Disparities in HIV Treatment and Physician Attitudes About Delaying Protease Inhibitors for Nonadherent Patients

Mitchell D. Wong, MD, PhD, William E. Cunningham, MD, MPH, Martin F. Shapiro, MD, PhD, Ronald M. Andersen, PhD, Paul D. Cleary, PhD, Naihua Duan, PhD, Hong Hu Liu, PhD, Ira B. Wilson, MD, MSc, Bruce E. Landon, MD, MBA, Neil S. Wenger, MD, for the HCSUS Consortium

BACKGROUND: **Current HIV treatment guidelines recommend delaying antiretroviral therapy for nonadherent patients, which some fear may disproportionately affect certain populations and contribute to disparities in care.**

OBJECTIVES: **To examine the relationship of physician's attitude toward prescribing protease inhibitors (PIs) to nonadherent patients with disparities in PI use and with health outcomes.**

DESIGN: **Prospective cohort study.**

PATIENTS AND SETTING: **A national probability sample of HIV-infected adults in the United States and their health care providers was surveyed between January 1996 and January 1998. We analyzed data on 1,717 patients eligible for PI treatment and the 367 providers who cared for them.**

MEASUREMENTS: **Providers' attitude toward prescribing PIs to nonadherent patients, time until patients' first receipt of PIs, mortality, and physical health status.**

MAIN RESULTS: **Eighty-nine percent of providers agreed that patient adherence is important in their decision to prescribe PIs (Selective) while 11% disagreed (Nonselective). Patients who had a Selective provider received PIs later than those with a Nonselective provider ($P = .05$). Adjusting for patient demographics and health characteristics and provider demographics, HIV knowledge, and experience, Latinos, women, and poor patients received PIs later if their provider had a Selective attitude but as soon as others if their provider had a Nonselective attitude. African-American patients received PIs later than whites, irrespective of their providers' prescribing attitude. Patients with Selective providers had similar odds of mortality than those with Nonselective providers (odds ratio, 1.1; 95% confidence interval, 0.6 to 2.0), but had slightly worse adjusted physical health status at follow-up (49.1 vs 50.4, respectively; $P = .04$), after controlling for baseline physical health status and other patient and provider covariates.**

CONCLUSIONS: **Most providers consider patient adherence an important factor in their decision to prescribe PIs. This attitude appears to account for the relatively later use of PI treatment among Latinos, women, and the poor. Given the rising HIV infection rates among minorities, women, and the poor, further investigation of this treatment strategy and its impact on HIV resistance and outcomes is warranted.**

KEY WORDS: **African Americans; health services accessibility; HIV; Latinos; patient compliance.**
J GEN INTERN MED 2004;19:366–374.

Received from the Division of General Internal Medicine and Health Services Research (MDW, WEC, MFS, HHL, NSW) and School of Public Health (WEC, MFS, RMA), University of California, Los Angeles, Calif; RAND (MFS, NSW), Santa Monica, Calif; Department of Health Care Policy (PDC, BEL), Harvard Medical School, Boston, Mass; Division of Clinical Care Research (IBW), Tufts New England Medical Center, Boston, Mass; and Department of Psychiatry (ND), University of California, Los Angeles, Calif. This paper was presented at the 24th Annual National Meeting for the Society of General Internal Medicine, May 2001, in San Diego, Calif.

Address correspondence and requests for reprints to Dr. Wong: UCLA, Division of General Internal Medicine and Health Services Research, 911 Broxton Plaza, Los Angeles, CA 90095-1736 (e-mail: miwong@mednet.ucla.edu).

Protease inhibitors (PIs), in combination with other antiretroviral medications, have dramatically improved outcomes for patients infected with the human immunodeficiency virus (HIV).[1–3] Unfortunately, HIV mortality rates remain higher among minorities, women, and injection drug users compared to others,[4,5] in part because these groups are less likely to receive combination therapy, even after controlling for illness severity, income, and health insurance.[6–13]

National HIV treatment guidelines recommend providers consider the patient's likelihood of adhering to medications when deciding to initiate antiretrovirals.[14–16] This is based on evidence that inadequate adherence promotes drug resistance and may lead to worse health outcomes.[17–21] By limiting therapy to adherent patients, we might slow the spread of drug-resistant HIV.[22] Some are concerned, however, that patient sociodemographic characteristics may influence physicians' judgments about adherence, which may ultimately contribute to disparities in treatment.[23–25]

Whether HIV care providers follow this guideline and whether this practice contributes to differences in treatment and outcomes is unknown. In the present study, we examined a nationally representative sample of HIV-infected individuals to determine whether certain populations (minorities, women, heavy alcohol and drug users, and the poor) receive PIs later than others and whether providers' attitudes toward delaying or withholding PI therapy for nonadherent patients account for these disparities. We also examined the impact of this prescribing practice on mortality and physical health status.

