ETHNIC DIFFERENCES IN HIV DISEASE PROGRESSION: A COMPARISON OF ASIAN/PACIFIC ISLANDERS AND WHITES LIVING IN HAWAII

Objective: To characterize the association of demographic factors with the relative hazards (RH) of developing AIDS or death among HIV-infected individuals of Asian/Pacific Islander (API) ethnicity and Whites.

Design: Cohort study

Setting: Hawaii State Health Department database of HIV-infected individuals

Patients or Participants: Hawaii Sero-Positivity and Medical Management (HSPAMM) program participants from January 1989 to November 2002

Interventions: None

Main Outcome Measures: Differences in the time to develop AIDS or death among HIV-infected individuals who reported being on highly active antiretroviral treatment (HAART) were examined by ethnicity, income, and CD4+ cell counts at HAART initiation by using Kaplan-Meier survival analysis and Cox proportional hazard analyses.

Results: The study was based on 516 HIVinfected individuals, who were primarily White (61.0%) and API (21.7%). Whites had a significantly higher CD4+ cell count (P<.01) and income (P<.01) than APIs at enrollment into HSPAMM. Lower income levels and CD4+ cell counts at HAART initiation were strongly associated with an increased RH of developing AIDS or dying. Despite having significantly lower incomes and CD4+ cell counts at enrollment, individuals of API ethnicity do not have an increased RH of developing the outcomes compared to Whites.

Conclusion: Lower income and CD4+ cell counts at HAART initiation significantly increased the RH of developing AIDS or dying among HIV-infected individuals. Asian/Pacific Islander (API) ethnicity was not a predictor of developing AIDS or dying. (*Ethn Dis.* 2006;16:262–267)

Key Words: Asian Pacific Islanders, Ethnicity, HIV Disease Progression, Socioeconomic Factors Sheri M. Shimizu, MS; Dominic C. Chow, MD; Alan R. Katz, MD; Suzanne Richmond-Crum, MPH; F. DeWolfe Miller, PhD

INTRODUCTION

Since 1996, the availability and widespread use of highly active antiretroviral treatment (HAART) regimens have dramatically improved the survival of HIV-infected individuals.¹ However, past reports have differed with regard to the effect of ethnicity on disease progression. Data from the Women's Interagency HIV and the Multicenter AIDS Cohort Studies suggests that HIV disease progression is associated with ethnicity when comparing African Americans and Hispanics to Whites.² Studies on HIV-infected veterans indicate that veterans of African-American and Hispanic ethnicities experience poorer survival than White veterans.³ Other recent studies indicate that ethnicity is not associated with disease progression if health care is free.⁴ Gray et al report that ethnicity does not affect

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Ethnic disparities among African Americans and Hispanics who have been associated with poorer survival rates include access to care, low income, lack of medical and drug insurance, social factors such as cultural differences, and lack of education about treatment and therapy.^{3,6,7} These ethnic disparities among minority populations are of growing concern in the United States.

HIV disease progression specifically comparing individuals of Asian/Pacific Islander (API) ethnicity to Whites has never been reported. However, recent studies have shown that APIs are more likely to be at an advanced stage of AIDS and have opportunistic infections at the time of diagnosis when compared with other racial groups.^{8,9} The Hawaii Sero-Positivity and Medical Management (HSPAMM) database of HIVinfected individuals is one of only a few national databases with a large number of HIV-infected persons of API ethnicity. In this study, we characterize the association of demographic factors with the relative hazards of developing AIDS or dying among HIV-infected individuals of API ethnicity compared to Whites.

