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Human Leukocyte Antigen Genotype and Risk of HIV Disease Progression before and after Initiation of Antiretroviral Therapy▽‡

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While the human leukocyte antigen (HLA) genotype has been associated with the rate of HIV disease progression in untreated patients, little is known regarding these relationships in patients using highly active antiretroviral therapy (HAART). The limited data reported to date identified few HLA-HIV disease associations in patients using HAART and even occasional associations that were opposite of those found in untreated patients. We conducted high-resolution HLA class I and II genotyping in a random sample ($n = 860$) of HIV-seropositive women enrolled in a long-term cohort initiated in 1994. HLA-HIV disease associations before and after initiation of HAART were examined using multivariate analyses. In untreated HIV-seropositive patients, we observed many of the predicted associations, consistent with prior studies. For example, HLA-B*57 ($\beta = -0.7$; 95% confidence interval [CI] $= -0.9$ to -0.5; $P = 5 \times 10^{-11}$) and Bw4 ($\beta = -0.2$; 95% CI $= -0.4$ to -0.1; $P = 0.009$) were inversely associated with baseline HIV viral load, and B*57 was associated with a low risk of rapid CD4$^+$ decline (odds ratio [OR] $= 0.2$; 95% CI $= 0.1$ to 0.6; $P = 0.002$). Conversely, in treated patients, the odds of a virological response to HAART were lower for B*57:01 (OR $= 0.2$; 95% CI $= 0.0$ to 0.9; $P = 0.03$), and Bw4 (OR $= 0.4$; 95% CI $= 0.1$ to 1.0; $P = 0.04$) was associated with low odds of an immunological response. The associations of HLA genotype with HIV disease are different and sometimes even opposite in treated and untreated patients.

Human leukocyte antigen (HLA) molecules play a central role in the immune response to HIV by presenting viral antigens to T cells. Specifically, HLA class I molecules are expressed on the cell surfaces of most nucleated cells, where they present intracellularly produced antigens to CD8$^+$ cytotoxic T lymphocytes (CTLs), the major effector cells of the adaptive immune system. HLA class II molecules are expressed by specialized antigen-presenting cells and present antigens from extracellular sources to CD4$^+$ T cells, major regulators of the adaptive immune response.

HLA genes are highly polymorphic, and these variations can result in differences in the antigen binding characteristics of HLA molecules. Prior studies have reported that specific HLA class I alleles are associated with the rate of HIV disease progression. In particular, a series of well-conducted prospective investigations have shown that HLA-B*57, B*27, the Bw4 allele group, and heterozygosity at HLA class I loci are each strongly associated with slower HIV disease progression (reviewed in references 9, 11, and 18). Conversely, the B*35(Px) group has been associated with rapid HIV disease progression (10, 15).

These prior studies, though, focused on specimens and data obtained prior to the use of highly active antiretroviral therapy (HAART). Few studies have examined the relationship of HLA polymorphism and HIV disease progression in individuals currently using HAART (2, 7, 35). Nonetheless, there is substantial interindividual heterogeneity in disease progression among patients using HAART, suggesting that genetic or other host factors may continue to influence HIV disease progression following HAART initiation. For example, 15% to 30% of individuals receiving virologically suppressive HAART

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do not attain substantial increases in $CD4^+$ T cell levels (16). However, the host factors associated with the risk of immunological nonresponse are not well known (16).

Among the three studies of which we are aware that examined the relationship of HLA genotype with outcomes in HAART users, only a single finding in one study was consistent with those in untreated patients, a positive association between class I heterozygosity and subsequent increases in $CD4^+$ count (7). In fact, B*57 (in two studies) and Bw4 (in one study) were associated with a smaller increase in $CD4^+$ count following HAART initiation (2, 35), inconsistent with the protective effects of these alleles found in numerous studies of patients prior to HAART.

The reasons for these counterintuitive results are unclear. However, no studies to our knowledge have examined the relation of HLA genotype with long-term risk of AIDS events in HAART users, nor have any studies examined HLA alleles other than those reported to be significant prior to HAART, i.e., to identify HLA associations with HIV disease progression that might only be significant in patients using HAART. In the current investigation, therefore, we studied the relation of the HLA genotype with HIV disease progression both before and after HAART initiation in a large, long-term prospective cohort of HIV-seropositive women.

MATERIALS AND METHODS

Study population. The Women's Interagency HIV Study (WIHS) is a prospective, multicenter cohort study of 2,793 HIV-seropositive and 975 at-risk HIV-seronegative women enrolled through similar sources at six clinical sites. The initial enrollment was conducted between October 1994 and November 1995, and a second recruitment occurred during 2001 and 2002. WIHS women are followed semiannually with physical exams, specimen collection including blood, and detailed questionnaires regarding health and behavior (5). The WIHS protocol was approved by each local institutional review board, and all participants signed informed consent. The current analyses used data and specimens collected through February 2008.

