B\*55, and B\*56 combined.

<sup>c</sup> CCR2\*F2 corresponds to allele 64I, and CCR5\*G2 carries the  $\Delta$ 32 mutation.

<sup>d</sup> CCR\*E/E represents homozygosity for the haplotype E, which is the most common CCR2–CCR5 haplotype that does not carry the CCR2\*64I and CCR5\* $\Delta$ 32 mutations [46].

**Table 2. Human immunodeficiency virus (HIV) RNA load during the initial 42 months of infection in subjects in the Multicenter AIDS Cohort Study and DC Gay cohorts with combinations of HLA-B\*55 and -B\*56 B22 and HLA Cw\*0303.**

Allele	No. of subjects	HIV RNA load, mean log <sub>10</sub> copies/mL ± SD
B22 negative	326	4.27 ± 0.69
B22 positive	18	4.75 ± 0.52
HLA-B*55 (B22)	14	4.80 ± 0.54
HLA-B*56 (B22)	5	4.56 ± 0.40
HLA-Cw*0303	27	4.52 ± 0.46
HLA-B22 positive and Cw*0303 negative	11	4.78 ± 0.50
HLA-B22 negative and Cw*0303 positive	20	4.45 ± 0.40
HLA-B22 positive and Cw*0303 positive	7	4.71 ± 0.59
HLA-B22 negative and Cw*0303 negative	306	4.26 ± 0.70

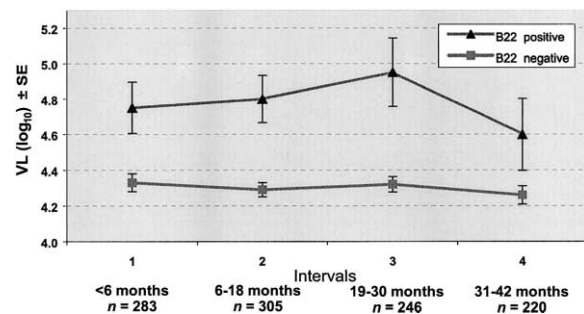
## DISCUSSION

In 3 separate groups from 3 HIV-1 subtype B-infected cohorts of North American and Dutch white men, the HLA-B22 serogroup (primarily, B\*55 and B\*56 alleles) was uniformly associated with higher early virus load and less favorable clinical disease course. These findings corroborate a similarly strong relationship previously reported for white subjects in Europe [13]. The inference of equal disadvantage for the far less common B\*54 allele is suggested by in vitro studies showing functional similarity of the B22 family members, presumably due to their similar peptide binding specificities and relatedness of their heavy chains, which differ by only 1–3 aa [27].

