# The Association of Race, Sociodemographic, and Behavioral Characteristics With Response to Highly Active Antiretroviral Therapy in Women

*Kathryn Anastos, MD,* Michael F. Schneider, MS,† Stephen J. Gange, PhD,† Howard Minkoff, MD,‡ Ruth M. Greenblatt, MD,§ Joseph Feldman, PhD,‡ Alexandra Levine, MD,‖ Robert Delapenha, MD,¶ and Mardge Cohen, MD# for the Women's Interagency HIV Study Collaborative Group*

**Objective:** To determine the association of race with clinical and laboratory outcomes after initiation of highly active antiretroviral therapy (HAART) in HIV-1–infected women in the United States.

**Study Design:** Prospective cohort study.

**Participants:** A total of 961 HIV-1–infected women participating in the Women's Interagency HIV Study initiating HAART between July 1, 1995 and September 30, 2003.

**Results:** Over a median of 5.1 years of follow-up, in univariate Cox regression analyses, white women were more likely than African American women to attain a virologic response (relative hazard [RH] = 1.34, $P = 0.005$), less likely to experience viral rebound (RH = 0.76, $P = 0.051$), and less likely to die (RH = 0.63, $P = 0.040$). There were no significant differences, however, among racial groups in outcomes after adjustment for pre-HAART $CD4^+$, HIV-1 RNA, history of AIDS-defining illness, age, antiretroviral therapy use, baseline HIV-1 exposure category, and post-HAART behavioral and clinical variables associated with poorer response (discontinuation of HAART, lower income, smoking, current drug use, and depression). Continuous HAART use and lack of depression differed by race and were the strongest predictors of favorable outcomes.

**Conclusion:** No significant differences by race were found in virologic, immunologic, or clinical outcomes after adjustment for continued HAART use and depression. These findings suggest that strategies to enhance HAART continuation, including assessing pharmacogenetic influences that may result in greater toxicity and discontinuation rates, and treating depression can improve individual and population-based effects of treatment and potentially mitigate racial disparities in AIDS-related outcomes.

**Key Words:** Race differences, HIV, highly active antiretroviral therapy, survival, women

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The efficacy of antiretroviral therapies has been studied predominantly in men of European descent. Concern has been raised that differences in behavior or in biologically determined pathways of drug metabolism and transport, which vary by race,[1–15] may impact unfavorably on response to highly active antiretroviral therapy (HAART) in groups other than white men. Although HAART has markedly improved the prognosis of HIV-1–infected individuals, not all demographic groups have benefited equally. In the United States, white men have experienced an 85% decline in mortality, compared with 50% and 65% declines in black women and men, respectively, from 1995 through 2001.[16] Although some of this variation may result from differential access to HAART,[17] the contribution of other factors, both behavioral and biologic, is not known.

Distrust of the health care system,[17,18] spiritual beliefs, access to ongoing health care,[18,19] differences in adherence,[20,21] and biologic effects could all influence the population-based effectiveness of HAART. Some immunogenetic and pharmacogenetic characteristics differ by race and could alter the efficacy or toxicity (and therefore continuation) of treatment, through altered drug transport,[1–6] drug metabolism,[7–11] or immunopathogenetic mechanisms.[12–15,22,23]

There are significant challenges in investigating racial and ethnic differences in biomedical processes.[24,25] Racial/ethnic categories are imprecise, overlap, and reflect "skin color, country of origin or ancestry, and language or dialect spoken"[24] rather than genotype. Race in HIV-1 disease represents a risk *marker*, with a higher prevalence of HIV-1 infection in African Americans and Hispanics both in the United States and in the

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From the *Departments of Medicine and Epidemiology and Population Health, Montefiore Medical Center, Bronx, NY; †Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; ‡Department of Obstetrics and Gynecology, Maimonides Medical Center and SUNY Health Sciences Center at Brooklyn, New York, NY; §Departments of Medicine and Epidemiology, University of California at San Francisco, CA; ‖University of Southern California School of Medicine, Los Angeles, CA; ¶Department of Medicine, Howard University College of Medicine, Washington, DC; and #Cook County Hospital, Chicago, IL.