Most HIV-seropositive WIHS women provided consent for genetic testing ($n = 2{,}556$). Among these women, we selected a stratified random sample ($n = 899$) for HLA testing. These strata were defined by $CD4^+$ count at enrollment (>500 [$n = 256$], 200 to 500 [$n = 125$], and <200 [$n = 125$] cells/μl) and also included all women who reported injection drug use (IDUs) at enrollment if not already included through sampling by $CD4^+$ count ($n = 393$). IDUs were oversampled in this fashion to ensure sufficient prevalence of hepatitis C virus (HCV) for studies of HLA and HCV viremia. We then excluded women who had received HAART prior to study enrollment ($n = 29$) and women with unknown HCV serostatus ($n = 10$).

Clinical AIDS was defined as self-report of any of the 23 individual AIDS-defining conditions specified in the 1993 CDC classification system for AIDS surveillance (4) and excluded "immunological AIDS" (i.e., a $CD4^+$ count of <200 cells/μl or a $CD4^+$ cell percentage of less than 14%). HAART was defined according to the recommendations of the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS 2008), as follows: the use of three or more antiretroviral medications, one of which has to be a protease inhibitor, a nonnucleoside reverse transcriptase inhibitor, one of the nucleoside reverse transcriptase inhibitors abacavir or tenofovir, an integrase inhibitor (e.g., raltegravir), or an entry inhibitor (e.g., maraviroc or enfuvirtide).

Trends in HAART and non-HAART use in the WIHS cohort have been previously reported in detail (13, 37). Briefly, monotherapy and non-HAART combination regimens were relatively common in the 1990s but declined over time such that these regimens have made up <5% of all regimens during the last 10 years. As measured by person visits (because the same woman could be on different regimens at different times), 80% of all reported regimens have been HAART, while 7% were monotherapy and 13% were non-HAART combination therapy.

Clinical laboratory testing. T cell subsets (no. of cells/μl) were determined by flow cytometry in laboratories participating in the AIDS Clinical Trials Quality Assurance Program (8). Plasma HIV RNA levels were measured through visit 6 with a nucleic acid sequence-based amplification method that had 4,000 copies/ml as its lower threshold of detection (Organon Teknika Corp., Durham, NC). Similar methods with greater sensitivity were used thereafter as they became clinically available (i.e., the lower threshold of detection was 400 copies/ml during visits 7 to 9 and 80 copies/ml thereafter). Phylogenetic analysis to determine HIV-1 subtype has not been conducted for all WIHS women, but all 18 subjects who have been typed were subtype B (23, 34). HCV serostatus was determined at baseline using a commercial second- or third-generation enzyme immunoassay, and HCV viremia was determined in HCV-seropositive women using either the COBAS Amplicor Monitor 2.0, as previously described (3), or the COBAS TaqMan assay (both from Roche Diagnostics, Branchburg, NJ).

HLA genotyping. Genomic DNA was prepared from subjects' lymphoblastoid B cell lines or from peripheral blood lymphocytes. Protocols for HLA genotyping have been standardized through the International Histocompatibility Working Group (http://www.ihwg.org). Briefly, HLA class I genes (HLA-A, -B, and -C) were amplified using locus-specific PCR primers flanking exons 2 and 3, the polymorphic segments of the class I genes. The 1-kb PCR products were blotted on nylon membranes and hybridized with a panel of sequence-specific oligonucleotide (SSO) probes. The HLA alleles were assigned by the reaction patterns of the SSO probes, according to known HLA sequences. Any ambiguous SSO probing was resolved by sequencing analysis, as previously described (15). HLA class II typing was conducted using high-resolution SSO typing for HLA-DQA, -DQB, and -DRB1 loci, using the polymorphic exon 2. DRB genotyping involved a two-step procedure. First, the broad serological DR types were determined using a pair of DRB generic primers and a panel of SSO probes. Allele-level DRB typing was then achieved by using group-specific primers to amplify the DRB alleles determined in the generic typing, followed by SSO hybridization. For DQA and DQB, locus-specific PCR was performed, followed by SSO hybridization. The number of women with complete allele information varied by HLA locus, as follows: 850 for HLA-A, 827 for HLA-B, 810 for HLA-C, 763 for HLA-DRB1, 470 for HLA-DQA1, and 471 for HLA-DQB1.

Statistical methods. (i) HIV disease prior to HAART initiation. Initial analyses examined the relation of HLA genotype with HIV viral load and $CD4^+$ T cell count at enrollment in HAART-naïve women. HIV viral load and $CD4^+$ count were $\log_{10}$ and square root transformed, respectively, to normalize these values and were analyzed using multivariable linear regression. These models were adjusted for self-reported race/ethnicity (i.e., non-Hispanic white, non-Hispanic black, Hispanic, and other) and HCV infection, as parameterized using three HCV dummy variables (i.e., HCV serostatus, HCV viremia, and unknown viremia). This addressed the fact that 18% of HCV-seropositive patients were not HCV viremic and that 46 HCV-seropositive patients lacked HCV RNA data (for these individuals, HCV serostatus was the only data available). As mentioned, 10 patients lacking both HCV serologic and RNA data were excluded.