METHODS

Data Collection

We examined data from the HIV Cost and Services Utilization Study (HCSUS), a prospective cohort study of a nationally representative sample of HIV-infected patients

who are receiving care and their providers. In the first stage of a multistage sampling design, we randomly selected metropolitan statistical areas and rural geographic areas. In the second stage, we selected individual and institutional medical providers identified through public health officials and local physicians caring for HIV patients. In this stage, we also selected providers who reported caring for HIV-infected patients through a screening survey of 4,000 randomly selected physicians. In the third stage, we sampled HIV-infected individuals from lists of eligible patients (age > 18 and known HIV infection) whom selected providers had seen in the clinic or hospital at least once between January 5 and February 29, 1996. The respondent sample was 67% of the total population that would have been represented if the agreement and response rates were 100% at each stage. Further details are described elsewhere.[7,26]

Subjects participated in 3 in-person or telephone interviews. We identified providers based on first follow-up (FU1) and baseline surveys asking patients to identify their health care providers.[27] Depending on the availability of this information, we chose providers in the following order: the physician in charge of their HIV care at FU1, the most recent HIV provider at FU1, their non-HIV primary care provider at FU1, their primary HIV provider at baseline, and their non-HIV primary care provider at baseline. Of the 2,864 patients, 222 (7.8%) did not list a provider. Of the 692 listed providers, we were able to contact 551 to complete a mailed, self-administered, written questionnaire. These surveys were completed in 1998 and 1999, about the same time as the second follow-up survey. A total of 412 providers completed the questionnaire (response rate 75%). Of the 2,642 patients with an identified provider, 1,896 (71.7%) had survey data from their provider. We excluded 5 providers, who cared for 15 patients, because they were nurses, 5 providers because their patients were dropped from the baseline sample, and 5 patients and 2 providers because of missing key data. We also excluded 159 patients ineligible for combination antiretroviral therapy according to treatment guidelines at the time the study was conducted (baseline CD4 count > 500 cells/mm^3).[14] The final analytic sample included 367 providers caring for 1,717 patients.

Measurement of Variables

We asked providers whether they agreed with the following statement using a 5-point response scale (strongly disagree to strongly agree), "Whether a patient is likely to be adherent is a very important factor when deciding whether or not to prescribe protease inhibitors." Providers were dichotomized into 2 groups: those who agreed or strongly agreed (Selective) and those who disagreed, strongly disagreed, or were unsure (Nonselective). Henceforth, we refer to this variable as "providers' prescribing attitude."

In addition to demographic characteristics, we asked providers about their years of clinical experience, specialty, HIV patient caseload, sexual preference (homosexual, bisexual, or heterosexual), preference not to treat intravenous drug users, and belief that many of their patients cannot adhere to PIs (5-point agree-disagree response scale). We assessed HIV knowledge using 11 true-false questions about HIV treatment (Cronbach's $\alpha = 0.64$).[27]

From a list of antiretrovirals, we asked patients which they used during the previous 6 months in the baseline survey and since the previous survey at follow-up. The list included four PIs: ritonavir, indinavir, saquinavir at baseline, and also nelfinavir at follow-up. At follow-up, we asked respondents when (month, year) they first started taking a PI. From these questions, we determined the date individuals first used a PI.

We calculated the number of days to first PI use since December 6, 1995, the date the Food and Drug Administration approved the first PI (saquinavir). Some individuals reported using a PI prior to this date, perhaps through a clinical trial. Some groups, including minorities, are less likely to participate in clinical trials,[28–30] and consequently have a disadvantage in accessing PIs early. To reduce this bias, time of first PI use was set to a small, positive number (i.e., 0.01 days) for individuals who reported PI use before December 6, 1995. Of note, all HCSUS patients were HIV-infected and enrolled in the study by this date and thus eligible for treatment based on HIV status. We classified individuals who did not receive a PI by the end of follow-up as being censored at their last interview date.

In addition to collecting demographic information, we asked patients about illicit drugs and alcohol use in the past year. We measured access to care using 6 questions regarding the affordability, availability, and convenience of medical care and about the accessibility of specialists (Cronbach's $\alpha = 0.74$) derived from the HIV Outcomes Study.[31] An HIV symptom index reflected a count of HIV-related symptoms.[32] We measured physical and mental health status derived from the HCSUS health-related quality of life measure.[33] We used the University of Michigan Composite International Diagnostic Interview (UM-CIDI) brief screener to determine whether patients had anxiety disorder, panic disorder, depression, or dysthymia.[34,35] We also asked patients whether they thought antiretrovirals were worth taking (using a 4-point response scale) and whether they had used any mental health services in the last 6 months.

At the second follow-up survey, we asked patients how many days they forgot to or purposely did not take their HIV medication and how many days they took their HIV medication exactly as their doctor prescribed over the prior week. Based on these 2 questions, individuals were classified as poorly adherent, somewhat adherent, and very adherent. This measure correlates well with other adherence measures using pill counts and Medication Event Monitoring Systems (MEMS)[36] and with virologic response.[36]

We obtained death data through December 31, 1999 from participant contacts and proxies, newspaper obituaries, a national death registry (Choice Point), and from searches of the National Death Index. We used social

security number to confirm matches for the latter two sources.

We imputed missing values for essential variables using a standard "hotdeck" strategy. We imputed less than 5% of CD4-positive lymphocyte counts, less than 3% of insurance and income values, and less than 0.5% of other key variables in the analyses.[12] A sensitivity analysis dropping individuals with missing data yielded comparable results.

Statistical Analysis

To examine the relationship of patient and provider characteristics with time to PI use, we used time-to-event analyses. We used parametric regression because the Cox proportional hazards assumption was violated. We chose a log-normal distribution based on log-likelihood statistics and Cox-Snell residual plots.[37] We used multiple logistic and linear regression to examine the association of providers' prescribing attitude with mortality and physical health status, respectively.