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Reprints: Kathryn Anastos, Women's Interagency HIV Study, 3311 Bainbridge Avenue, Bronx, NY 10467 (e-mail: kanastos@verizon.net).

world. It may also be a true risk *factor*, with a direct etiologic relationship to HIV-1 disease progression or response to antiretroviral therapy (ART), derived from ancestral history and mediated in part or *in toto* by immunogenetic and pharmacogenetic mechanisms.

We investigated population-based responses to HAART stratified by self-categorized race in the Women's Interagency HIV Study (WIHS), with the understanding that there are limitations in data regarding race and ethnicity. Based on the previous finding that a polymorphism in the gene encoding P-glycoprotein (*MDR1* position 3435 CC genotype) has been associated with increased P-glycoprotein activity, and is most frequent in people of African descent,[1] we hypothesized that African American women would exhibit a poorer response to HAART even after adjustment for sociodemographic factors, continuation of HAART, and self-reported adherence. Throughout this report we have used the term "race" rather than "ethnicity" and attempted to define categories that adhere to ancestral history, acknowledging that such classification has inherent inaccuracies.

## METHODS

### Study Population

WIHS is a multicenter prospective cohort study of HIV-1 infection in women in 5 United States cities. WIHS methods have been described previously.[26] Briefly, 2628 women (2059 HIV-1 seropositive and 569 seronegative) were enrolled in 1994 and 1995. Informed consent was obtained from all participants after approval by the committee on human experimentation at the collaborating institutions. Semiannually, WIHS participants were interviewed and examined, and laboratory specimens were obtained. After 5 years, the retention rate in the WIHS was approximately 80%.[27]

At each study visit, using photo medication cards, participants reported ART use since the previous visit. HAART was defined as combinations of ≥2 nucleoside reverse transcriptase inhibitors (NRTIs) with at least 1 protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitor (NNRTI); 1 NRTI with at least 1 PI and at least 1 NNRTI; a regimen containing ritonavir and saquinavir in combination with 1 NRTI and no NNRTIs; and an abacavir-containing regimen of ≥3NRTIs (in the absence of both PIs and NNRTIs).[28,29] Adherence measures previously described[30] were introduced in October 1998. Participants were categorized dichotomously by whether or not they reported taking all drugs as prescribed at least 95% of the time.[30]

### Outcome Variables

We estimated the time from HAART initiation to marker response (virologic and immunologic) and to onset of clinical events (incident AIDS-defining illness [ADI]), death, and death from AIDS. Additionally, we investigated the time from virologic response (HIV-1 RNA ≤80 copies/mL) to subsequent virologic failure (HIV-1 RNA >1000 copies/mL after virologic response) and the time from immunologic response ($CD4^+$ lymphocyte counts ≥100 cells more than nadir pre-HAART $CD4^+$) to subsequent immunologic failure ($CD4^+$ lymphocyte counts below nadir pre-HAART level after immunologic response).

ADIs consistent with 1993 Centers for Disease Control surveillance definition, but excluding immunologic criterion of low CD4,[31] were ascertained through self-report or confirmed through cancer and tuberculosis registries. Incident ADIs included any report of a clinical condition *except* cervical cancer, Kaposi sarcoma, non-Hodgkin lymphoma, tuberculosis, or wasting syndrome in women who had reported that specific illness prior to HAART initiation. ADIs reported at the same study visit at which HAART was first reported were not classified as incident.

Methods for ascertainment of cause and date of death have been described previously.[32]

### Primary Exposure

The primary exposure of interest was self-categorized race, defined as African American (Hispanic and non-Hispanic), white (Hispanic and non-Hispanic), and Hispanic (women identifying as Hispanic but neither African American nor white).

### Laboratory Methods

Plasma HIV-1 RNA was measured using the isothermal nucleic acid sequence–based amplification method (Nuclisens, Organon Teknika Corp., Durham, NC) with a lower limit of detection of 80 copies/mL. Lymphocyte subsets were quantified using standard flow cytometric methods in laboratories participating in the National Institutes of Health/National Institute of Allergy and Infectious Diseases Flow Cytometry Quality Assessment Program.[33]

### Statistical Analysis

We investigated responses after HAART initiation using Cox regression. Univariate models assessed the differences in virologic, immunologic, and clinical outcomes among the 3 racial groups. Multivariate models measured heterogeneity in outcomes by race, adjusting for pre-HAART variables of self-reported ADIs, nadir $CD4^+$ count, peak HIV-1 RNA, age, prior ART use, and self-reported HIV-1 exposure category. We adjusted for post-HAART time-varying exposures of continued HAART use, depression, income, cigarette smoking, current drug use, and adherence. Depression was defined as a score of ≥16 on the Center for Epidemiologic Studies Depression scale, at the same visit at which the outcomes were measured.[34]

## RESULTS

Of the 2059 HIV-1–seropositive women, 1277 (62.0%) initiated HAART, and 961 (75.3%) met all selection criteria (Fig. 1). The median follow-up after HAART initiation was 5.1 years (interquartile range, 3.2–6.3 years).