The number of covariates in these models was carefully limited in part because recent statistical studies have demonstrated that genetic association models are generally unaffected by control for multiple covariates and have recommended restricting the number of adjustment variables (27). Therefore, factors such as smoking and other behavioral covariates—factors not thought to be influenced by the HLA genes under study—were not included in our models. HCV was included in these models because HCV infection may influence HIV disease progression and is also associated with HLA (12, 26). Similarly, race/ethnicity is strongly related to HLA genotype and may be related to other genetic factors related to HIV disease progression.

We then examined HLA associations with incident clinical AIDS (among women free of clinical AIDS at baseline) using continuous-time (i.e., exact-calendar-date) Cox models that controlled for race/ethnicity, HCV infection, baseline $CD4^+$ count (>500, 200 to 500, and <200 cells/μl), and baseline HIV RNA level (≤100,000 versus >100,000 copies/ml). Inclusion of baseline $CD4^+$ count, HIV RNA level, and HCV infection in these models controlled for both initial disease status and the probability of selection by our stratified random sampling design; i.e., we essentially addressed the following question: among women who were otherwise similar in relation to starting immune status and HCV infection, did HLA genotype help explain the heterogeneity in HIV disease progression? These analyses were limited to the period prior to the widespread use of HAART to minimize the possibility of "confounding by indication" (i.e., selection bias related to early initiation of HAART [1]). Specifically, we censored all data after September 1996 when the prevalence of HAART use first exceeded 5% of WIHS subjects. Women who died, were lost to follow-up, or missed more than a single visit (two or more consecutive visits) were censored at their last appropriate study visit.

We additionally examined the relation of HLA genotype with $CD4^+$ decline. The short pre-HAART follow-up time, though, limited our ability to accurately estimate slopes, because these levels are known to have substantial intraindi-

vidual variability (28, 36). To address this issue, we used previously published methods and compared cases who had a rapid and persistent $CD4^+$ T cell count decline to those who maintained their $CD4^+$ count—two clearly defined groups (38). Specifically, the cases were women with >50 $CD4^+$ cells/mm^3 at baseline who met the following definition: compared with baseline, the $CD4^+$ T cell counts at both the second and third visit either (i) fell into a lower $CD4^+$ T cell stratum (based on 4 strata, namely, >500, 200 to 500, 50 to 200, and <50 $CD4^+$ T cells/mm^3) or (ii) had a >50% reduction in count (within the same stratum). Control patients were women whose $CD4^+$ count remained at ≥95% of the baseline value through the first three visits. These analyses were conducted using logistic regression and controlled for race/ethnicity, HCV infection, and baseline $CD4^+$ count.

We focused our analysis on the alleles and allele groups with an *a priori* high prior probability of association in HAART-naïve women, based on a recent comprehensive review of the literature (18) and other large studies (10, 14, 30, 40). No adjustment for multiple comparisons was conducted for these *a priori* hypothesized associations. However, we also conducted exploratory analyses of alleles without a high prior probability of association. These exploratory analyses adjusted for multiple comparisons by using Bonferroni corrections. Our study included 114 alleles and allele groups with >3% prevalence (a cutoff used previously [25]), and statistical significance was defined as P values of $<0.05/(114 = 0.0004)$ for all exploratory analyses. While there are other less conservative methods for addressing multiple comparisons which are commonly employed, none of these methods to our knowledge can readily account for important covariates.

(ii) HIV disease after HAART initiation. The time of HAART initiation was set as the visit an HIV-seropositive WIHS woman first reported using medications meeting the definition of HAART. Initial analyses examined the association of HLA genotype with the short-term virological and immunological response to HAART. Consistent with an earlier study (31), a virological response was defined as a reduction in the HIV RNA level by >90%, or to undetectable levels, for at least two consecutive visits within 12 months of HAART initiation and was limited to women who had detectable plasma HIV RNA levels prior to HAART initiation. In additional sensitivity analyses, we more restrictively defined a virological response as only undetectable HIV RNA to determine if this affected our findings. The short-term immunological response was evaluated among the subset of women who met the definition of a virological responder and was defined as in prior studies (19, 32) as a $CD4^+$ T cell count increase of ≥50 cells/μl following at least two sequential consecutive visits (6 months) showing a virological response.

These analyses were conducted using logistic regression controlling for race/ethnicity, HCV infection, $CD4^+$ count, and HIV viral load at the visit prior to HAART initiation, as well as the enrollment period (1994 to 1995 or 2001 to 2002). Analyses of virological response also controlled for self-reported adherence (≥95% or <95%) to the prescribed HAART regimen during the first 12 months of HAART use. Lastly, we evaluated new "incident" occurrences of AIDS-defining conditions following HAART initiation. These analyses were conducted using multivariate Cox models with censoring and adjustment for confounding variables as described above.