All multivariate models included patient and provider characteristics. Patient characteristics were race/ethnicity, age, gender, education, HIV exposure mode, annual family income (cutoff < $25,000), insurance type, self-reported access to care, CD4 count, symptom index, physical and mental health status, presence of psychiatric illness, mental health service use in the last 6 months, homelessness, recent drug or heavy alcohol use, belief that antiretrovirals are worth taking, and geographic region. Provider characteristics were prescribing attitude (Selective vs Nonselective), race, gender, years in practice as a physician (10 years or more vs less than 10 years), specialty (infectious disease, general internal medicine or family practice, vs other), HIV knowledge score, sexual preference (heterosexual vs homosexual/bisexual), HIV caseload (more than 50, 20 to 49, vs 1 to 19 patients), preference not to treat injection drug users (agree vs disagree), belief that many patients cannot adhere to their medication regimen (agree vs disagree), and clinical setting (academic vs nonacademic, private vs public, large vs small practice).

We hypothesized that minorities, women, those with lower income, and heavy alcohol/drug users would receive PIs later than others, and that this disparity would exist if patients had a Selective provider but not if they had a Nonselective provider. Consequently, we included interaction terms between providers' prescribing attitude and patient race/ethnicity, gender, alcohol/drug use, and annual family income. We also tested other two-way interaction terms among these variables. Only the interaction between gender and alcohol/drug use was statistically significant at $P < .10$ and retained in the final multivariable model.

For comparison of patient and provider characteristics, t tests and χ^2 statistics were used to compare continuous and categorical variables, respectively. Variance estimates were adjusted for the complex, multistage sampling design. We used the Huber-White method to adjust the variance estimates of the model parameters for the potential clustering effect that would result from several patients sharing the same provider.[38] All analyses were weighted to account for differential sampling probabilities, patient and provider nonresponse, and the probability that a patient could have been sampled through multiple providers. We used a bootstrapping technique to estimate 95% confidence intervals for adjusted time ratios, predicted median times to first PI use, and adjusted physical health status.[39] STATA 7.0 software (College Station Tx) was used for all analyses.

RESULTS

Patient and Provider Characteristics

Mean patient age of the analytic sample was 39 years (Table 1). Twenty-two percent were female and half were white. Men having sex with men was the most common HIV exposure mode (48%), followed by injection drug use (24%) and high-risk heterosexual intercourse (19%). Having excluded those with CD4 count > 500 cells/mm^3, almost two-thirds had an AIDS diagnosis at baseline and 76% had received a PI before the end of the study follow-up.

A comparison of the demographic and clinical characteristics of included and excluded subjects revealed few differences (Table 1). The study and excluded patient groups were similar with respect to demographics, physical and mental health status, insurance type, and self-reported access to care. Excluded subjects were more likely to be homeless ($P = .03$) and less likely to agree that antiretrovirals are worth taking ($P = .02$) and to have received a PI during the study ($P = .0008$). Because we excluded those with CD4 counts above 500 cells/mm^3, the excluded group had higher CD4 counts and was less likely to have an AIDS diagnosis. The remaining analyses were weighted to account for the potential bias induced by the exclusion of a portion of the original sample.

Of the 367 providers included in this study, 89% of providers had a Selective prescribing attitude, that is, agreed that adherence was an important factor in their decision to prescribe PIs. Seventy-nine percent were male and 73% were white. The mean age of providers was 46 years. Fifty-five percent were general internists or family practitioners, 42% were infectious disease specialists, and the remaining providers were nurse practitioners, physician assistants, gastroenterologists, pulmonologists, or other specialists. Most HCSUS providers had 50 or more HIV patients in their practice (88%) and 61% of providers correctly answered 80% or more of the 11 true-false HIV knowledge questions.

Time Until First Protease Inhibitor Use

Patients with a Selective provider ($n = 1,522$, 89%) received PIs later than those with a Nonselective provider ($n = 195$, 11%). From the parametric time-to-event models, we estimated time ratios (analogous to hazard ratios from a Cox model but interpreted as the relative median time to an event for one group compared to their reference). The unadjusted time ratio was 1.21 (95% confidence interval