The 961 participants included 573 (59.6%) African American, 184 (19.2%) white, and 204 (21.2%) Hispanic women. African American women were older, less educated, initiated HAART at later calendar times, and were more likely to report pre-HAART use of cigarettes and cocaine, crack, or heroin than white women (Table 1). Hispanic women were more

 

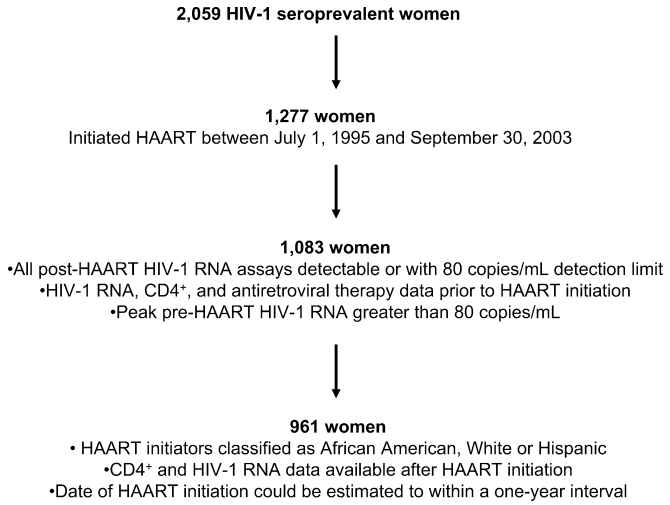


**FIGURE 1.** Study population determined by selection criteria.

likely to be depressed, to have an annual income of ≤$12,000, not to have completed high school, and to report not using ART at ≥1 visits after HAART initiation (55.4%), compared with white (27.7%) and African American women (44.7%) (Table 1).

## Univariate and Multivariate Analyses of Laboratory and Clinical Outcomes

Table 2 presents the number (and percentage) of women in each ethnic group with each outcome after HAART initiation. White women exhibited better immunologic and virologic response and lower rates of immunologic and virologic failure, AIDS defining illnesses, and all-cause and AIDS deaths.

In univariate analyses of the hazard of each of the outcomes after HAART initiation (Table 3, model 1), white women were more likely than African American women to experience virologic response (relative hazard [RH] = 1.34, $P = 0.005$), less likely to experience virologic rebound (RH = 0.76, $P = 0.051$), and less likely to die of any cause (RH = 0.63, $P = 0.040$). Figure 2 shows the estimated cumulative survival stratified by race. After nearly 8 years, African American women were less likely to survive (70.0%) compared with white (80.0%) and Hispanic women (76.5%).

Also shown in Table 3 are multivariate Cox regression analyses adjusted for pre-HAART exposures including ART use, age (per 10 years), ADI, nadir $CD4^+$ cell count, peak HIV-1 RNA, HIV-1 exposure category (model 2), and for time-varying post-HAART exposures of depression, drug use, cigarette smoking, income (model 3), and post-HAART antiretroviral