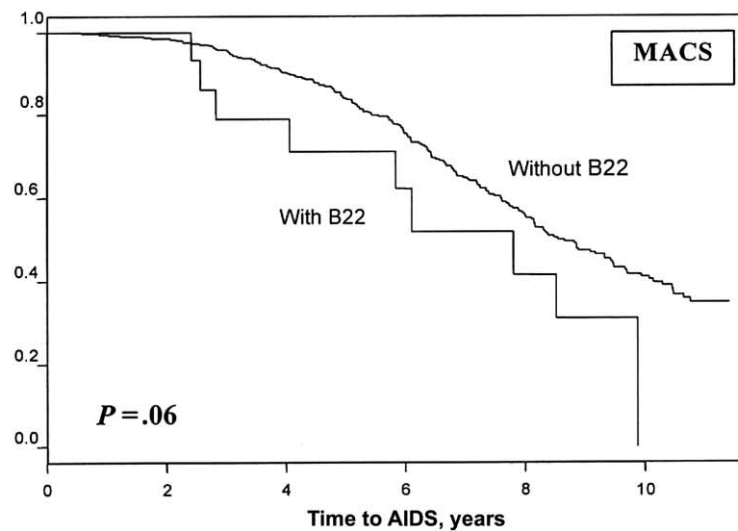
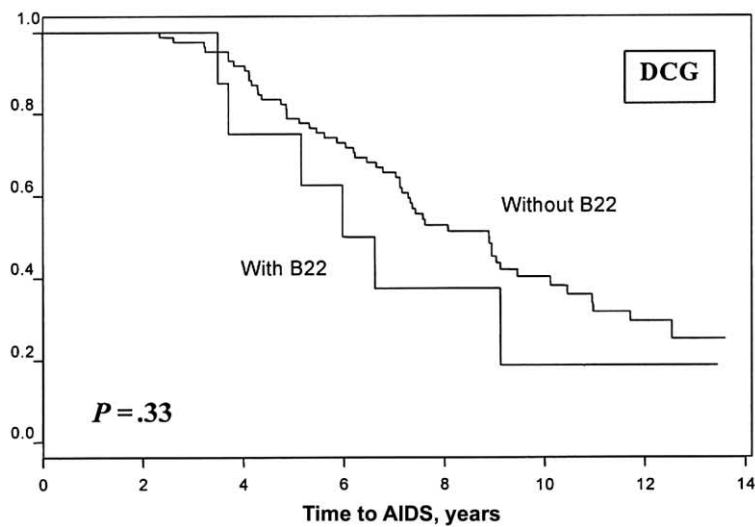
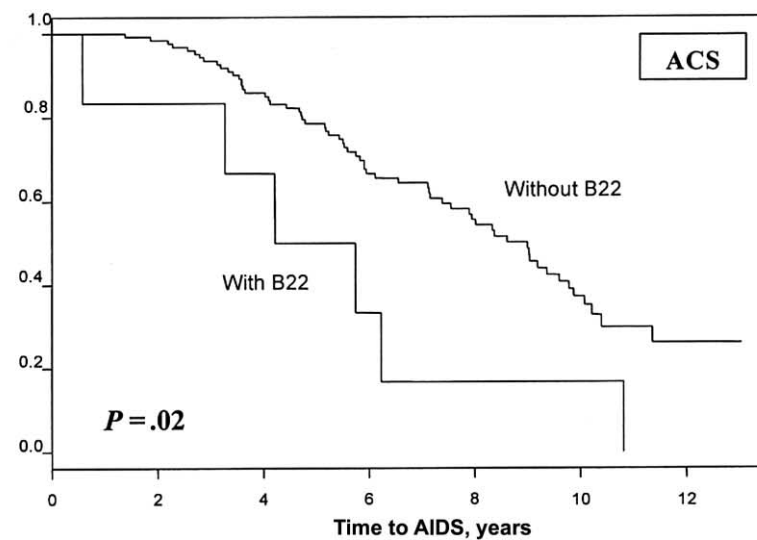
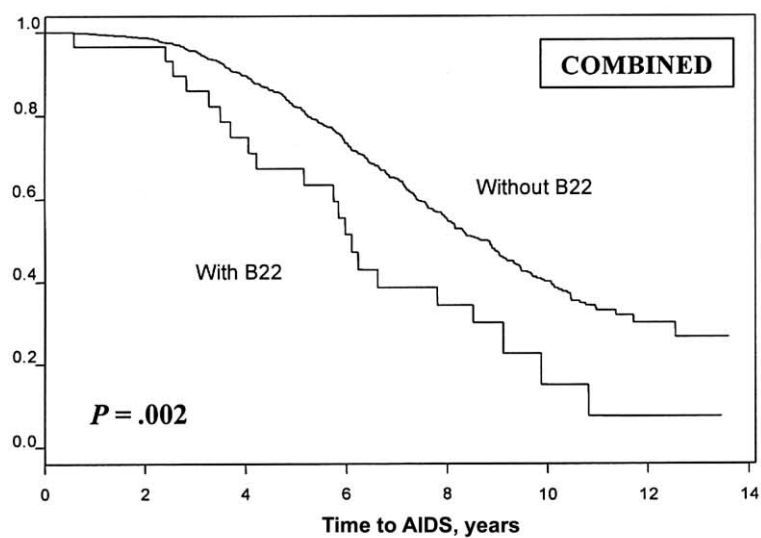
Although the reason for the adverse B22 effect is not clear, alternatives to a causal association seem unlikely. First, typical selection bias must have been minimal, because the relationship was consistent in the 3 independently assembled white populations and in the French cohort where its effect was originally documented [13]. Age and prospective ascertainment of HLA class I alleles, of incident HIV-1 infection, of early HIV RNA load, and of later disease were uniform in each cohort. Likewise, allele and marker frequencies, mean HIV-1 RNA loads, and AIDS-free time were similar across cohorts. Second, bias produced by ethnic admixture was highly improbable, requiring that, in each of 3 rather diverse cohorts, the B22 lineage marked an ethnic subset in which another coincident genetic trait actually conferred the risk. Third, analysis of LD revealed no strong relationships with alleles at nearby loci; in particular, the commonly linked Cw\*0303 did not explain or augment the B22 effect. Fourth, the B22 serogroup was not associated with any specific AIDS-defining condition, and the impact of B22 on

early HIV-1 RNA levels further precluded explanation by such an alternative relationship.