Table 1. Comparison of Patient Characteristics by Inclusion in the Study Sample

Patient Characteristics	Study Sample	Excluded	*P* Value
N	1717	1147	
Mean age, y (95% CI)	39.1 (38.4 to 39.7)	38.2 (37.3 to 39.0)	.09
Female, %	22.5	22.7	.93
Ethnicity, %			.23
White	51.8	45.1	
African-American	30.8	35.9	
Hispanic	14.8	15.9	
Other	2.6	3.1	
Education, %			.72
Less than high school	25.8	23.6	
High school diploma	26.6	28.8	
Some college	28.7	27.9	
College degree	19.0	19.8	
Annual Income, %			.83
$0–5,000	19.2	20.5	
$5–10,000	26.4	25.0	
$11–25,000	25.7	26.5	
$25,000 or more	28.8	28.0	
Insurance, %			.68
Uninsured	19.5	20.2	
Medicaid	28.6	30.3	
Private	31.2	32.9	
Medicare	20.7	16.7	
Mean self-reported access to care (95% CI)*	7.9 (7.6 to 8.1)	7.6 (7.3 to 8.0)	.26
HIV risk factor, %			.88
Injection drug use	24.1	24.1	
Homosexual intercourse	48.0	49.6	
High-risk heterosexual intercourse	18.6	18.1	
Other	9.3	8.2	
Baseline CD4 count, %			<.0001
> 500 cells/mm^3	0	24.9	
200–499	41.4	31.0	
50–199	32.6	24.4	
< 50	26.0	19.7	
CDC AIDS diagnosis, %	64.2	50.0	.0005
Mean HIV symptom index* (95% CI)	24.2 (22.1 to 26.4)	24.7 (22.5 to 27.0)	.68
Mean summary health scores† (95% CI)			
Physical health	49.8 (48.9 to 50.8)	50.3 (49.0 to 51.6)	.51
Mental health	50.2 (49.4 to 50.9)	49.7 (48.5 to 50.9)	.52
One or more psychiatric illness, %‡	47.0	50.4	.29
Used mental health services, %	24.6	28.3	.20
Drug or heavy alcohol use, %	17.0	18.8	.40
Homeless, %	0.6	1.6	.03
Agrees that antiretrovirals are worth taking, %	84.2	77.8	.03
Region, %			.07
Northeast	24.7	24.7	
Midwest	10.2	12.6	
South	43.2	23.9	
West	22.0	38.9	
Had a provider who agrees that adherence is an important factor in their decision to prescribe protease inhibitor (Selective provider)	89.3	87.8	.52
Received a protease inhibitor during study follow-up, %	76.2	60.0	.0008

Scale ranges from 0 to 100 with higher score indicating better access to care.

* *Scale ranges from 0 to 100 with higher score indicating more symptoms.*

† *Based on SF-12 health status measure. Scale ranges from 0 to 100 with higher scores indicating better health.*

‡ *Presence of 1 or more of the following psychiatric conditions: panic disorder, anxiety disorder, depression, or dysthymia.*

CI, confidence interval.

Table 2. Bivariate and Multivariate Time-to-Event Models of First Use of Protease Inhibitors

	Bivariate		Multivariate*	
Independent Variable	Time Ratio	95% CI	Time Ratio	95% CI
Provider prescribing attitude				
Non-Selective provider (reference)	1.00	—	1.00	—
Selective provider	1.21	(1.06 to 1.36)	1.17	(1.01 to 1.35)
Disadvantaged patient populations				
Whites (reference)	1.00	—	1.00	—
African Americans	1.54	(1.38 to 1.72)	1.31	(1.17 to 1.48)
Latinos	1.15	(1.01 to 1.31)	1.12	(1.00 to 1.29)
Other race/ethnicity	1.01	(0.78 to 1.28)	0.96	(0.75 to 1.20)
Men (reference)	1.00	—	1.00	—
Women	1.27	(1.14 to 1.41)	1.12	(0.98 to 1.28)
Annual family income >$25,000 (reference)	1.00	—	1.00	—
Annual family income ≤$25,000	1.32	(1.19 to 1.48)	1.18	(1.05 to 1.34)
No drug or heavy alcohol use (reference)	1.00	—	1.00	—
Illicit drug or heavy alcohol use	1.11	(0.98 to 1.27)	1.05	(0.92 to 1.19)

** Multivariate model also includes other patient and provider covariates. Patient covariates are education, HIV risk factor, CD4 count, symptom index, physical health status, mental health status, presence of anxiety disorder, panic disorder, dysthymia or depression, use of mental health services in last 6 months, type of health insurance coverage, self-reported access to care, homelessness, belief that antiretrovirals are worth taking, and geographic region. Provider covariates are gender, race, years in practice, specialty, HIV knowledge, sexual preference, preference not to treat drug users, belief that their patients cannot adhere to their medications, HIV caseload, and practice setting.*
Time ratios represent the median time to first protease inhibitor use for a group compared to that of the reference group.
CI, confidence interval.

[CI], 1.06 to 1.36) for those with a Selective provider compared to those with a Nonselective provider (Table 2). We then adjusted for all patient covariates (demographics, CD4 count, HIV symptoms, mental and physical health status, insurance and access to care, and drug/alcohol use) and provider covariates (demographics, HIV caseload, knowledge, specialty and experience, attitude toward drug users, practice setting, and geographic region). The adjusted median time to first PI use for those with a Selective provider was 344 days compared to 295 days for those with a Nonselective provider (time ratio [TR], 1.17; 95% CI, 1.01 to 1.35; Table 2).

In unadjusted analyses, the time ratios of first PI use were 1.54 for African Americans (95% CI, 1.38 to 1.72) and 1.15 for Latinos (95% CI, 1.01 to 1.31) compared to whites, 1.27 for women compared to men (95% CI, 1.14 to 1.41), 1.32 for those with an annual family income $25,000 or less compared to those with more income (95% CI, 1.19 to 1.34), and 1.11 for drug or heavy alcohol users compared to nonusers (95% CI, 0.98 to 1.27) (Table 2). After adjusting for patient and provider covariates, these disparities remained for African Americans (TR, 1.31; 95% CI, 1.17 to 1.48), Latinos (TR, 1.12; 95% CI, 1.00 to 1.29), and those with less income (TR, 1.18; 95% CI, 1.05 to 1.34), but not for women (TR, 1.12; 95% CI, 0.98 to 1.28) or drug/heavy alcohol users (TR, 1.05; 95% CI, 0.92 to 1.19).