RESULTS

Demographic and clinical characteristics of the study population. Selected characteristics of the 860 HIV-seropositive women in this study are shown in Table 1. Study women were largely in their late thirties to early forties at enrollment and were majority black, non-Hispanic. Thirty-one percent of study women reported clinical AIDS at enrollment, and 30% had received prior antiretroviral therapy (but not HAART). As expected based on the study sampling design (see Materials and Methods), HIV-seropositive women included in the current investigation were more likely to be HCV seropositive than those HIV-seropositive women who were not enrolled in this substudy (65% versus 24%; $P < 0.01$). Furthermore, study women had higher baseline $CD4^+$ T cell counts (a median of 397 versus 325 cells/μl) and were more likely to be black, non-Hispanic, and less likely to be Hispanic than the HIV-seropositive women who were not included (all $P < 0.01$). Overall, the subjects enrolled in this substudy had a median number of four visits or 1.5 years of follow-up (involving 2,615 person visits of data) prior to the widespread use of HAART and post-HAART initiation follow-up time of 8.5 years (involving 7,678 person visits).

TABLE 1. Characteristics of HIV-seropositive women at enrollment[d]

Characteristic	Value
Median age in yrs (IQR)[c]	38 (33–43)
Race/ethnicity (no. of women [%])	
Black, non-Hispanic	538 (63)
White, non-Hispanic	130 (15)
Hispanic	170 (20)
Other	22 (3)
Recruitment cycle (no. of women [%])	
1994-1995	832 (97)
2002	28 (3)
$CD4^+$ T cell count (no. of women [%])[a]	
<200 cells/μl	201 (23)
200–500 cells/μl	340 (40)
>500 cells/μl	315 (37)
Median HIV $\log_{10}$ viral load (IQR)	4.1 (3.6–4.9)
No. of women with clinical AIDS (%)	269 (31)
No. of women with prior antiretroviral therapy (%)	259 (30)
HCV status (no. of women [%])	
HCV seropositive	563 (65)
HCV RNA positive[b]	423 (82)

[a] Among the 856 women with baseline $CD4^+$ cell counts.
[b] Percentage among 517 HCV-seropositive women tested for HCV RNA.
[c] IQR, interquartile range.
[d] A total of 860 women were analyzed.

HIV disease prior to HAART initiation. We examined HLA alleles and allele groups with a frequency of >3% in our population. Table 2 shows the subset of these alleles with a high prior probability of association based on earlier studies and their relationships with HIV disease cross-sectionally at enrollment and prospectively before women initiated HAART. Results for all other class I and II alleles are shown in Table S1 in the supplemental material.

Our cross-sectional analyses of HIV viral load included all subjects ($n = 860$), while analyses of $CD4^+$ count at enrollment excluded four of these women who lacked $CD4^+$ data. Of 15 alleles and allele groups with a high prior probability of association with untreated HIV disease, 13 had cross-sectional associations with $CD4^+$ count and/or HIV viral load at enrollment that were in the predicted direction, showing that the WIHS population was not dissimilar to those studied in earlier investigations. The HLA-B*57 allele group, for example, had a very strong and highly significant positive association with the $CD4^+$ count at enrollment ($\beta = 226$; 95% confidence interval [CI] = 166 to 285; $P = 6 \times 10^{-11}$) and a negative association with the $\log_{10}$ HIV viral load at enrollment ($\beta = -0.7$; 95% CI = −0.9 to −0.5; $P = 5 \times 10^{-11}$) in models that adjusted for race/ethnicity and HCV infection.

Additional alleles with associations in the predicted direction at enrollment included B*18:01, B*27:05, B*57:01, B*57:03, B*58:02, the B*27 group, the B*35(Px) group, the Bw4 homozygous group, the Bw4-80I homozygous group, the common HLA-B allele group, the rare HLA-B allele group,

TABLE 2. HLA associations with HIV disease progression before HAART initiation (pre-HAART)[g]

Allele/allele group[e]	No. of women[f]	$CD4^+$ cell count at enrollment (β [95% CI]) (n = 856)[a,b]	Log_{10} HIV RNA level at enrollment (β [95% CI]) (n = 860)[b]	Rapid $CD4^+$ decline (OR [95% CI]) (n = 253; 82 events)[c]	Incident AIDS (HR [95% CI]) (n = 523; 86 events)[d]
B*18:01	49	−119 (−204, −34)	0.1 (−0.2, 0.4)	0.4 (0.1, 2.0)	0.6 (0.2, 1.7)
B*27:05	33	103 (0, 206)	−0.5 (−0.9, −0.2)	0.6 (0.1, 3.6)	0.8 (0.2, 3.7)
B*27	44	94 (5, 183)	−0.4 (−0.7, −0.1)	1.0 (0.2, 4.4)	1.5 (0.6, 3.8)
B*51:01	55	−79 (−159, 1)	0.1 (−0.2, 0.3)	1.5 (0.4, 4.5)	1.8 (0.9, 3.5)
B*57:01	29	151 (41, 261)	−0.8 (−1.2, −0.4)	0.1 (0, 0.9)	2.2 (0.8, 6.4)
B*57:03	64	240 (167, 314)	−0.7 (−1.0, −0.5)	0.3 (0.1, 1.0)	0.5 (0.2, 1.6)
B*57	99	226 (166, 285)	−0.7 (−0.9, −0.5)	0.2 (0.1, 0.6)	1.0 (0.5, 2.0)
B*58:01	65	66 (−9, 140)	−0.1 (−0.4, 0.1)	1.2 (0.4, 4.0)	1.0 (0.4, 2.5)
B*58:02	46	−87 (−175, 2)	0.4 (0.1, 0.7)	2.4 (0.6, 8.7)	1.2 (0.6, 2.7)
C*04:01	246	−78 (−122, −35)	0.2 (0.1, 0.4)	0.9 (0.4, 1.7)	0.9 (0.6, 1.5)
B*35(Px)	142	−74 (−128, −20)	0.2 (0.0, 0.4)	2.6 (1.2, 5.9)	1.0 (0.5, 1.8)
Bw4 homozygosity	156	53 (2, 104)	−0.2 (−0.4, −0.1)	1.1 (0.6, 2.2)	1.0 (0.5, 1.7)
Bw4-80I homozygosity	48	132 (47, 217)	−0.5 (−0.7, −0.2)	0.3 (0.1, 1.1)	0.3 (0.0, 1.8)
B common	207	−59 (−106, −13)	0.3 (0.1, 0.4)	5.5 (2.6, 11.5)	0.6 (0.3, 1.1)
B rare	207	10 (−38, 57)	−0.2 (−0.3, 0)	0.7 (0.3, 1.4)	1.2 (0.7, 2.0)

