

## Special Article

## PARTICIPATION IN RESEARCH AND ACCESS TO EXPERIMENTAL TREATMENTS BY HIV-INFECTED PATIENTS

ALLEN L. GIFFORD, M.D., WILLIAM E. CUNNINGHAM, M.D., M.P.H., KEVIN C. HESLIN, RON M. ANDERSEN, PH.D., TERRY NAKAZONO, DALE K. LIEU, M.D., MARTIN F. SHAPIRO, M.D., PH.D., AND SAMUEL A. BOZZETTE, M.D., PH.D., FOR THE HIV COST AND SERVICES UTILIZATION STUDY CONSORTIUM

**ABSTRACT**

**Background** Although there is concern that minority groups and women are underrepresented in research involving patients with human immunodeficiency virus (HIV) infection, the available data are inconclusive.

**Methods** We used nationally representative data from the HIV Cost and Services Utilization Study to determine the characteristics of the participants and nonparticipants in trials of medications for HIV infection and whether or not patients had access to experimental treatments. A probability sample of 2864 persons, representing all 231,400 adults with known HIV infection who are cared for in the contiguous United States, were interviewed on three occasions between 1996 and 1998. They were asked about participation in clinical research studies of medications and past receipt of experimental medications for HIV.

**Results** We estimate that 14 percent of adults receiving care for HIV infection participated in a medication trial or study; 24 percent had received experimental medications; and 8 percent had tried and failed to obtain experimental treatments. According to multivariate models, non-Hispanic blacks and Hispanics were less likely to be participating in trials than non-Hispanic whites (odds ratio for participation among non-Hispanic blacks, 0.50 [95 percent confidence interval, 0.28 to 0.91]; odds ratio among Hispanics, 0.58 [95 percent confidence interval, 0.37 to 0.93]) and to have received experimental medications (odds ratios, 0.41 [95 percent confidence interval, 0.32 to 0.54] and 0.56 [95 percent confidence interval, 0.41 to 0.78], respectively). Patients who were cared for in private health maintenance organizations were less likely to participate in trials than those with fee-for-service insurance (odds ratio, 0.43 [95 percent confidence interval, 0.21 to 0.88]). Women were not underrepresented in research trials and had a similar likelihood of receiving experimental treatments.

**Conclusions** Among patients with HIV infection, participation in research trials and access to experimental treatment is influenced by race or ethnic group and type of health insurance. (N Engl J Med 2002; 346:1373-82.)

Copyright © 2002 Massachusetts Medical Society.

**C**LINICAL research should involve diverse populations of patients.<sup>1-3</sup> Race, sex, and other sociodemographic factors can influence the course of disease, the response to treatment, the types of toxic effects, and health-related behavior, and the degree of diversity can therefore affect the generalizability of the results.<sup>4-9</sup> Choosing research cohorts that resemble the target clinical population may improve the likelihood that new therapies will be accepted by patients and their doctors. Many patients with serious diseases have few or no options for conventional treatment, so enrollment in trials of experimental treatments or new applications of existing medications can be the only means of access to needed care.<sup>10,11</sup>

Human immunodeficiency virus (HIV) infection is a case in point. The course of HIV disease is affected by the biology of the host and socially influenced health-related behavior. Those with HIV often have special needs and few options: their median household income is about one third that of typical households in the United States; they are four times as likely to be members of an underserved minority than to be white; and conventional therapy for HIV commonly fails.<sup>12-14</sup>

Available studies suggest that minority groups and women are underrepresented in trials of treatment for HIV infection. However, these studies lack accuracy and detail because they have been confined to selected sites or because they compare the proportions of known trial participants of different races or ethnic groups and sexes with estimates of the proportions in the overall population.<sup>15-18</sup> Although such

From the Center for Research in Patient-Oriented Care and the Quality Enhancement Research Initiative in HIV, Veterans Affairs San Diego Healthcare System, San Diego (A.L.G., D.K.L., S.A.B.); the University of California, San Diego, School of Medicine, La Jolla (A.L.G., D.K.L., S.A.B.); the University of California at Los Angeles, Los Angeles (W.E.C., K.C.H., R.M.A., T.N., M.E.S.); and RAND Health, Santa Monica (M.E.S., S.A.B.) — all in California. Address reprint requests to Dr. Gifford at the Veterans Affairs San Diego Healthcare System and the University of California, San Diego, 3350 La Jolla Village Dr. (111N-1), San Diego, CA 92161, or at agifford@ucsd.edu.

comparisons are attractively simple, they are problematic, because data from most privately funded trials, unpublished studies, and expanded-access programs are unavailable; because the local or national surveillance data used for comparison may not represent all the patients for whom investigational therapies would be appropriate; and because the characteristics of persons who do not participate in trials are not accounted for.<sup>19-21</sup> To address these issues, we used nationally representative data from the HIV Cost and Services Utilization Study (HCSUS) to determine the characteristics of the participants in trials of medications for HIV and whether or not patients with HIV had access to research trials and experimental treatments.