Next, we sought to determine the effect of providers' prescribing attitude on these disparities in time to first PI use. We performed a multivariate analysis that included all patient and provider covariates and interaction terms between providers' prescribing attitude and race/ethnicity, gender, income, and drug/heavy alcohol use. We then estimated the time ratios for the various patient subpopulations adjusted for providers having a Nonselective prescribing attitude and then adjusted for providers having a Selective prescribing attitude. If patients had a Selective provider, time to PI use was later for African-Americans, Latinos, women, and those with lower incomes compared to their reference, but not for heavy alcohol/drug users (Table 3). The time ratios were 1.32 (95% CI, 1.16 to 1.51) and 1.16 (95% CI, 1.00 to 1.33) for African Americans and Latinos, respectively, compared to whites; 1.21 for women compared to men (95% CI, 1.04 to 1.38); 1.20 for those with less income compared to those with more income (95% CI, 1.05 to 1.37); and 1.13 for drug/heavy alcohol users compared to nonusers (95% CI, 0.98 to 1.31). In contrast, if patients had a Nonselective provider, these disparities were absent, with one exception. The time ratio for African Americans compared to whites with a Nonselective provider was 1.40 (95% CI, 0.99 to 1.97), which was not statistically significant and, contrary to our hypothesis, larger in magnitude than the time ratio if the provider was Selective.

In order to better illustrate these differences in time to first PI use, we also estimated the median time to first PI use, adjusted for patient and provider covariates (Table 4). The median time to first PI use if the provider was Nonselective was not statistically different when comparing patients by race/ethnicity, gender, income, or heavy alcohol/drug use. Fifty percent of African Americans had received a PI by 351 days after the first PI became available,

Table 3. Ratio of Time Until First Protease Inhibitor Use by Race/Ethnicity, Gender, Income, and Heavy Alcohol/Drug Use, Adjusted for Providers' Selective Versus Nonselective Prescribing Attitude*

	Adjusted for providers' prescribing attitude			
	Nonselective Provider		Selective Provider	
	Time Ratio	95% CI	Time Ratio	95% CI
Whites (reference)	1.00	—	1.00	—
African-Americans	1.40	(0.99 to 1.97)	1.32	(1.16 to 1.51)
Latinos	0.94	(0.69 to 1.32)	1.16	(1.00 to 1.33)
Other race/ethnicity	1.04	(0.49 to 2.71)	0.97	(0.75 to 1.23)
Men (reference)	1.00	—	1.00	—
Women	0.74	(0.49 to 1.10)	1.21	(1.04 to 1.38)
Annual family income >$25,000 (reference)	1.00	—	1.00	—
Annual family income ≤$25,000	1.10	(0.85 to 1.47)	1.20	(1.05 to 1.37)
No drug or heavy alcohol use (reference)	1.00	—	1.00	—
Illicit drug or heavy alcohol use	0.90	(0.71 to 1.21)	1.13	(0.98 to 1.31)

** Multivariate models are adjusted for the covariates listed in the table and also for other patient and provider covariates. Patient covariates are education, HIV risk factor, CD4 count, symptom index, physical health status, mental health status, presence of anxiety disorder, panic disorder, dysthymia, or depression, use of mental health services in last 6 months, type of health insurance coverage, self-reported access to care, homelessness, belief that antiretrovirals are worth taking, geographic region, and interaction terms for gender by drug/alcohol use. Provider covariates are gender, race, years in practice, specialty, HIV knowledge, sexual preference, preference not to treat drug users, belief that their patients cannot adhere to their medications, HIV caseload, and practice setting.*
Time ratios represent the median time to first protease inhibitor use for a group compared to that of the reference.
CI, confidence interval.

compared to 251 days for whites—a difference of 100 days (95% CI, −6 to 219). Women tended to receive PIs earlier than men—a difference of −79 days (95% CI, −179 to 40).

If, however, the provider had a Selective prescribing attitude, Latinos, women, and those with lower incomes received PIs later than their comparison groups. The difference in median time to first PI use was 50 (95% CI, 1 to 98) days for Latinos compared to whites, 71 days (95% CI, 16 to 125) for women compared to men, 60 days (95% CI, 17 to 102) for those with less income compared to those more wealthy, and 51 days (95% CI, −1 to 117) for drug or heavy alcohol users compared to nonusers. African Americans also received PIs later than whites (difference of 98 days; 95% CI, 51 to 148) if their provider was Selective. However, the magnitude of this difference was similar to the estimated difference if the provider was Nonselective.

Current HIV guidelines recommend physicians consider adherence in the decision to initiate antiretrovirals only when CD4 counts are greater than 200 cells/mm^3 because delaying treatment can have adverse outcomes when CD4 counts are low.[16] A subset analysis of individuals with baseline CD4 counts below 200 revealed results similar to the original results. Excluding poorly adherent persons also did not substantially change the original results. Of note, adherence was measured at the end of the study. Though adherence may affect the time PI therapy is initiated, the reverse may be true, that is, length of time on therapy is likely to influence later adherence. Because of this temporal ambiguity problem, we did not include adherence as a covariate in the analyses.