**TABLE 1.** Characteristics of 961 Women's Interagency HIV Study Participants Initiating HAART

| | African American n = 573 | White n = 184 | Hispanic n = 204 | *P* Value |
|---|---|---|---|---|
| Date of HAART initiation* | October 1997 (January 1997, February 1999) | February 1997 (August 1996, August 1998) | April 1997 (October 1996, April 1998) | <0.001† |
| Age at last pre-HAART visit* | 40.3 (34.6, 45.2) | 38.0 (34.1, 42.0) | 37.0 (32.6, 41.8) | <0.001† |
| Pre-HAART peak HIV-1 RNA* | 83,000 (24,000, 250,000) | 78,500 (18,500, 285,000) | 78,000 (18,000, 255,000) | 0.779† |
| Pre-HAART nadir $CD4^+$* | 199 (92, 319) | 214 (91, 330) | 216 (102, 342) | 0.479† |
| % With pre-HAART AIDS | 47.5 | 43.5 | 44.6 | 0.570‡ |
| % With positive hepatitis C serology at study entry | 44.6 | 40.7 | 37.4 | 0.181‡ |
| % ART naive prior to HAART initiation | 15.5 | 19.6 | 19.6 | 0.262‡ |
| Baseline risk category | | | | |
| % IDU | 33.0 | 36.1 | 29.2 | 0.009‡ |
| % Heterosexual risk | 42.2 | 49.7 | 40.6 | |
| % Transfusion risk | 4.9 | 3.3 | 3.5 | |
| % No identified risk | 19.9 | 10.9 | 26.7 | |
| % With any drug use§ at last pre-HAART visit | 19.6 | 10.4 | 9.0 | <0.001‡ |
| % Depressed at last pre-HAART visit | 50.7 | 42.3 | 57.4 | 0.019‡ |
| % Smoked cigarettes at last pre-HAART visit | 61.1 | 46.7 | 38.0 | <0.001‡ |
| % With income ≤$12,000 at last pre-HAART visit | 64.4 | 36.6 | 70.4 | <0.001‡ |
| % Not completing high school at study entry | 34.5 | 15.9 | 54.5 | <0.001‡ |
| % With ≥95% adherence‖ to therapy at HAART initiation | 74.1 | 78.0 | 73.9 | 0.845‡ |
| % With no antiretroviral therapy following HAART initiation during at least 1 study visit | 44.7 | 27.7 | 55.4 | <0.001‡ |

*All values are medians (interquartile range) unless otherwise noted.
†*P* values from a Kruskal-Wallis test of medians.
‡*P* values from a Pearson $\chi^2$ test of overall association.
§Any drug use defined to be cocaine, heroine, or crack.
‖Data after October 1998 for a total 297 participants: 201 African American women, 50 white women, and 46 Hispanic women.
IDU, intravenous drug use.

**TABLE 2.** Descriptive Statistics of Virologic, Immunologic, and Clinical Outcomes After HAART Initiation by Race/Ethnicity*

| Race/Ethnicity | Virologic Response | | Virologic Rebound | | Immunologic Response | | Immunologic Failure | | Incident ADI | | Death | | AIDS Death | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| African American | 59.9% | 343/573 | 63.5% | 205/323 | 76.8% | 440/573 | 38.1% | 161/423 | 42.4% | 232/547 | 19.7% | 113/573 | 8.2% | 47/573 |
| White | 71.7% | 132/184 | 55.3% | 68/123 | 81.0% | 149/184 | 31.7% | 46/145 | 37.7% | 66/175 | 13.6% | 25/184 | 4.4% | 8/184 |
| Hispanic | 64.7% | 132/204 | 69.1% | 87/126 | 75.0% | 153/204 | 49.3% | 72/146 | 38.4% | 76/198 | 15.2% | 31/204 | 8.3% | 17/204 |

*Median follow-up 5.1 years. All values are % with event.

therapy use (model 4). In model 2, white women remained more likely than African Americans to experience virologic response and less likely to have virologic rebound. After including continued ART use following HAART initiation (model 4), however, there were no significant differences by race in virologic, immunologic, or clinical responses to HAART, although there were trends ($0.050 \leq P < 0.100$) toward better immunologic response in white women and lower incidence of new ADIs in Hispanic women.

Table 4 presents the impact of each exposure (included in model 4) on the 7 different outcomes. Continued HAART use was the strongest predictor of favorable virologic, immunologic, and clinical responses, with a 16-fold increased likelihood of virologic response and an approximately two-thirds decreased risk of experiencing virologic or immunologic failure or death from AIDS. Because of this strong association with continued HAART use, we performed additional analyses limited to the 541 women who did not report discontinuing ART use at any time after HAART initiation (Table 3, model 5). There were no significant differences by race in any of the assessed outcomes after restricting analyses to women who remained on ART or HAART.