[a] β estimates were obtained from analyses of untransformed $CD4^+$ counts to facilitate interpretation. Statistical significance, however, was obtained from analyses using square-root-transformed values (see Table S1 in the supplemental material). Four women lacked baseline $CD4^+$ T cell data.

[b] Linear regression models adjusted for race/ethnicity and HCV infection.

[c] Logistic regression models adjusted for race/ethnicity, HCV infection, and baseline $CD4^+$ count.

[d] Cox regression models adjusted for race/ethnicity, HCV infection, baseline $CD4^+$ count, and baseline HIV RNA level.

[e] In addition to individual alleles, the analyses included HLA-B and -C alleles that act as ligands for killer immunoglobulin-like receptors (KIR), namely, the Bw4 and Bw4-80I groups (30) and groups C1 and C2 (24), allele zygosity (HLA-B homozygosity was too rare [<3%] for inclusion) (10, 39), and allele frequency at the HLA-B locus (7, 33, 40). Allele frequency was examined by comparing alleles with moderately common genotypes (second and third quartiles of allele frequency) to those with rare (first quartile) or common (fourth quartile) genotypes (7, 33). This table shows the results from alleles and allele groups with a high prior probability of association with untreated HIV progression. Other exploratory results are shown in Table S1 in the supplemental material.

[f] The number of women homozygous or heterozygous for a given allele or allele group in the total study population (n = 860). Analysis-specific allele frequencies are shown in Table S1 in the supplemental material.

[g] HR, hazard ratio. Note that shading indicates statistically significant associations.

and C*04:01. One exploratory allele, C*07:01, had significant associations with high $CD4^+$ counts at enrollment (β = 87; 95% CI = 40 to 134; $P_{corrected}$ = 0.03) and low log_{10} HIV viral loads at enrollment (β = −0.3; 95% CI = −0.5 to −0.2; $P_{corrected}$ = 0.01) after correction for the number of tests performed (see Table S1 in the supplemental material).

Although the pre-HAART follow-up was fairly short, we observed inverse associations between rapid $CD4^+$ count decline and B*57 alleles individually (B*57:01: odds ratio [OR] = 0.1, 95% CI = 0 to 0.9; B*57:03: OR = 0.3, 95% CI = 0.1 to 1.0) and as a group (B*57: OR = 0.2, 95% CI = 0.1 to 0.6), consistent with the cross-sectional results. We also observed positive associations of rapid $CD4^+$ count decline with the B*35(Px) group (OR = 2.6; 95% CI = 1.2 to 5.9) and with having a common HLA-B allele (OR = 5.5; 95% CI = 2.6 to 11.5). However, no alleles showed association with incident AIDS during the short follow-up period.

HIV disease after HAART initiation. To study the occurrence of new AIDS events, we focused on the 503 women who initiated HAART during follow-up and had $CD4^+$ counts and HIV RNA levels measured within the year prior to initiating therapy. A subset of 372 of these women had complete virological data for the 12 months (three consecutive visits) following HAART initiation and detectable plasma HIV RNA levels prior to HAART initiation, and these data were used to evaluate the short-term virological response to HAART. We additionally examined the short-term immunological response to HAART among the subset of 176 women who achieved a virological response. Four women with undetectable plasma HIV RNA levels prior to HAART initiation were not included in our analyses of virological and immunological responses.

We first examined the enrollment characteristics of those who did versus did not initiate HAART or were excluded from these analyses for other reasons. Some women, for example, died (n = 74) or were lost to follow-up (n = 51) prior to the widespread use of HAART (as defined in Materials and Methods), while other women died (n = 79) or were lost to follow-up (n = 26) in the HAART era without ever initiating HAART. Still other women were excluded because they lacked $CD4^+$ counts and HIV RNA levels measured within the year prior to initiating therapy (n = 54), because they started HAART only on their last WIHS visit and thus had no follow-up data (n = 17) or because they are still being followed but have not initiated HAART (n = 56). Overall, women included in our analyses of HAART initiators were less likely to have a $CD4^+$ count of <200 (P = 0.01), to have clinical AIDS (P < 0.01), or to be HCV seropositive (P = 0.04) than excluded women.