## METHODS

### Sources and Weighting of Data

We analyzed data from the HCSUS sample, which represents all adults 18 years of age or older who were receiving care for known HIV infection in the 48 contiguous United States in early 1996, except those who were cared for only in prison or active-duty military facilities or emergency departments.<sup>22,23</sup> We used multistage sampling methods to assemble the study population of 2864 persons; we used related methods to construct analytic weights with which we adjusted the survey data to represent the entire reference population of 231,400 adults receiving care for HIV in the contiguous United States outside of the military, prisons, and emergency rooms. We constructed weights using each patient's probabilities of being sampled and of visiting the care site during the study period. Characteristics of those who did not respond to the full survey were collected and used to increase weights for the respondents most similar to nonrespondents.<sup>23</sup> Details of the sampling and survey methods and interview questions are available elsewhere.<sup>22-26</sup>

### Interviews

The RAND institutional review board and, when available, a local board, reviewed and approved all forms, materials, and procedures. After written informed consent had been given, participants were interviewed, usually in person, on three occasions (once between January 1996 and April 1997, once between December 1996 and July 1997, and once between August 1997 and January 1998). Interviews were conducted in English or Spanish, by centrally trained research personnel using computerized personal interviewing devices and locally identified and approved interpreters for interviews in languages other than English or Spanish. All interviewers had full access to survey experts and investigators for any questions that arose in the field.

### Classification of Respondents

During the base-line interview, we collected information on sociodemographic characteristics, risk factors for exposure to HIV, health insurance, and attitudes and beliefs. Race or ethnic group was determined on the basis of the answer to the question "Which of these would you say is your main racial or ethnic group?" The response options included non-Hispanic white, non-Hispanic black, Hispanic, American Indian or Alaskan Native, Asian or Pacific Islander, mixed race, or some other single race. Subgroups defined according to risk factors for HIV were mutually exclusive. Participants with intravenous drug use were so classified. Men who did not use intravenous drugs but who had sex with other men were classified as men who have sex with men. Those who fell into neither of these categories and who were heterosexually active were so

classified, unless they had been infected with HIV through blood products. Persons infected through blood products and those without defined risk factors for exposure to HIV were classified as "other."<sup>27</sup>

### Participation in Research and Access to Experimental Medications

The response options were chosen to minimize the possibility of errors of omission or misclassification regarding whether those interviewed were participants in trials. We assessed participation in medication trials by the answers to the questions "Are you currently participating in any clinical trials or clinical research studies?" and "What services are being provided in the trial [or trials]?" Respondents chose among specific options regarding the provision of medications, medical care, and checkups, alone or in combination.

Participants obtained experimental medications through clinical trials or approved clinical protocols involving investigational new drugs. Expanded-access programs, programs based on the compassionate use of investigational new drugs, and parallel-track protocols are Food and Drug Administration–approved mechanisms to allow doctors and patients in the United States to obtain promising experimental HIV drugs.<sup>11</sup> We assessed the lifetime history of use of experimental treatments by the answer to the question "Have you ever tried to get experimental drugs or treatments through a clinical trial or expanded access?" Those who answered "yes" were asked, "Were you able to get experimental drugs or treatments when you tried to?" We calculated the perceived unmet need for experimental medications as the proportion of patients who tried but failed to obtain them. We used data abstracted from medical records to validate clinical measures and receipt of treatments.

### Other Variables

Participants were asked two questions about each of the following issues in order to rate them on a Likert scale: their trust in providers, their desire for health information, and their participation in decisions about treatment (Cronbach's alpha for internal consistency, 0.86, 0.64, and 0.76, respectively). They were asked one question about their attitude toward antiretroviral medications.<sup>26,28-31</sup>

We used a Web-based system (<http://www.randmcnally.com/>) to calculate the distance from each participant's primary care site to the nearest site where research on HIV was being conducted by an AIDS Clinical Trials Group (ACTG) or one of the Community Programs for Clinical Research on AIDS (CPCRA) during the HCSUS field period.