Mortality and Physical Health Status

We examined 2 health outcomes, death before December 31, 1999 and physical health status at the second follow-up. We controlled for patient baseline covariates (demographics, CD4 count, physical and mental health status, HIV-related symptoms, presence of psychiatric illness, health insurance, access to care, homelessness, belief that antiretrovirals are worth taking, HIV risk factor, and drug/alcohol use) and provider covariates (race, years in practice, specialty, HIV knowledge, sexual preference, preference not to treat drug users, belief that their patients cannot adhere to their medications, HIV caseload, and practice setting). The adjusted odds of death were 1.1 times greater among those with a Selective provider than those with a Nonselective provider (odds ratio; 95% CI, 0.6 to 2.0). The adjusted physical health status, controlling for all covariates including baseline physical health status, was 50.4 for those with a Nonselective provider (95% CI, 27.6 to 66.8) and 49.1 for those with a Selective Provider (95% CI, 26.4 to 65.5). This difference was statistically significant ($P = .04$).

DISCUSSION

Current treatment guidelines recommend that physicians consider several factors in their decision to prescribe antiretrovirals to asymptomatic patients, including "assessment of adherence potential."[16] We found that among providers caring for a nationally representative sample of HIV-infected adults, 89% agreed that adherence is an

Table 4. Predicted Median Days Until First Protease Inhibitor Use by Race/Ethnicity, Gender, Income, and Heavy Alcohol/Drug Use, Adjusted for Providers' Selective Versus Nonselective Prescribing Attitude*

	Adjusted for Providers' Prescribing Attitude			
	Nonselective Provider		Selective Provider	
	Predicted Median Days to First PI Use (95% CI)	Difference in Predicted Median Days to First PI Use Compared to Reference (95% CI)	Predicted Median Days to First PI Use (95% CI)	Difference in Predicted Median Days to First PI Use Compared to Reference (95% CI)
Race/ethnicity				
Whites	251 (205 to 297)	reference	311 (284 to 333)	reference
African Americans	351 (260 to 451)	100 (–6 to 219)	409 (368 to 445)	98 (51 to 148)
Latinos	235 (176 to 311)	–16 (–89 to 80)	360 (316 to 404)	50 (1 to 98)
Other race ethnicity	261 (120 to 555)	10 (–137 to 436)	300 (228 to 379)	–10 (–80 to 71)
Gender				
Men	306 (249 to 362)	reference	329 (305 to 350)	reference
Women	227 (155 to 309)	–79 (–179 to 40)	400 (356 to 443)	71 (16 to 125)
Annual family income, $				
>25,000	262 (202 to 334)	reference	306 (267 to 337)	reference
≤25,000	287 (238 to 333)	26 (–58 to 104)	366 (339 to 388)	60 (17 to 102)
Drug/heavy alcohol use				
Nonuser	287 (239 to 330)	reference	342 (319 to 361)	reference
User	254 (201 to 328)	–32 (–93 to 56)	394 (336 to 447)	51 (–1 to 117)

* *Multivariate models are adjusted for the covariates listed in the table and also for other patient and provider covariates. Patient covariates are education, HIV risk factor, CD4 count, symptom index, physical health status, mental health status, presence of anxiety disorder, panic disorder, dysthymia, or depression, use of mental health services in last 6 months, type of health insurance coverage, self-reported access to care, homelessness, belief that antiretrovirals are worth taking, and geographic region. Provider covariates are gender, race, years in practice, specialty, HIV knowledge, sexual preference, preference not to treat drug users, belief that their patients cannot adhere to their medications, HIV caseload, and practice setting.*

CI, confidence interval.

important factor in their decision to prescribe PIs. This suggests that the great majority of providers caring for HIV-infected individuals in the United States concur with current treatment recommendations. Furthermore, patients with providers who agreed with this prescribing practice received PIs later than those with providers who disagreed, suggesting that providers' prescribing behavior reflects their prescribing attitude.

Some have objected to the current treatment guidelines regarding adherence as a prescribing criterion for fear that it may disproportionately affect minorities, the poor, and those with alcohol or drug use problems, resulting in greater disparities in use of antiretrovirals.[23–25] We found PI use was later for Latinos, women, and those with less income. However, these differences occurred only if patients had a Selective provider and not a Nonselective provider. African-Americans appeared to use PIs later than whites regardless of providers' prescribing attitude.

Though delaying therapy appears to increase some disparities in treatment, the practice of delaying therapy is not clearly beneficial or harmful. Those with a Selective provider had slightly lower physical health status at follow-up than those with a Nonselective provider, but this difference was very small and probably not clinically meaningful. Also, providers' prescribing attitude was not associated with a difference in mortality. Caution is warranted in interpreting these results, however. While we have information on providers' prescribing attitude, we do not know whether they delayed treatment for a particular individual based on his/her likely adherence. Ideally, we would have compared outcomes for individuals with and without delayed treatment. Furthermore, the natural progression of HIV can be slow, and inadequate follow-up time in our study may have limited our ability to detect differences in outcomes. These results highlight the need for long-term study of the impact of delaying therapy for nonadherent patients on outcomes.

Regardless of whether delaying therapy for nonadherent patients is beneficial or not, providers might be delaying therapy for the wrong patients. We performed 2 sensitivity analyses, one limited to those who reported adequate or very good adherence and another limited to those with baseline CD4 counts of less than 200. Both of these groups probably should have received treatment, yet the sensitivity analyses demonstrated disparities in PI use only among those with Selective providers.