Two alleles, HLA-B*57:01 (OR = 0.2; 95% CI = 0.0 to 0.9; P = 0.03) and B*58:01 (OR = 0.3; 95% CI = 0.1 to 0.9; P = 0.03), and the Bw4-80I homozygous allele group (OR = 0.3; 95% CI = 0.1 to 1.0; P = 0.04) were associated with low odds of virological response to HAART; i.e., a reduction in the HIV RNA level by >90% or to undetectable levels, during at least two sequential visits within 12 months of HAART initiation (shown in Table 3). The broader Bw4 homozygous group had a borderline association (OR = 0.6; 95% CI = 0.3 to 1.0; P = 0.05) with virological response. In contrast, other alleles and allele groups with a high prior probability of association with

TABLE 3. HLA associations with HIV disease progression after HAART initiation (post-HAART)[h]

Allele/allele group[f]	No. of women[g]	Response to HAART (OR [95% CI])		New AIDS events (HR [95% CI]) (n = 503; 219 events)[e]
		Virological (n = 372; 176 events)[a,b]	Immunological (n = 176; 45 events)[c,d]	
B*18:01	29	1.9 (0.7, 5.5)	0.7 (0.2, 2.5)	1.2 (0.6, 2.2)
B*27:05	23	1.4 (0.4, 4.2)	0.8 (0.2, 3.7)	0.6 (0.2, 1.4)
B*27	30	1.2 (0.4, 3.4)	0.5 (0.1, 2.1)	0.7 (0.4, 1.4)
B*51:01	35	0.9 (0.4, 2.3)	1.6 (0.4, 7.2)	1.6 (1.0, 2.6)
B*57:01	15	0.2 (0.0, 0.9)	0.2 (0.0, 2.4)	1.2 (0.5, 2.8)
B*57:03	33	1.7 (0.7, 4.3)	0.4 (0.1, 1.6)	0.7 (0.4, 1.3)
B*57	53	0.9 (0.4, 1.9)	0.6 (0.2, 1.7)	0.8 (0.5, 1.3)
B*58:01	36	0.3 (0.1, 0.9)	0.5 (0.1, 2.3)	1.1 (0.6, 1.8)
B*58:02	22	1.0 (0.3, 2.7)	1.8 (0.2, 18.0)	1.2 (0.6, 2.2)
C*04:01	148	1.4 (0.8, 2.3)	1.3 (0.6, 2.8)	1.0 (0.7, 1.3)
B*35(Px)	80	1.5 (0.8, 2.8)	1.4 (0.4, 4.2)	1.0 (0.7, 1.4)
Bw4 homozygosity	91	0.6 (0.3, 1.0)	0.4 (0.1, 1.0)	1.0 (0.7, 1.4)
Bw4-80I homozygosity	29	0.3 (0.1, 1.0)	0.4 (0.1, 2.3)	0.8 (0.4, 1.5)
B common	134	0.7 (0.4, 1.2)	1.5 (0.6, 4.0)	1.1 (0.8, 1.5)
B rare	127	1.3 (0.7, 2.2)	1.0 (0.4, 2.3)	1.2 (0.9, 1.6)

[a] Defined as a reduction in the HIV RNA level by >90%, or to undetectable levels, for at least two sequential visits within 12 months of HAART initiation.
[b] Logistic regression models adjusted for race/ethnicity, HCV serostatus, HCV viremia status, pre-HAART $CD4^+$ count, pre-HAART HIV viral load, enrollment period, and self-reported adherence.
[c] Defined as a $CD4^+$ count increase of ≥50 cells/μl following at least two sequential visits of virologic suppression.
[d] Logistic regression models adjusted for race/ethnicity, HCV serostatus, HCV viremia status, pre-HAART $CD4^+$ count, pre-HAART HIV viral load, and enrollment period.
[e] Cox regression models adjusted for race/ethnicity, HCV serostatus, HCV viremia status, pre-HAART $CD4^+$ count, pre-HAART HIV viral load, enrollment period, and self-reported adherence as a time-dependent covariate.
[f] Alleles and allele groups with a high prior probability of association with untreated HIV progression. Other exploratory results are shown in Table S1 in the supplemental material. Allele group definitions are described in Table 2.
[g] The number of women homozygous or heterozygous for a given allele or allele group in the population of women who initiated HAART (n = 503). Analysis-specific allele frequencies are shown in Table S1 in the supplemental material.
[h] Note that shading indicates statistically significant associations.

untreated HIV disease progression were not significantly associated with virological response, nor did any associations with exploratory alleles retain statistical significance after adjustment for the number of tests performed. In sensitivity analyses that used only undetectable HIV RNA to define virological response, the Bw4-80I homozygous group remained significantly associated with virological response to HAART (OR = 0.2; 95% CI = 0.1 to 0.8; P = 0.02), whereas B*57:01 and B*58:01, while retaining their inverse associations, became nonsignificant (see Table S1 in the supplemental material).