### Comparison Data

To provide a context for our findings, we assembled basic sociodemographic data for all participants in ACTG trials who were enrolled between 1996 and 1998 (i.e., during the HCSUS field period) and for participants in studies of HIV drugs published in the English-language literature.<sup>32</sup> Studies were identified by a Medline computer search for 1996 through 2000 with the keywords "HIV infections" and "drug therapy" and with results limited to reports on clinical trials. We reviewed the abstracts of articles to identify primary reports and to eliminate pediatric studies and studies conducted outside the United States. We abstracted and totaled the data on participants from the articles we identified. Details are provided in Supplementary Appendix 1 (available with the full text of this article at <http://www.nejm.org>). Finally, we obtained data from reports by the Centers for Disease Control and Prevention (CDC) on the race or ethnic group and sex of all patients with AIDS in the United States.<sup>33</sup>

### Statistical Analysis

All analyses of HCSUS data were weighted and adjusted for the complex sampling design with the use of the Taylor series linear

ization method, and all P values are two-tailed.<sup>34</sup> We used "hot deck" imputation to fill in missing values, which accounted for less than 5 percent of data on CD4+ lymphocyte counts, less than 3 percent of data on insurance and income, and less than 0.5 percent of data for other essential variables.<sup>35</sup> We identified univariate predictors of participation in medication trials, of lifetime use of experimental treatments from a study or expanded-access program, and of perceived unmet need for experimental treatments. We estimated multivariate logistic-regression models to determine which factors were independent predictors of participation in research on medication for HIV infection and of lifetime use of experimental medications.

## RESULTS

### Race or Ethnic Group

On the basis of our data, we estimate that, in 1996, 62 percent of HIV-infected adults participating in medication trials were white, whereas only 49 percent of all those receiving care for HIV infection were white. At that time, whites accounted for 44 percent of the patients with AIDS whose cases had been reported to the CDC (Fig. 1). Blacks accounted for 23 percent of the adults participating in treatment trials but for 33 percent of those receiving care for HIV infection and 37 percent of patients with reported AIDS cases. The percentage of trial participants who were white was similar to the 63 percent in published, peer-reviewed HIV studies and higher than the 54 percent of ACTG enrollees. These data suggest that whites are overrepresented in clinical trials related to HIV.<sup>22,32,33</sup> The proportions of women in the various research and clinical groups were similar (Fig. 1).

### Predictors of Participation in Research

Examination of population-based participation rates showed that, during the two years of follow-up in HCSUS, an estimated 14 percent of the 231,400 HIV-infected adults who had been receiving HIV care in early 1996 participated in a medication trial or study; 24 percent received experimental treatment at some time during the course of their HIV treatment; and 8 percent tried and failed to obtain experimental treatments. Race or ethnic group, the primary risk factor for HIV, level of education, type of health insurance, severity of HIV disease, proximity to a major clinical-trial center (ACTG or CPCRA), and attitudes toward health care providers and HIV medications were significantly associated with participation or lack of participation in medication trials according to univariate analyses. The differences among subgroups were substantial: non-Hispanic black race, less than a high-school education, private insurance through a health maintenance organization (HMO), and receipt of primary care 8 miles (12.8 km) or more from a major clinical-trial center were each associated with a reduction of about 50 percent in the likelihood of participating in a medication trial (Table 1).

In a multiple regression model with adjustment

for characteristics of the patient, the type of health insurance, and attitudes about health care, both non-Hispanic black and Hispanic patients had significantly lower odds than non-Hispanic whites of participating in a medication trial. Patients in private HMOs participated less often than those with private fee-for-service insurance; those who were receiving care farther from the nearest clinical-trial center participated less often than those who were receiving care less than 1 mile (1.6 km) away from such a center; and men participated less often than women (Table 2). There was no difference between men and women in terms of the likelihood of receiving experimental treatments.