**TABLE 3.** The Relationship Between Race/Ethnicity and Virologic, Immunologic, and Clinical Outcomes After HAART Initiation

| | Virologic Response | | Virologic Rebound | | Immunologic Response | | Immunologic Failure | | Incident ADI | | Death | | AIDS Death | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RH | *P* Value | RH | *P* Value | RH | *P* Value | RH | *P* Value | RH | *P* Value | RH | *P* Value | RH | *P* Value |
| Model 1* | | | | | | | | | | | | | | |
| African American | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA |
| White | 1.34 | 0.005 | 0.76 | 0.051 | 1.17 | 0.091 | 0.75 | 0.087 | 0.82 | 0.145 | 0.63 | 0.040 | 0.51 | 0.081 |
| Hispanic | 1.09 | 0.385 | 1.07 | 0.612 | 0.91 | 0.312 | 1.37 | 0.026 | 0.79 | 0.073 | 0.68 | 0.059 | 0.92 | 0.776 |
| Model 2† | | | | | | | | | | | | | | |
| African American | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA |
| White | 1.32 | 0.007 | 0.74 | 0.037 | 1.20 | 0.056 | 0.71 | 0.043 | 0.81 | 0.146 | 0.71 | 0.124 | 0.56 | 0.127 |
| Hispanic | 1.07 | 0.508 | 1.03 | 0.851 | 0.91 | 0.343 | 1.44 | 0.013 | 0.78 | 0.074 | 0.81 | 0.307 | 1.01 | 0.985 |
| Model 3‡ | | | | | | | | | | | | | | |
| African American | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA |
| White | 1.27 | 0.053 | 0.95 | 0.766 | 1.29 | 0.019 | 0.77 | 0.253 | 0.85 | 0.380 | 1.01 | 0.969 | 0.67 | 0.375 |
| Hispanic | 1.03 | 0.811 | 1.18 | 0.304 | 0.86 | 0.178 | 1.42 | 0.063 | 0.75 | 0.099 | 0.82 | 0.474 | 1.01 | 0.978 |
| Model 4§ | | | | | | | | | | | | | | |
| African American | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA |
| White | 1.22 | 0.115 | 0.96 | 0.801 | 1.22 | 0.069 | 0.89 | 0.602 | 0.89 | 0.500 | 1.11 | 0.718 | 0.75 | 0.536 |
| Hispanic | 1.07 | 0.560 | 1.12 | 0.462 | 0.88 | 0.217 | 1.34 | 0.122 | 0.75 | 0.094 | 0.81 | 0.440 | 1.03 | 0.929 |
| Model 5‖ | | | | | | | | | | | | | | |
| African American | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA |
| White | 1.23 | 0.177 | 1.14 | 0.601 | 1.16 | 0.271 | 1.04 | 0.910 | 0.83 | 0.433 | 0.95 | 0.867 | 0.49 | 0.193 |
| Hispanic | 1.10 | 0.576 | 0.83 | 0.486 | 1.05 | 0.773 | 1.73 | 0.089 | 0.60 | 0.073 | 1.01 | 0.973 | 0.99 | 0.987 |
| Model 6¶ | | | | | | | | | | | | | | |
| African American | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA | 1 | NA |
| White | 1.23 | 0.143 | 0.79 | 0.201 | 0.93 | 0.656 | 0.85 | 0.488 | 0.96 | 0.839 | 0.50 | 0.055 | 0.21 | 0.136 |
| Hispanic | 1.04 | 0.798 | 1.02 | 0.905 | 0.84 | 0.298 | 1.81 | 0.003 | 1.01 | 0.936 | 1.13 | 0.633 | 2.16 | 0.054 |

*Model 1: Univariate analyses.

†Model 2: Multivariate analyses adjusted for ART use prior to HAART initiation, age at last pre-HAART visit, pre-HAART AIDS status, pre-HAART nadir $CD4^+$ cell count, and pre-HAART peak HIV-1 RNA, and self-reported baseline HIV-1 exposure category.

‡Model 3: Multivariate analyses adjusted for exposures included in model 2 plus time-varying exposures following HAART initiation, which includes depression (Center for Epidemiologic Studies Depression score >16), current drug use (any cocaine, crack, or heroine), cigarette smoking, and income.

§Model 4: Multivariate analyses adjusted for exposures included in model 3 plus antiretroviral therapy used following HAART initiation.

‖Model 5: Multivariate analyses adjusted for all exposures included in model 3 among those women who remained on HAART or ART after HAART initiation (n = 541 participants).

¶Bivariate analyses (n = 568 participants) adjusted for time-varying adherence exposure.