Whether or not certain groups are less adherent remains unclear. Previous studies have found mixed results, several showing comparable adherence by gender, race/ethnicity,

socioeconomic status, and drug use.[21,40–42] Regardless, providers appear unable to accurately identify poorly adherent patients.[43–45] In one study, the sensitivity and specificity of providers' estimate of nonadherence to antiretrovirals (< 80% of pills taken) was only 40% and 85%, respectively.[44] Another study found a 19% agreement between providers' predictions and patient's actual adherence to HIV treatment.[45]

Finally, providers appear to make judgments about adherence based on superficial characteristics. In a study using scenarios, providers believed that African Americans and injection drug users would be less adherent than others even though only demographic and disease severity information was provided.[46] An observational study also found that physicians predicted lower adherence among individuals actively using drugs.[45]

A limitation of our study is that we may have surveyed providers who did not originally prescribe PIs to study patients. Though we made extensive efforts to identify each patient's primary HIV care provider, patients could have changed providers or received PIs from a different HIV care provider. However, any such misattribution would likely bias our results toward finding no effect.

Another limitation is that some unobserved differences may exist between patients who are cared for by Selective and Nonselective providers. Also, given that only 11% of patients had a Nonselective provider, we might have lacked adequate statistical power to detect some differences. Finally, we examined only a subset of the original HCSUS patient cohort due to patient and provider nonresponse. However, the potential bias is likely to be minimal given that the study and excluded patients had similar demographic characteristics and that the analyses were weighted to adjust for this response bias.

Since HCSUS was conducted several years ago, studies have found that adherence, while still very important, may not be as critical to successful outcomes as once thought. Patients derive benefit from antiretrovirals even after resistance to them has developed, in part because resistant HIV strains may be less harmful.[47] Also, drug resistance is probably unavoidable at the population level as resistance occurs commonly even when adherence is good.[48] Nevertheless, current guidelines still recommend that physicians consider adherence in their treatment decisions given that better adherence leads to better HIV suppression and outcomes.[16,47] Thus, physicians probably have not changed their prescribing practice regarding nonadherent patients since HCSUS was conducted, and our results remain pertinent to current care and to understanding existing disparities in treatment.

The present study suggests that the practice of delaying treatment for nonadherent patients may contribute to differences in antiretroviral treatment by gender, Latino ethnicity, and income. Some populations may be less adherent, and thus providers may be helping them save therapy for when they need it most. On the other hand, growing evidence suggests that physicians are unable to accurately assess adherence. Their assessments might incorporate subtle biases that could explain some of the disparities we observed. If so, delaying antiretroviral treatment may contribute to inequitable care. Future studies need to determine how physicians operationalize their stated approach (Selective vs Nonselective) and the impact that this approach to treatment has on the development of viral resistance and patient outcomes. Until we better understand the health consequences of delaying therapy and using adherence as a prescribing criterion, every effort must be made to accurately assess adherence, especially for those who are often thought to be less adherent.

This research is supported by grants from the Agency for Healthcare Research and Quality, The Robert Wood Johnson Foundation, the Universitywide AIDS Research Program, and by the Health Resources Service Administration through a National Research Service Award.

We thank Robin Beckman and Terry Nakazono for their statistical and programming assistance in creating the analytic weights.

REFERENCES

1. Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. JAMA. 1998;279:450–4.
2. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338:853–60.
3. Forrest DM, Seminari E, Hogg RS, et al. The incidence and spectrum of AIDS-defining illnesses in persons treated with antiretroviral drugs. Clin Infect Dis. 1998;27:1379–85.
4. Lemp GF, Hirozawa AM, Cohen JB, Derish PA, McKinney KC, Hernandez SR. Survival for women and men with AIDS. J Infect Dis. 1992;166:74–9.
5. Poundstone KE, Chaisson RE, Moore RD. Differences in HIV disease progression by injection drug use and by sex in the era of highly active antiretroviral therapy. AIDS. 2001;15:1115–23.
6. Moore RD, Stanton D, Gopalan R, Chaisson RE. Racial differences in the use of drug therapy for HIV disease in an urban community. N Engl J Med. 1994;330:763–8.
7. Shapiro MF, Morton SC, McCaffrey DF, et al. Variations in the care of HIV-infected adults in the United States: results from the HIV Cost and Services Utilization Study. JAMA. 1999;281:2305–15.
8. Moore RD, Hidalgo J, Sugland BW, Chaisson RE. Zidovudine and the natural history of the acquired immunodeficiency syndrome. N Engl J Med. 1991;324:1412–6.
9. Stein MD, Piette J, Mor V, et al. Differences in access to zidovudine (AZT) among symptomatic HIV-infected persons. J Gen Intern Med. 1991;6:35–40.
10. Strathdee SA, Palepu A, Cornelisse PG, et al. Barriers to use of free antiretroviral therapy in injection drug users. JAMA. 1998;280:547–9.
11. Anderson KH, Mitchell JM. Differential access in the receipt of antiretroviral drugs for the treatment of AIDS and its implications for survival. Arch Intern Med. 2000;160:3114–20.
12. Andersen R, Bozzette S, Shapiro M, et al. Access of vulnerable groups to antiretroviral therapy among persons in care for HIV disease in the United States. HCSUS Consortium. HIV Cost and Services Utilization Study. Health Serv Res. 2000;35:389–416.
13. Sambamoorthi U, Moynihan PJ, McSpiritt E, Crystal S. Use of protease inhibitors and non-nucleoside reverse transcriptase inhibitors among Medicaid beneficiaries with AIDS. Am J Public Health. 2001;91:1474–81.