METHODS

Study Population

The HSPAMM program was started in 1989 and has since provided a means to monitor HIV infection in Hawaii. The HSPAMM program provides semiannual visits for all its participants with However, recent studies have shown that Asian/Pacific Islanders are more likely to be at an advanced stage of AIDS and have opportunistic infections at the time of diagnosis when compared with other racial groups.^{8,9}

their own primary care physicians. An HSPAMM visit consists of a patient questionnaire, a health provider questionnaire, a general physical examination, and collection of laboratory samples. The patient questionnaire is selfadministered and consists of 43 questions, which include the patient's demographic characteristics, risk factors, medical history, medication use, and signs and symptoms. The questionnaires given at each HSPAMM visit are intended to capture changes since the previous visit. The physician medical history includes the patient's clinical signs, symptoms, health status, onset of opportunistic infections, review of all organ systems, and development of HIV-associated diseases. The generalized physical examination completed by the physician includes the patient's vital signs and an assessment of all organ systems. The laboratory portion of the HSPAMM visit includes CD4+/CD8+ cell counts, chemistry panel (electrolytes and liver function tests), complete white blood cell differential, Papanicolaou testing for women, and hepatitis B and C serologic tests. HIV viral load test results were not incorporated into the HSPAMM database until after 1997 and were therefore not included in the analysis. All data collected from participants are recorded under an individualized code number, known only by the treating physician and participant, to insure confidentiality.

For the present analysis, institutional review board exemptions were granted from the University of Hawaii Committee on Human Studies and the Hawaii State Department of Health. Included in this analysis were all HSPAMM participants who reported initiation of HAART from July 1995 to November 2002, the date of analysis in this study. The HAART regimens were defined to include the use of: 1) two or more nucleoside analogue reverse transcriptase inhibitors (NRTIs) in combination with at least one protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI); 2) one NRTI in combination with at least one protease inhibitor and at least one NNRTI; 3) a regimen containing ritonavir and saquinavir in combination with one NRTI; or 4) an abacavir sulfate-containing regimen of three or more NRTIs in the absence of PIs and NNRTIs.

Participants were excluded from survival analysis if they developed AIDS before they began HAART therapy. Participants were followed in the study from the date of HAART initiation through November 30, 2002, the date of analysis.

Outcome Variables

The primary outcome variables for the survival analysis were death and the development of AIDS. AIDS was determined in accordance with the US Centers for Disease Control and Prevention (CDC) 1993 case definition of opportunistic infections or neoplasms.¹⁰ AIDS-defining events and deaths were captured on a physician questionnaire, and CD4+ cell counts were captured from laboratory results. For analysis of survival times, all deaths of any cause were considered.

Exposure Variables

The primary exposure variable for disease progression was ethnicity and was broken down into the following groups: White, African American, Hispanic, American Indian, API, and other. Secondary exposure variables included age, sex, stratified values of income (<\$10,000, \$10,000-\$19,999, \$20,000-\$29,999, \$30,000-\$39,999, \$40,000-\$49,999, \$50,000-\$59,000, \geq \$60,000), and stratified CD4+ cell counts at HAART initiation (<200 cells/mm³, 200-350 cells/mm³, 351-500 cells/mm³, >500 cells/mm³).

Statistical Methods

Differences between ethnic groups and demographic characteristics were evaluated by using one-way analysis of variance. Inter-group differences were determined by using a two-sided *t* test. An $\alpha \leq .05$ was considered significant. Factors that were analyzed included: ethnicity, sex, age, CD4+ cell count at HAART initiation, and income.

The time to AIDS or death was defined as the number of days from the first record of HAART therapy to the first physician visit with an AIDS diagnosis, first laboratory results that indicated an AIDS-defining event, or death. We included participants who were lost to followup but censored observations regarding their survival time. For persons who were AIDS free or alive at the end of followup, we censored observations regarding time to development of AIDS or death. To eliminate survival bias, participants with an AIDS diagnosis before HAART initiation were excluded from survival analysis.

Kaplan-Meier estimates were used to determine differences between ethnic groups and survival time. Univariate and multivariate comparisons of disease progression were evaluated by using proportional hazard regression models. Factors that were examined included: ethnicity, age, sex, categorized values of income, and CD4+ cell counts at HAART initiation. The multivariate model for progression to the event included: age, sex, stratified values of income, and CD4+ cell counts at HAART initiation. Multivariate models were analyzed by selected ethnicities. The reference categories for the estimation and testing of relative hazards