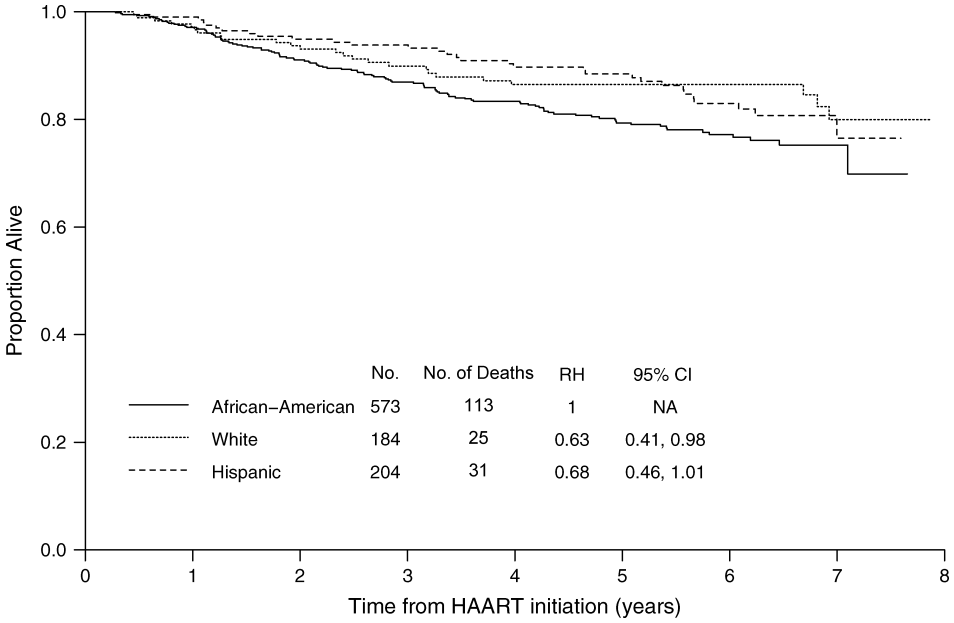


**FIGURE 2.** Kaplan-Meier plots of cumulative survival after HAART initiation stratified by race.

Depression (Table 4) was significantly associated with poorer virologic response, increased likelihood of immunologic failure, incident ADI, and a higher risk of all-cause, but not AIDS-related, death. Current drug use was associated with death from AIDS and a greater risk of incident ADI.

## Bivariate Analyses of Race and Adherence

Since we had collected detailed adherence data only at study visits after October 1998, we analyzed the association of adherence with both laboratory and clinical outcomes, while adjusting for race (Table 3, model 6). Among the 297 women (30.9%) with adherence data at HAART initiation, we found no statistically significant differences ($P$ = 0.845) between adherence to therapy at HAART initiation and race (Table 1). At least 73% of each racial group reported at least 95% adherence. Higher adherence was strongly associated with favorable virologic and immunologic responses and with reduced risk of a new ADI (Table 4).

**TABLE 4.** Multivariate Analyses* Assessing the Relationship Between Both Pre-HAART and Post-HAART Exposures With Virologic, Immunologic, and Clinical Outcomes After HAART Initiation

| Exposure | Virologic Response RH | Virologic Rebound RH | Immunologic Response RH | Immunologic Failure RH | Incident ADI RH | Death RH | AIDS Death RH |
|---|---|---|---|---|---|---|---|
| ART naive prior to HAART initiation | 1.77† | 0.82 | 0.96 | 0.72 | 1.29 | 0.94 | 1.41 |
| Age at last pre-HAART visit (per 10 years) | 1.19‡ | 0.91 | 1.12‡ | 1.00 | 0.98 | 1.36‡ | 1.18 |
| Pre-HAART AIDS | 0.98 | 1.04 | 0.93 | 0.92 | 2.19† | 1.35 | 1.62 |
| Pre-HAART nadir $CD4^+$ cell count (per 100 cells) | 1.08† | 1.02 | 1.09† | 1.27† | 0.86† | 0.61† | 0.30† |
| Pre-HAART peak HIV-1 RNA (per $\log_{10}$) | 0.62† | 1.48† | 1.02 | 0.89 | 1.38† | 1.61† | 1.63 |
| Therapy used following HAART | | | | | | | |
| No therapy | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Mono/combination therapy | 8.55† | 0.30† | 4.07† | 0.59‡ | 0.72 | 0.53 | 0.71 |
| HAART | 16.14† | 0.26† | 7.04† | 0.31† | 0.74 | 0.46† | 0.33† |
| Depression (CESD > 16) | 0.81‡ | 1.22 | 0.96 | 1.98† | 1.62† | 1.65‡ | 1.06 |
| Current drug use§ | 0.89 | 1.23 | 0.85 | 1.11 | 1.49‡ | 1.04 | 2.35‡ |
| Currently smoke cigarettes | 0.72† | 1.30 | 1.04 | 0.93 | 1.18 | 1.38 | 1.05 |
| Income <$12,000 | 0.91 | 1.25 | 0.98 | 1.45‡ | 1.19 | 1.64‡ | 1.39 |
| Adherence‖ | 2.19† | 0.37† | 1.47‡ | 0.66‡ | 0.65† | 0.67 | 0.53 |