We also studied immunological response to HAART. While the Bw4 homozygous and Bw4-80I groups had similar associations with low odds of immunological response (Table 3), and B*57:01 and B*58:01 also had an inverse association with odds of immunologic response, only the association with the broad Bw4 homozygous group reached statistical significance (OR = 0.4; 95% CI = 0.1 to 1.0; P = 0.04). No other significant associations with immunological response were observed, either among alleles with a high prior probability of association with untreated HIV disease progression or among the exploratory alleles, after correction for the number of tests performed (Table 3; see also Table S1 in the supplemental material).

Because B*57:01 and B*58:01 are members of the Bw4 and Bw4-80I allele groups, we studied the extent to which these two individual alleles might have accounted for the Bw4 and Bw4-80I findings. After excluding women with B*57:01 and B*58:01, the Bw4-virological response relationship became null (OR = 1.0; 95% CI = 0.5 to 1.9; P = 0.92), as did the Bw4-80I-virological response relationship. In contrast, the relation of Bw4 with immunological response was not meaningfully altered by these exclusions (OR = 0.4; 95% CI = 0.1 to 1.0; P = 0.06) or even by additionally excluding women with B*27 (OR = 0.3; 95% CI = 0.1 to 0.9; P = 0.04). Too few subjects with Bw4-80I without B*57:01 and B*58:01 were available to study in relation to immunological response.

Prior studies of HAART-naïve patients found that B*57 alleles had among the strongest and most consistent associations with the rate of HIV disease progression (18). Therefore, we additionally examined whether poor outcomes in B*57:01-positive women who initiated HAART could relate to a high prevalence of characteristics associated with HIV disease progression. B*57:01-positive women who did and did not initiate HAART were similar in relation to age, race/ethnicity, recruitment cohort, HIV viral load, HCV status, and the prevalence of other alleles associated with higher rates of HIV disease progression [e.g., B*58:02, B*35(Px), and C*04:01]. While B*57:01-positive HAART initiators did have lower $CD4^+$ counts at enrollment than those who did not initiate HAART (median $CD4^+$ counts = 424 and 682, respectively; P = 0.04), as mentioned previously, our statistical models addressed this by appropriately adjusting for $CD4^+$ and HIV RNA levels at the visit prior to HAART initiation (see "Statistical methods"). B*57:01-positive HAART initiators were also more likely than noninitiators to have received prior antiretroviral therapy (33% versus 0%; P = 0.04), but inclusion of this as a covariate in our models had no meaningful effect on the findings (data not shown).

Lastly, we examined HLA associations with long-term risk of new AIDS-defining conditions following HAART initiation.

This analysis involved all 503 women, and there was considerable follow-up time and a large number of AIDS-defining events. However, no significant associations were observed, with either high prior probability alleles or exploratory alleles (Table 3; see also Table S1 in the supplemental material).

DISCUSSION

We conducted high-resolution HLA class I and II genotyping in a large, long-term prospective cohort of HIV-seropositive women, many of whom were enrolled in 1994, prior to the widespread use of HAART. This design allowed us to study HLA associations with HIV disease both before and after the introduction of HAART in a single population. Our results in women before they initiated HAART confirmed many of the previously reported associations between HLA and HIV disease in untreated patients, showing that our population was not dissimilar from those reported in previous studies of patients not using HAART. However, in treated patients, we observed few HLA associations. In fact, we detected only three significant HLA associations with virological response to HAART, each of them opposite to those that would be predicted based on prior results from untreated patients.

Specifically, B*57:01, B*58:01, and the Bw4-80I group were strongly associated with failure to control HIV replication following HAART initiation. Similar associations between these alleles and immunological response to HAART were also observed, although these relationships were nonsignificant, possibly because we had less extensive data to examine this endpoint. That is, the immunological response was only assessed among the subset of 176 women who were using effective HAART (i.e., those who had a virological response). The larger Bw4 allele group, which includes the Bw4-80I group (30) and other HLA-B alleles with the Bw4 serological epitope (22), also showed inverse associations with virological and immunological responses to HAART. In exploring these results further, however, we found that associations of B*57:01 and B*58:01 might have accounted for the associations of Bw4 and Bw4-80I with virological response. In contrast, though, we found no evidence that B*57:01 and B*58:01 accounted for the association of Bw4 with immunological response. We cannot therefore exclude the possibility that epistatic interactions between HLA and killer immunoglobulin-like receptor (KIR) genes may influence the response to HAART, as Bw4 alleles can act as a ligand for KIR.

We are aware of only three prior studies of HLA genotype and HIV disease in treated patients (2, 7, 35). As in the current investigation, few associations between HLA and HIV disease were observed, and in two of these studies, B*57 was associated with poor $CD4^+$ recovery following HAART initiation (2, 35). Bw4 homozygosity was also associated with poor $CD4^+$ recovery in one of these studies (35).