Table 1. Demographic characteristics

	AIDS Free at HAART Initiation	%	AIDS at HAART Initiation	%
Median age (years)	45		45	
Sex				
Male	464	89.9%	496	90.5%
Female	52	1.1%	52	9.5%
Total	516		548	
Ethnicity				
White	315	61.0%	320	58.4%
African American	20	3.9%	17	3.1%
Hispanic	38	7.4%	37	6.8%
American Indian	6	1.2%	5	.9%
Asian Pacific Islander	112	21.7%	136	24.8%
Other	25	4.8%	31	5.7%
Missing	0	0%	2	.4%
Asian Pacific Islanders				
Chinese	3	2.7%	9	6.6%
Filipino	21	18.8%	22	16.2%
Hawaiian/Part	42	37.5%	58	42.6%
Japanese	22	19.6%	12	8.8%
Mixed Non-Hawaiian	10	8.9%	6	4.4%
Other Asian	12	10.7%	20	14.7%
Missing	2	1.8%	9	6.6%
Risk factors*				
MSM	406	78.7%	423	77.2%
IDU	52	1.1%	71	13.0%
MSM and IDU	38	7.4%	38	6.9%
Heterosexual	18	3.5%	14	2.6%
Blood products	11	2.1%	8	1.5%
Other	9	1.7%	15	2.7%
Unknown	13	2.5%	29	5.3%
Place born				
Hawaii	119	23.1%	129	23.5%
US Mainland	326	63.2%	339	61.9%
Pacific Island	8	1.6%	9	1.6%
Asia	11	2.1%	23	4.2%
Other	30	5.8%	34	6.2%
Missing	22	4.3%	14	2.6%

 $\mathsf{MSM}{=}\mathsf{men}$ who have sex with men; $\mathsf{IDU}{=}\mathsf{injection}$ drug use.

* Participants may have indicated more than one risk factor

(RHs) were CD4+ cell counts >500 cells/mm³ and income >\$60,000. All analyses were implemented by statistical packages: SPSS version 11.5 (SPSS Inc., Chicago, Ill, USA) and JMP Statistical Analysis Software version 5.1 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Demographic Findings

During the study period, 1064 HSPAMM participants initiated HAART therapy. Of these, 548 (51.5%) had an AIDS diagnosis at HAART initiation and were excluded from the study. The study sample was based on 516 (48.5%) subjects that did not have a previous diagnosis of AIDS at initiation of HAART therapy. The baseline demographic and clinical characteristics of the HSPAMM participants who initiated HAART are shown in Table 1. No significant differences were found between those who were AIDS free at HAART initiation and those who had an AIDS diagnosis before HAART initiation.

As seen in Table 2, a strong association was found when enrollment CD4+ cell counts were compared between Whites and APIs (P < .01). Whites had a mean enrollment CD4+ cell count of 520 cells/mm³ while APIs had a mean enrollment CD4+ cell count of 434 cells/mm³. However, no significant difference was seen in CD4+ cell counts at HAART initiation between Whites and APIs. Income was highly significant when compared between ethnic groups (P<.01). Whites generally have a higher income when compared to APIs, and fewer of those in the White group had an income <\$10,000 per year.

Overall median follow-up time for the study group was 912 days (range 2617 days). Median follow-up time was 909 days (range 2426 days) for APIs and 1025 days (range 2617 days) for Whites. The median time to death or AIDS-defining event was 822 days (range 2422 days). Median time to death or AIDS-defining event was 814 days (range 2422 days) and 849 days (range 2270 days) for APIs and Whites respectively.

Univariate Analysis

Income and CD4+ cell counts at HAART initiation were strongly associated with increased relative hazards of developing AIDS or dying (see Table 3). Univariate analyses revealed no significant differences in survival rates among ethnic groups (log rank 4.6, P=.46). No significant differences were seen in survival rates of injection drug users (RH 1.07, 95% CI 0.76–2.5).