*In additional to exposures reported, each analysis was also adjusted for self-reported baseline HIV-1 exposure category and race/ethnicity.
†$P$ value < 0.01.
‡0.01 ≤ $P$ value < 0.05.
§Current drug use defined to be cocaine, heroine, or crack.
‖Results from bivariate analyses of adherence and race/ethnicity with specified outcome.
CESD, Center for Epidemiologic Studies Depression scale.

### Bivariate Analyses of Race and Depression on HAART Discontinuation

Depression reported following HAART initiation was associated with HAART discontinuation (RH = 1.40, $P$ = 0.004). Race, however, was the stronger predictor of discontinuation, with white women less than half as likely as African American (RH = 0.43, $P < 0.001$) or Hispanic women (RH = 0.32, $P < 0.001$) to discontinue therapy independent of depression (data not shown). Thus, the higher prevalence of depression did not explain the higher rate of HAART discontinuation in African American and Hispanic women.

## DISCUSSION

HIV infection, hypertension, diabetes, and trauma are responsible for most of the 6-year lower life expectancy of African Americans compared with whites in the United States.[35] HIV disease accounts for 11.2% of the disparity, almost as much as ischemic heart disease (5.5%), stroke (2.8%), and cancer (3.4%) combined.[35] In our study investigating the relationship of race with response to HIV-1 treatment among 961 women initiating HAART, white women had more favorable virologic, immunologic, and clinical responses to HAART. The poorer responses to HAART found in African American and Latina women, however, were explained largely by HAART discontinuation and to a lesser extent, by depression. Although discontinuation of therapy may be secondary to toxicity that results from specific genetic determinants of drug metabolism and transport, both depression and therapy discontinuation are potentially mutable. This suggests that treating depression and ascertaining and addressing reasons for treatment discontinuation could substantially improve outcomes in African American and Latina women.

Pharmacokinetics of antiretroviral agents is influenced by genetically determined factors that vary by individual ancestral history. Several studies have demonstrated that African Americans experience higher toxicity and higher rates of discontinuing therapy.[8,10,11] For example, investigators have found slower clearance or higher rates of central nervous system toxicity and discontinuation of efavirenz associated with polymorphisms of the 2B6 pathway of the cytochrome P450 system.[10,11] Thus, biologic mechanisms resulting in greater drug toxicity may account for the racial differences we found in HAART discontinuation.

Polymorphisms in *MDR1*, the gene that codes for P-glycoprotein (P-gp), also vary by race.[1–6] P-gp is a transport protein that exports its substrates out of cells, raising concern that the efflux of antiretroviral agents from the cell could result in both greater toxicity and lower efficacy. Although Africans, Asians, Europeans, and African and European Americans have been shown to differ in the proportion of specific polymorphisms at 2 alleles in *MDR1*,[1–6] the influence of these polymorphisms on drug levels or the efficacy and toxicity of treatment is controversial. Some studies indicate a clinical difference,[1–3,5] whereas others do not.[4,36] It remains worrisome, however, that the direction of all differences in our study favored white women. Indeed, the relative hazard of 0.49 for death from AIDS (Table 3, model 5) in white compared with African American women *who continued on therapy*, would be very significant clinically, if real ($P$ = 0.193 in our study). Host genetic variations in factors that influence bioavailability and clearance of antiretroviral drugs may contribute to racial differences in outcomes after HAART initiation, either directly by limiting bioavailability, or indirectly by influencing HAART continuation or adherence, and deserve further study. Of note, the clinical effects of the pharmacogenetic mechanisms described here are unpredictable, will not be the same for all of the currently approved antiretroviral agents, and would not be expected to influence regimens consisting entirely of NRTIs.