Patients who had positive attitudes toward anti-retroviral medications and trust in their HIV care provider at base line had higher rates of subsequent enrollment in medication trials. However, neither patients' trust in their provider nor their desire for information or for involvement in making decisions about their care was independently associated with participation in trials, according to multivariate analyses (Table 3). Furthermore, neither removing variables related to attitudes in order to assess the effects of characteristics of the patient and of the type of health insurance alone nor removing variables related to health insurance in order to assess characteristics of the patient alone changed the size or significance of the effect of race or ethnic group or other patient-related variables on the likelihood of participation in a medication trial (data not shown).

### Changes in Participation Rates

The proportion of the patients participating in HIV research who were non-Hispanic blacks (20 percent at base line) did not increase between the HCSUS base line and follow-up, and non-Hispanic blacks were more likely than other patients to withdraw from or stop participating in trials during that time (Fig. 2). Forty-six percent of all those who were enrolled in a trial at base line were enrolled in a trial at follow-up. Among those enrolled in a trial at base line, the rate of participation at follow-up was higher among non-Hispanic whites (53 percent) than among non-Hispanic blacks (25 percent,  $P=0.04$ ), higher among those with a college education (65 percent) than among those with only a high-school education (39 percent,  $P<0.001$ ), and higher among patients with private fee-for-service insurance (62 percent) than among uninsured patients (37 percent,  $P=0.05$ ); the rates were similar among women (41 percent) and among men (47 percent,  $P=0.42$ ).

### Access to Experimental Medications

A total of 32 percent of the adults receiving care for HIV infection had tried to get experimental med-

ication, and 24 percent had used an experimental medication at some time while receiving care.<sup>11,20,21,36</sup> Non-Hispanic white patients, men who had sex with men, patients with higher incomes, a higher level of education, or private health insurance, and those who received care closer to a clinical-trial center were all more likely to have received experimental medications at some time while receiving HIV care (Table 1).

In multivariate analyses with adjustment for the stage of disease and other characteristics of the patient and the type of health insurance, non-Hispanic whites, patients with higher levels of education, and patients receiving care closer to a clinical-trial center all remained more likely to have received experimental medications (Table 2). Most of the differences in participation rates were attributable to differences in the rates at which experimental medications were sought. However, even among those who sought experimental medications, non-Hispanic whites received them more often than non-Hispanic blacks (77 percent vs. 69 percent,  $P=0.008$ ), and patients with private fee-for-service insurance received them more often than uninsured patients or those insured by private HMOs (83 percent, 69 percent, and 71 percent, respectively;  $P=0.03$  for the three-way comparison).

When we adjusted for the severity of disease (as evaluated in terms of the CD4+ lymphocyte count), participants in research on medications were more likely than other patients to have received indicated prophylaxis against *Pneumocystis carinii* pneumonia (odds ratio, 1.8; 95 percent confidence interval, 1.4 to 2.3), prophylaxis against *Mycobacterium avium* complex (odds ratio, 1.6; 95 percent confidence interval, 1.1 to 2.3), and protease-inhibitor medications (odds ratio, 3.3; 95 percent confidence interval, 2.3 to 4.6). Research participants also had more frequent measurements of CD4+ lymphocytes recorded in their medical records than did nonparticipants ( $P=0.04$ ), as well as more visits to the doctor ( $P=0.004$ ).

## DISCUSSION

There are important reasons to be concerned about disparities among groups of patients with HIV in terms of enrollment in medication trials and expanded-

access programs. Society and future patients benefit when participation in research is broad enough that results may be generalized to the patients receiving care who will eventually use the drugs. Current patients also benefit: although the efficacy of experimental treatments is unproven and the risk of harm is real, these treatments are often important and welcome alternatives for seriously ill patients who have few other options. Patients who have few social resources may also receive primary care, case management, and other resources by participating in research. Advocacy groups and federal legislators have emphasized the need for patients to have access to trials and investigational treatments.<sup>37</sup>