Multivariate Analysis

Figure 1 shows the Cox proportional hazard survival curve for time to AIDS or death for APIs and Whites. After adjusting for potential confounders, a nonsignificant increase in risk of disease progression was seen among APIs, with a RH of 1.12 (95% CI 0.67–1.84).
 Table 2.
 Baseline characteristics of 516 persons who were AIDS free at enrollment and initiated HAART

	APIs	%	Whites	%
Per capita income*				
<\$10,000	30	28.8%	45	14.8%
\$10,000–19,999	15	14.4%	35	11.5%
\$20,000-29,999	20	19.2%	56	18.4%
\$30,000–39,999	10	9.6%	48	15.7%
\$40,000-49,999	11	1.6%	48	15.7%
\$50,000-59,999	6	5.8%	23	7.5%
≥\$60,000	12	11.5%	50	16.4%
Missing	8	7.7%	10	3.3%
Mean age in years \pm SD*	43 ± 9.9		47 ± 7.8	
Mean CD4+ cell count at enrollment cells/mm ³ \pm SD*	434 ± 215		520 ± 341	
Mean CD4+ cell count at HAART initiation cells/mm ³ \pm SD	484 ± 195		515 ± 343	
* P <.05 when APIs are compared to Whites.				

Table 3 shows the RHs adjusted for age, sex, income, and CD4+ cell counts at HAART initiation. Lower income levels and lower CD4+ cell counts at HAART initiation were significantly associated with increased relative hazards of developing AIDS or dying. Individuals who had a lower income had more than three times the risk of developing AIDS or dying than those with higher incomes. This finding was especially evident in individuals that had an income <\$29,999 per year. The association between CD4+ cell counts at HAART initiation and increased RH of developing AIDS or dying that was seen in univariate analyses persisted in the adjusted model.

Interactions were found between lower income levels and lower initial CD4+ cell counts (RH 5.22, 95% CI 2.91–9.31) when income levels were

Table 3. Univariate and multivariate analysis of factors associated with disease progression among 5169 persons who were AIDS free at enrollment and initiated HAART

	Rela			
Variable	Crude RH, (95% Cl)	P value	Adjusted RH, (95% CI)	P value
Age	1.01 (.98–1.04)	.48	1.03 (.99–1.10)	.14
Sex (male vs female)	.94 (.37–2.34)	.59	1.11 (.38–3.24)	.85
Income*				
≥\$60,000	1.00		1.00	.07
<\$10,000	3.36 (1.23-9.10)	<.01	5.19 (1.46-18.50)	<.01
\$10,000–19,999	2.46 (.80-7.58)	.04	3.63 (.93-14.20)	.06
\$20,000-29,999	2.91 (1.03-8.25)	.09	3.07 (.84-11.20)	.09
\$30,000-39,999	1.87 (.58-6.00)	.34	2.61 (.64-1.60)	.18
\$40,000-49,999	.42 (.08-2.10)	.70	.82 (.13-5.00)	.83
\$50,000-59,999	1.47 (.35-6.20)	.29	2.15 (.42-1.90)	.36
CD4+ cell count at HAART in	nitiation†			
\geq 500 cells/mm ³	1.00		1.00	<.01
351–500 cells/mm ³	2.03 (.81-5.14)	.24	1.77 (.63-5.01)	.28
200–350 cells/mm ³	8.35 (3.71–18.80)	<.01	6.91 (2.82–16.90)	<.01

 \ast The multivariate model was adjusted for age, sex, and CD4+ cell count.

† The multivariate model was adjusted for age, sex, and income.

dichotomized as <\$29,999 or not and having a CD4+ cell count was dichotomized as 200–350 cells/mm³ at HAART initiation or not. However, when the interaction term was adjusted for CD4+ cell counts at HAART initiation and lower income levels, the interaction term no longer retained significance and did not improve the fit of the model. Interactions were not found between lower income levels and ethnicity.

DISCUSSION

This study shows that ethnic differences exist in baseline age, income, and CD4+ cell counts at enrollment into HSPAMM. The APIs have significantly lower incomes (P<.01) and enroll into HSPAMM at lower CD4+ cell counts than Whites (P < .01). These results may indicate that APIs are of lower socioeconomic status and delay accessing healthcare services for their HIV infection when compared to Whites. Despite having significantly lower incomes and lower CD4+ cell counts at enrollment into HSPAMM, APIs do not have an increased risk of developing AIDS or death compared to Whites after initiating HAART.