Racial disparities in health outcomes, including HIV-1–related illness, have also been attributed to social determinants such as lower socioeconomic status, lower educational attainment, and differential access to and quality of health care services.[17,18,37–43] Even in a setting of a national universal health care system, lower socioeconomic status was shown to be associated with reduced access to HAART. Among HAART recipients, however, socioeconomic status did not affect virologic response.[42] Similarly, in the United States, where health care is not universally available, HIV-1–infected persons of color are less likely to receive antiretroviral therapy when indicated[40,41] or to access state entitlement programs.[39,40] In our study, although we focused on women who reported initiating and thus had some access to HAART, the differences in therapy continuation may be associated with more subtle and complex differences in access to and quality of care that we were unable to measure.

The association of HAART discontinuation with depression suggests that identification and treatment of depression can improve the effect of HAART. We and others have previously reported that depression predicted HAART discontinuation,[44] poorer laboratory responses[45] while on antiretroviral therapy, and a greater likelihood of AIDS-related deaths and that treatment of depression was associated with reduced mortality.[46,47] However, the association of race with HAART discontinuation was not explained by depression, suggesting that ascertaining and rectifying the causes of discontinuing indicated therapy by women of color could also improve their response to HAART. Our current findings also support studies that have found no difference by race in immunologic[48] or virologic responses.[41] Adherence was associated with better responses in our study, but adherence did not vary by race. This is in contrast to some prior studies in populations mostly or exclusively male, in which white race was associated with higher rates of adherence.[49–51] It is possible that our ascertainment of adherence did not completely describe differences by race or that such differences are less marked in women. Further investigation is warranted.

The Institute of Medicine Report concluded that there is "clear and convincing evidence for racial disparities in health care" in the United States.[52] Some of this disparity may be attributable to difficulties in communication: whites are half as likely as Latinos in the United States to perceive difficulty communicating with their physician, and one-third less likely than African Americans.[53] Latinos and African Americans are less likely to trust their provider to diagnose and choose therapy in the patient's best interest.[54] These mechanisms could influence HAART discontinuation and the diagnosis and treatment of depression. An important next step will be to

 

ascertain directly from patients their reasons for discontinuing HAART.

A limitation of our study is the low rate of HIV-related clinical outcomes after HAART initiation, particularly in AIDS deaths (16 per 1000 person-years), limiting our ability to rule out a clinically significant difference by race in clinical outcomes. A methodologic limitation of our study is that some of the exposures, specifically depression and HAART discontinuation, were ascertained at the same visit as the virologic and immunologic endpoints. In addition, HAART discontinuation could have been the result of virologic or immunologic failure, rather than the cause. The very large relative hazards, the strength of the association of HAART continuation with both laboratory and clinical outcomes, and similar findings when analyses were limited to women who continued HAART, however, suggest that some or even most of the improvement in outcomes results from the continuation of therapy. These analyses complement our other reports demonstrating the consequences of HAART discontinuation.[55,56]

Another significant limitation of our study, as in most studies that attempt to investigate the impact of race, is the impossibility of defining race as a biologic construct. We used women's self-classification of race and ethnicity to group them by common ancestry, comparing all women self-identifying as "black" (of African ancestry) with all women self-identifying as white (of European ancestry). In addition, there were 204 women self-identifying as Hispanic, a term that defines ethnicity and not race, but not identifying themselves as either black or white, and for whom there were some significant differences in baseline characteristics and in clinical outcomes. As reviewed recently,[57] ancestrally determined differences in drug transport or metabolism may carry clinical significance, and the large majority of studies of the efficacy and tolerability of antiretroviral regimens have been performed in populations of predominantly European ancestry. The trend toward poorer outcomes in African American and Latina women, especially AIDS-related deaths, deserves further investigation with longer follow-up in this and other cohorts, to confirm that there is not a significant difference by race. Also important for HIV-1–infected African American and Latina women in the United States is the diagnosis and treatment of depression and exploration and rectification of the factors related to HAART discontinuation, as these may be contributing substantially to poorer health status, including death, among HIV-infected women of color.

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