The disadvantage of B22 alleles may have relevance to the similar prominent negative effects observed with HLA-B\*35 and B\*53 alleles [4, 5, 7, 11, 19, 28]. These and other members of the B7 “supertype,” characterized by their partially homologous peptide-binding motifs, contain a proline at the position corresponding to the HLA-binding pocket position 2 (P2) and certain alternative residues corresponding to pocket position 9 (P9) [29–31]. According to one current hypothesis [19], the widely observed deleterious B\*35 effect is likely due exclusively to particular B\*35 alleles (primarily, B\*3502 and B\*3503 in white subjects) and the very closely related B\*53 (in persons of African descent). This subset, called the Px group, ostensibly fails to bind peptides containing a tyrosine (Y) in P9 [29, 32, 33] but rather prefer methionine (M), leucine (L), or isoleucine (I). This preference distinguishes them from B\*3501 (the more common B\*35 allele in both ethnic whites and Africans) and B\*3508 (another less common white allele) alleles that prefer Y at P9. Although relatively few motifs for B22 have been examined, their peptide-binding motifs are considered to be more flexible than those for B\*35 alleles [27, 34]. The only known HIV-1 p24 epitope presented by a B22 (B\*55) carrier does not have Y at P9 [34]. It is possible, that with no apparent affinity for Y at P9, the B22 group may resemble the prognostically unfavorable Px group of B\*35 alleles. Data against this assumption come from the work on other members of the B7 supertype. Several alleles from the B7 supertype (B\*0702–5, B\*5101–5, B\*6701, and B\*8101) that also bind motifs containing a P2 proline and a P9 M/L/I [30, 35, 36] have not been epidemiologically associated with poor response to HIV-1. In subjects of African descent, B\*8101 has been found more frequently in patients classified as slow progressors with subtype



**Figure 1.** Mean virus loads (VLs) at 4 intervals in the combined group of human immunodeficiency virus seroconverters. Repeated measures of VLs were analyzed by the SAS MIXED procedure [26]. The overall difference between the B22-positive and -negative subjects was significant ( $P = .004$ ). Interaction between B22 and the 4 time points was not significant ( $P = .93$ ).  $P$  values are adjusted for other variables influencing the VL.



**Figure 2.** Kaplan-Meier plots of time-to-AIDS in B22-group carriers and others in combined Multicenter AIDS Cohort Study (MACS), Amsterdam Cohort Study (ACS) and DC Gay (DCG) cohorts. Significance of the differences between the carriers and others was determined by the log-rank test.

**Table 3. Proportional hazards analysis for progression to AIDS with and without HLA-B22 (*B\*54*, *\*55*, and *\*56*) in the Multicenter AIDS Cohort Study (MACS), the DC Gay (DCG) Cohort, and the Amsterdam Cohort Study (ACS).**

Cohort, strata	Time-to-AIDS, median years (95% CI)	RH (95% CI) <sup>a</sup>	P <sup>b</sup>
ACS (N = 140)			
B22 negative (n = 134)	9.00 (7.39–9.78)		
B22 positive (n = 6)	4.98 (3.28–6.23)	2.04 (0.83–5.02) <sup>c</sup>	.02
MACS (N = 438)			
B22 negative (n = 423)	8.54 (8.01–9.47)		
B22 positive (n = 15)	7.80 (4.06–9.88)	1.44 (0.70–2.95) <sup>d</sup>	.06
DCG (N = 93)			
B22 negative (n = 85)	8.89 (7.29–10.12)		
B22 positive (n = 8)	6.30 (3.71–9.12)	1.57 (0.56–4.36) <sup>e</sup>	.33
Combined (N = 671)			
B22 negative (n = 642)	8.65 (8.08–9.17)		
B22 positive (n = 29)	6.11 (4.22–8.51)	1.76 (1.11–2.80) <sup>f</sup>	.002

**NOTE.** CI, confidence interval; RH, relative hazard.

<sup>a</sup> Adjusted for commonly accepted markers of progression (*HLA*-class I homozygosity, *HLA-B\*27*, *B\*57*, *B\*35*, and *B\*53* along with specific *CCR2-CCR5* haplotypes [24, 25]).