14. Report of the NIH Panel to Define Principles of Therapy of HIV Infection. Ann Intern Med. 1998;128(12 Part 2):1057–78.
15. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services and the Henry J. Kaiser Family Foundation. Ann Intern Med. 1998;128(12 Part 2):1079–100.
16. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. November 10, 2003. Bethesda, MD.
17. Condra JH. Resistance to HIV protease inhibitors. Haemophilia. 1998;4:610–5.
18. Molla A, Korneyeva M, Gao Q, et al. Ordered accumulation of mutations in HIV protease confers resistance to ritonavir. Nat Med. 1996;2:760–6.
19. Moutouh L, Corbeil J, Richman DD. Recombination leads to the rapid emergence of HIV-1 dually resistant mutants under selective drug pressure. Proc Natl Acad Sci USA. 1996;93:6106–11.
20. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. AIDS. 1999;13:1099–107.
21. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000;133:21–30.
22. Little SJ, Daar ES, D'Aquila RT, et al. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. JAMA. 1999;282:1142–9.
23. Bangsberg D, Tulsky JP, Hecht FM, Moss AR. Protease inhibitors in the homeless. JAMA. 1997;278:63–5.
24. Eckenwiler L. Justice and access to therapies for AIDS. AIDS Public Policy J. 1999;14:20–5.
25. Lerner BH, Gulick RM, Dubler NN. Rethinking nonadherence. Historical perspectives on triple-drug therapy for HIV disease. Ann Intern Med. 1998;129:573–8.
26. Bozzette SA, Berry SH, Duan N, et al. The care of HIV-infected adults in the United States. HIV Cost and Services Utilization Study Consortium. N Engl J Med. 1998;339:1897–904.
27. Landon BE, Wilson IB, Wenger NS, et al. Specialty training and specialization among physicians who treat HIV/AIDS in the United States. J Gen Intern Med. 2002;17:12–22.
28. Gifford AL, Cunningham WE, Heslin KC, et al. Participation in research and access to experimental treatments by HIV-infected patients. N Engl J Med. 2002;346:1373–82.
29. Hankins C, Lapointe N, Walmsley S. Participation in clinical trials among women living with HIV in Canada. Canadian Women's HIV Study Group. CMAJ. 1998;159:1359–65.
30. Stone VE, Mauch MY, Steger K, Janas SF, Craven DE. Race, gender, drug use, and participation in AIDS clinical trials. Lessons from a municipal hospital cohort. J Gen Intern Med. 1997;12:150–7.
31. Cunningham WE, Hays RD, Ettl MK, et al. The prospective effect of access to medical care on health-related quality-of-life outcomes in patients with symptomatic HIV disease. Med Care. 1998;36:295–306.
32. Mathews WC, McCutchan JA, Asch S, et al. National estimates of HIV-related symptom prevalence from the HIV Cost and Services Utilization Study. Med Care. 2000;38:750–62.
33. Hays RD, Cunningham WE, Sherbourne CD, et al. Health-related quality of life in patients with human immunodeficiency virus infection in the United States: results from the HIV Cost and Services Utilization Study. Am J Med. 2000;108:714–22.
34. Bing EG, Burnam MA, Longshore D, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch Gen Psychiatry. 2001;58:721–8.
35. Wittchen HU, Kessler RC, Zhao S, Abelson J. Reliability and clinical validity of UM-CIDI DSM-III-R generalized anxiety disorder. J Psychiatr Res. 1995;29:95–110.
36. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med. 2001;134:968–77.
37. Klein J, Moeschberger M. Survival Analysis Techniques for Censored and Truncated Data. New York, NY: Springer-Verlag; 1997.
38. Huber P. The Behavior of Maximum Likelihood Estimates Under Non-Standard Conditions. Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics Probability. 1967;1:221.
39. Davison AC, Hinkley DV. Bootstrap Methods and Their Application. Cambridge, UK: Cambridge University Press; 1997.
40. Roca B, Gomez CJ, Arnedo A. Adherence, side effects and efficacy of stavudine plus lamivudine plus nelfinavir in treatment-experienced HIV-infected patients. J Infect. 2000;41:50–4.
41. Stone VE, Hogan JW, Schuman P, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the her study. J Acquir Immune Defic Syndr. 2001;28:124–31.
42. Wutoh AK, Brown CM, Kumoji EK, et al. Antiretroviral adherence and use of alternative therapies among older HIV-infected adults. J Natl Med Assoc. 2001;93:243–50.
43. Miller LG, Liu H, Hays RD, et al. How well do clinicians estimate patients' adherence to combination antiretroviral therapy? J Gen Intern Med. 2002;17:1–11.
44. Bangsberg DR, Hecht FM, Clague H, et al. Provider assessment of adherence to HIV antiretroviral therapy. J Acquir Immune Defic Syndr. 2001;26:435–42.
45. Escaffre N, Morin M, Bouhnik AD, et al. Injecting drug users' adherence to HIV antiretroviral treatments: physicians' beliefs. AIDS Care. 2000;12:723–30.
46. Bogart LM, Catz SL, Kelly JA, Benotsch EG. Factors influencing physicians' judgments of adherence and treatment decisions for patients with HIV disease. Medical Decis Making. 2001;21:28–36.
47. Bangsberg DR, Deeks SG. Is average adherence to HIV antiretroviral therapy enough? J Gen Intern Med. 2002;17:812–3.
48. Bangsberg DR, Charlebois ED, Grant RM, et al. High levels of adherence do not prevent accumulation of HIV drug resistance mutations. AIDS. 2003;17:1925–32.