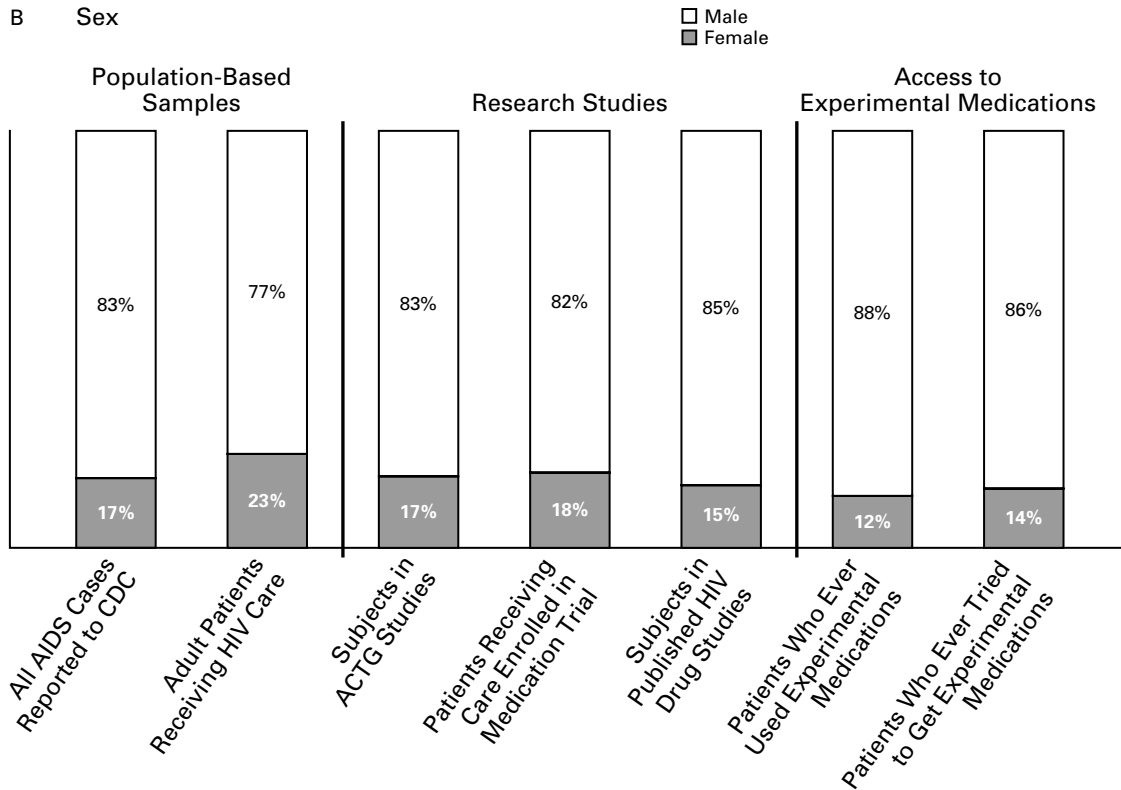
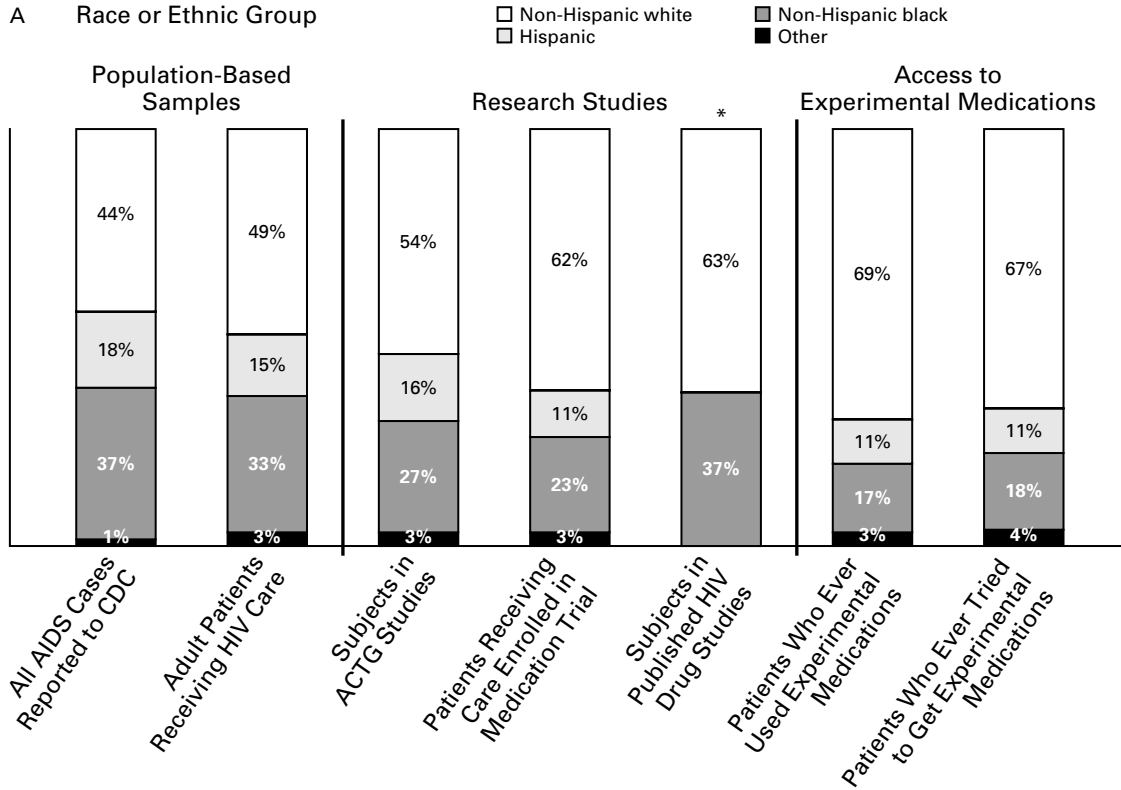
More HIV-infected patients than patients with other serious diseases do obtain experimental treatments. We estimate that 14 percent of HIV-infected adults receiving care in the United States participated in a medication trial during the study period; by comparison, enrollment in cooperative group trials of the National Cancer Institute during a similar period was estimated at only 4 percent among adults with cancer who were 20 to 49 years of age and 1.5 percent among those 50 years of age or older.<sup>38</sup> We also estimated that 24 percent of adult patients receiving care for HIV infection received experimental medications through a trial or an expanded-access program at some time. However, our data suggest that about 18,500 patients (8 percent of the patients receiving HIV care) had tried and failed to get experimental treatments.