<sup>b</sup> Log-rank test for equality of survivorship functions across strata.

<sup>c</sup> P = .13.

<sup>d</sup> P = .11.

<sup>e</sup> P = .39.

<sup>f</sup> P = .02.

C infection (J.T., C. Wilson, S. Allen, and R.A.K., unpublished data). Thus, the B22 association reflects some compatibility with, but not clear support for, the motif-based hypothesis about differential effects of *B\*35* subtype.

If B22 is capable of presenting a larger variety of peptides derived from HIV-1 than the *B\*35* alleles with the P9 restriction, viral equilibrium and disease course would have been expected to be indifferent to the presence of B22 [37]. The observed unfavorable outcome could imply that effective presentation and response depend less on linear binding motifs and more on conformational ones not immediately apparent from the peptide sequence alone. Alternatively, *B\*35/B\*53* and B22 may share certain physical characteristics that make them unfavorable for HIV-1 peptide presentation, not because of their binding motifs but because of their interaction with chaperones [38, 39]. Finally, although we could not discern stronger effects from alleles at the nearby loci examined, the observed vulnerability may still reflect effects of other unidentified markers on the

B22-carrying haplotypes (e.g., alleles described for the neighboring major histocompatibility complex class I-related chain genes and major histocompatibility complex class III genes).

Further indications that B22 (and perhaps other members of the B7 supertype) might have a more general effect on the immune response are the reports that the predominantly Asian *HLA-B\*54* confers susceptibility to other viral infections: immunological nonresponse to hepatitis B virus surface antigen [40], myelopathy due to human T-lymphotropic virus type I [41], and progression of liver injury [42] and unresponsiveness to interferon- $\alpha$  treatment [43] in hepatitis C virus infection. The relatively low frequencies of B22 alleles in white subjects may have precluded recognition of a more-generic mechanism governing chronic viral infection.

If all B22 alleles pose equivalent risk for poor control of HIV-1 viremia and accelerated course of disease, the impact may be expected to be greater in Asian populations, where the combined prevalence of the 3 alleles is >10%, triple the prevalence in white subjects and those of African descent [44, 45]. Interaction of *B\*54* with the predominant HIV-1E and HIV-1C subtypes more prevalent in Asia could differ from that of *B\*55* and *B\*56*, with subtype B viruses more common in regions inhabited by white subjects. Therefore, confirmation of our findings in HIV-1-infected Asian subjects is critical. Meanwhile, investigators studying infection in persons of Asian descent should be alert to the potential clinical and epidemiologic consequences of *B\*54*, along with other previously documented *HLA* determinants of HIV disease progression.

**Table 4. Relative hazard (RH) of AIDS for B22 (*B\*54*, *\*55*, and *\*56*), mutually adjusted for other associated genetic markers and cohort effect, in the combined Multicenter AIDS Cohort Study, DC Gay (DCG) Cohort, and Amsterdam Cohort Study (N = 671).**

Marker	No. of subjects	RH (95% CI)	P
B22 serogroup	29	1.76 (1.11–2.79)	.02
<i>B*27</i> or <i>B*57</i>	108	0.50 (0.34–0.72)	.0003
<i>B*35</i> or <i>B*53</i>	130	1.53 (1.17–2.00)	.002
Class I homozygosity	204	1.31 (1.03–1.66)	.03
<i>CCR2*E/E</i> <sup>a</sup>	75	1.33 (0.94–1.88)	.11
<i>CCR2*F2</i> <sup>b</sup>	115	0.92 (0.68–1.24)	.57
<i>CCR5*G2</i> <sup>b</sup>	112	0.83 (0.61–1.27)	.23
<i>HLA-Cw*0303</i>	85 <sup>c</sup>	1.42 (0.99–2.03)	.06

**NOTE.** P < .0001 for the model; no variables other than those shown were included.

<sup>a</sup> *CCR2\*E/E* represents homozygosity for the haplotype E, which is the most common *CCR2-CCR5* haplotype that does not carry the *CCR2\*64I* and *CCR5\* $\Delta$ 32* mutations [46].

<sup>b</sup> *CCR2\*F2* corresponds to allele 64I, and *CCR5\*G2* carries the  $\Delta$ 32 mutation [46].

<sup>c</sup> Because of the lack of high-resolution *HLA-Cw* typing in the DCG cohort, all *HLA-Cw\*03*-positive subjects from that cohort were included in this analysis.

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