The current investigation was the first to examine the relation of HLA genotype with the long-term risk of AIDS events in treated patients and to examine HLA alleles other than those already reported to be significant in untreated patients. The cohort involved extensive person-years of observation and included a substantial number of AIDS events. Thus, if a relationship between HLA genotype and risk of AIDS-defining conditions in treated patients had been present, we would likely have detected it, but no such associations were found.

Overall, it increasingly appears that most of the HLA associations with HIV disease in untreated patients are not observed in treated individuals, and in fact, some of these relationships may be opposite one another. The reasons there may be different HLA genotype associations in treated versus untreated HIV disease progression are unknown. One possible explanation for the limited number of HLA associations in treated patients may reflect a reduced role for immune genes in the inhibition of HIV replication, because HAART has very strong antiviral effects regardless of a patient's HLA genotype. Second, HAART exerts strong selective pressure on the HIV quasispecies, and HIV variants associated with drug resistance, largely in the *pol* and *env* genes (21), are common in patients exposed to antiretroviral therapies (17). CTLs recognize epitopes in *gag*, *nef*, and *pol* (6), so it is possible that therapy-associated selection pressures on *pol* could change the distribution of HIV antigens presented to T cells, thereby altering established HLA associations. Even if this hypothesis is correct, though, it remains unclear why the few HLA associations in HAART users that we and others observed involved specific HLA genotypes that are highly protective in HAART-naïve patients but are high risk in treated patients.

Important limitations of this study must also be considered in the interpretation of the findings. First, we must consider the possibility that a bias related to study design explains the observed inverse associations. While our analyses adjusted for cofactors associated with both HLA genotype and HIV disease progression (i.e., conventional confounders), we cannot exclude the possibility that other factors unrelated to HLA could also have influenced the results through less conventional pathways (e.g., common effects) (see a recent review of this topic [20]). It is also possible that women with HLA genotypes associated with slow untreated disease progression had delayed HAART initiation compared to other women; that is, women with protective HLA genotypes may have been HIV infected for longer periods of time prior to HAART initiation. While we controlled for the $CD4^+$ count prior to HAART initiation, it is possible that other, independent factors associated with long-term HIV infection (e.g., chronic immune activation) may explain the observed inverse associations between protective HLA genotype and response to HAART. As in a prior study (35), though, we could not directly examine this issue because the dates of HIV seroconversion for the vast majority of WIHS women are unknown. Cohorts in which duration of HIV infection is known or can be accurately estimated would be best suited to address this issue. One might additionally ask whether hypersensitivity to abacavir could explain why some patients with the B*57:01 genotype (and the Bw4-80I genotype, which includes B*57:01) do not respond to HAART (29). In the current cohort, however, only three women with B*57:01 received abacavir during the time period studied, and exclusion of these women from the data set did not meaningfully change the results (data not shown).

Another important consideration in the interpretation of these results is the impact of survival bias. That is, women with rapid HIV disease progression may be underrepresented in the WIHS cohort because they did not live long enough to be enrolled and initiate HAART. The impact of this bias is that

HLA genotypes that predispose to rapid disease progression with too little prevalence for analysis may have been underrepresented (we studied only HLA alleles with >3% prevalence). While this may have limited our ability to detect associations with certain alleles related to rapid progression, we note that all of the HLA alleles found to be strongly associated with HIV progression in prior studies were included in our analysis, having been found in >3% of women in our cohort. We also note that AIDS-defining conditions in WIHS are ascertained by participant self-report, and so it is possible that there was some misclassification in AIDS diagnoses, which may have attenuated the statistical power for our analyses of AIDS events. Even if this were the case, it is unlikely that misclassification completely explains the lack of HLA associations with AIDS in HAART users, since there were many AIDS events and a long duration of follow-up, as described above.

The current findings regarding HLA and HAART predominantly reflect data on HAART initiation from the late 1990s. HAART regimens have improved in recent years, and we cannot exclude the possibility that the results would be different in women using current regimens. Furthermore, most (77%) HAART initiators had used nucleoside reverse transcriptase inhibitor (NRTI) monotherapy or combination therapy prior to initiating HAART, and thus, the prevalence of NRTI resistance mutations may have been higher in the studied HAART initiators than would be expected in an antiretroviral naïve population. To address this issue, we controlled for prior antiretroviral use in additional sensitivity analyses of virological and immunological responses (as described above), but inclusion of this additional covariate did not meaningfully change the results (data not shown). Our study was also necessarily limited by the number of different analytic approaches that could be presented for outcomes for which there is no universally accepted definition (e.g., virological response to HAART). In the current study, for example, we *a priori* chose two definitions that we and others have used for virological response and found the results to be equivalent. Lastly, we could not conduct extensive subset analyses given the modest prevalences of many alleles.

In conclusion, the paucity of HLA associations with HIV disease progression in treated patients may reflect the effectiveness of HAART in suppressing viral replication irrespective of host genotype. However, virological and immunological nonresponses to HAART are not uncommon, and further study is warranted to determine the relation of this with HLA genotype and other host factors. Understanding why several alleles (notably alleles that are protective against HIV disease progression in untreated women) are associated with a greater risk of virological and immunological nonresponses to HAART could provide new insights into this important clinical issue.

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