Our findings confirm that there are disparities among racial or ethnic groups in the rate of study enrollment, as others have observed in selected populations of patients with HIV or inferred from the racial or ethnic composition of particular trial cohorts; moreover, these findings suggest that such disparities persisted up to four years after the National Institutes of Health (NIH) issued guidelines for increasing the enrollment of members of minority groups. These findings are especially striking in view of the fact that the HCSUS is a study limited to patients receiving care for HIV infection, so that imbalances among racial or ethnic groups in basic access to care did not contribute to the differences we found. The effects of race or ethnic group were seen

**Figure 1 (facing page).** Distribution of Race or Ethnic Group (Panel A) and Sex (Panel B) of Adult Patients with Human Immunodeficiency Virus (HIV) or the Acquired Immunodeficiency Syndrome (AIDS) in Population-Based Samples, Research Studies, and Access to Experimental Medications between 1996 and 1998.

Some published studies of HIV drugs (18 percent of the studies, accounting for 17 percent of study subjects) reported race as white or nonwhite only; therefore, for subjects in published HIV drug studies (indicated by the asterisk), only white and nonwhite proportions are shown. CDC denotes Centers for Disease Control and Prevention, and ACTG AIDS Clinical Trials Group. Because of rounding, percentages may not total 100.

PARTICIPATION IN RESEARCH BY HIV-INFECTED PATIENTS



**TABLE 1.** ESTIMATED NUMBER OF PATIENTS WITH HIV PARTICIPATING IN CLINICAL TRIALS OF MEDICATIONS OR RESEARCH STUDIES AND NUMBER WHO EVER RECEIVED EXPERIMENTAL TREATMENT.\*