The effect of ethnicity in HIVinfected individuals is complex and could be influenced by social as well as biological factors. Findings suggest possible ethnic differences in the pathogenesis and clinical manifestations of HIV infection.¹¹⁻¹⁸ Different ethnic groups exhibit variations in human cellular genes that may influence CD4+ cell counts, viral "setpoints," clinical disease progression, and survival. Human leukocyte antigens, which vary by ethnicity, have been studied as potential cofactors in HIV disease progression.^{11,12,18} Studies show a 32-base pair deletion mutation in the CCR5 gene has been associated with resistance against HIV-1.13-17 Such a genetic variant occurs in 10% to 17% of



Figure 1. Cox proportional hazard survival curve from HAART initiation to AIDS or death comparing APIs and Whites

Whites.¹⁴ In a recent study of 1912 individuals living in Hawaii, Lu et al found an absence of this mutation among 1096 APIs.¹⁷ This variant may offer some protection against infection and is also associated with slower HIV disease progression in later stages of disease. As the HSPAMM database does not test for such genetic factors, the ability to examine them was beyond the scope of this study.

Our survival analyses showed that lower income and lower CD4+ cell counts at HAART initiation were significantly associated with an increased risk of developing AIDS or dying. These results persisted after adjusting for covariates in the model.

Only a few studies have focused on the association of ethnicity and HIV disease progression. While previous studies in the United States have indicated an association between ethnicity and HIV disease progression,² our study seems to coincide with studies in Denmark.⁴ Like the Denmark studies, access to HIV health care and HAART is free for most HSPAMM participants, and ethnicity does not significantly affect disease progression. Although access to health care and HAART is free for most HSPAMM participants, our results show that income and CD4+ cell counts at HAART initiation affect disease progression. Other studies have also documented the relationship between socioeconomic status and health.¹⁸⁻²⁰ For persons of lower socioeconomic status, treatment adherence may be lower and regular follow-up visits with a primary care physician may be less frequent, resulting in decreased survival rates.

Currently, no other studies focus directly on the disease progression of HIV-infected APIs compared with Whites. Other studies suggest that HIV-infected APIs have different health-seeking behaviors when compared to individuals of other ethnicities.^{8,21,22} Although APIs use hospitalbased HIV clinics at relatively high Our survival analyses showed that lower income and lower CD4+ cell counts at HAART initiation were significantly associated with an increased risk of developing AIDS or dying.

rates, they use other HIV services, such as case management, housing assistance, day/respite care, food/nutrition, substance-abuse treatment, and health-education services, in relatively low numbers.²¹ These studies cite cultural and economic factors that influence healthseeking behaviors and may explain why individuals of API ethnicity in our study enroll into programs like HSPAMM at lower CD4+ cell counts, which indicates a possible delay in accessing health services.

Historically APIs have disproportionate rates of hepatitis B (HBV) in the United States.^{23,24} In the HSPAMM database, HBV co-infection occurred in 4.2% of APIs and 2.1% of Whites. Hepatitis B (HBV) co-infection did not significantly affect survival rates in HSPAMM participants. This coincides with previous studies that did not detect any impact of HBV coinfection on HIV disease progression.^{25,26} The constraints in the HSPAMM database in citing the cause of death, examine liver-related mortality in HIV-infected patients.

Limitations of this cohort study are mainly limitations of the database. The HSPAMM program was originally designed as a natural history study, and thus no prestudy control or endpoints were determined. Further, we could not capture information regarding HAART adherence. As HSPAMM participants are a self-referred group seeking medical care for their HIV infection, the findings from this patient population may not be directly generalizable to all HIVinfected persons. The HSPAMM participants may reflect a greater proportion of lower income, under- or uninsured HIV-infected persons who use state-subsidized treatment options.

In summary, lower CD4+ cell counts at HAART initiation and lower income significantly increased the risk of developing AIDS or dying among HIV-infected individuals. Although API ethnicity was associated with lower CD4+ cell counts at enrollment and lower incomes compared to Whites, API ethnicity was not a predictor of developing AIDS or dying.

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AUTHOR CONTRIBUTIONS

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