VARIABLE	PATIENTS IN THE UNITED STATES RECEIVING HIV CARE AT BASE LINE	PATIENTS PARTICIPATING IN A MEDICATION TRIAL OR STUDY AT ANY INTERVIEW		PATIENTS WHO EVER RECEIVED EXPERIMENTAL TREATMENT	
	weighted no.	%	P value	%	P value
All patients	231,400	14±2		24±2	
Race or ethnic group			0.003		<0.001
Non-Hispanic white	114,000	18±2		34±3	
Non-Hispanic black	75,800	10±2		12±2	
Hispanic	34,200	11±2		17±3	
Other†	7,400	15±4		27±5	
Sex			0.10		<0.001
Male	179,200	15±2		27±3	
Female	52,200	11±2		13±2	
Age			0.41		0.05
18–34 yr	79,100	13±2		21±2	
35–49 yr	125,900	15±2		26±3	
≥50 yr	26,400	12±2		23±4	
HIV risk category			0.02		<0.001
Man who has sex with men	112,400	16±2		32±3	
Injection drug user	55,800	15±2		20±3	
Heterosexual	42,700	9±2		11±2	
Other	20,500	9±2		18±4	
Level of education			0.02		<0.001
College graduate	44,600	19±3		41±4	
Some college	65,600	15±2		26±2	
High-school graduate	63,500	13±1		20±3	
Some high school	57,700	10±1		13±2	
Employment status			0.87		0.08
Not working	145,100	14±1		22±2	
Working full- or part-time	86,300	14±3		27±3	
Annual income			0.10		<0.001
≥\$25,000	65,900	18±3		35±4	
\$10,000–\$24,999	60,200	12±2		23±2	
\$5,000–\$9,999	59,700	14±2		21±3	
\$0–\$4,999	45,600	11±2		13±2	
Health insurance‡			<0.001		<0.001
Private fee-for-service	38,200	20±5		37±6	
Private HMO	35,500	10±2		28±3	
Medicare	44,300	18±2		28±2	
Medicaid	67,600	13±2		17±3	
None	45,700	10±2		17±2	
Region			0.06		0.02
Northeast	57,100	13±3		18±4	
South	82,900	10±1		19±3	
Midwest	25,700	21±6		29±6	
West	65,700	17±4		34±5	
Nadir CD4+ lymphocyte count			<0.001		<0.001
≥500/mm <sup>3</sup>	21,900	7±2		8±2	
200–499/mm <sup>3</sup>	86,700	13±3		17±2	
50–199/mm <sup>3</sup>	68,200	13±1		29±3	
0–49/mm <sup>3</sup>	54,600	18±2		36±3	
No. of patients with HIV cared for in the physician's practice			0.12		0.01
≥500	41,200	13±2		24±3	
100–499	137,400	16±2		26±3	
10–99	44,300	9±3		15±3	
1–9	8,500	8±4		35±9	
Distance to closest HIV clinical-trial center§			0.04		0.05
0–1 mi	45,200	22±4		36±6	
2–7 mi	60,700	14±3		27±4	
8–74 mi	61,300	11±2		16±3	
≥75 mi	63,100	11±2		21±3	

\*Estimates were calculated on the basis of a probability sample of 2864 patients. Plus–minus values are estimated proportions ±SE.

†The “other” category in this analysis included American Indian, Alaskan Native, Asian or Pacific Islander, and mixed race, as well as any other single race.

‡Because of rounding, the weighted numbers total less than 231,400.

§To convert values for distance to kilometers, multiply by 1.6. The distance was missing for 8 subjects, representing 1100 patients receiving care.

**TABLE 2.** FACTORS ASSOCIATED WITH PARTICIPATING IN A CLINICAL TRIAL OR STUDY OF HIV MEDICATION AND WITH EVER HAVING RECEIVED EXPERIMENTAL TREATMENT.\*

VARIABLE	PARTICIPATION IN AN HIV MEDICATION TRIAL OR STUDY AT FOLLOW-UP INTERVIEW	EVER HAVING RECEIVED EXPERIMENTAL TREATMENT
	adjusted odds ratio (95% CI)	
Race or ethnic group		
Non-Hispanic white	1.00	1.00
Non-Hispanic black	0.50 (0.28–0.91)	0.41 (0.32–0.54)
Hispanic	0.58 (0.37–0.93)	0.56 (0.41–0.78)
Other†	0.80 (0.35–1.82)	0.65 (0.29–1.44)
HIV risk category		
Man who has sex with men (or other risk category)	1.00	1.00
Injection drug user	1.22 (0.68–2.17)	1.02 (0.78–1.33)
Heterosexual	0.73 (0.42–1.27)	0.68 (0.49–0.95)
Sex		
Male	1.00	1.00
Female	1.40 (1.04–1.88)	0.98 (0.76–1.27)
Age		
18–34 yr	1.00	1.00
35–49 yr	0.88 (0.64–1.21)	1.11 (0.89–1.38)
≥50 yr	0.92 (0.57–1.51)	1.02 (0.67–1.55)
Level of education		
College graduate	1.00	1.00
Some college	0.71 (0.46–1.09)	0.71 (0.56–0.91)
High-school graduate	0.47 (0.28–0.81)	0.55 (0.41–0.74)
Some high school	0.58 (0.29–1.14)	0.42 (0.28–0.64)
Health insurance		
Private fee-for-service	1.00	1.00
Private HMO	0.43 (0.21–0.88)	0.75 (0.51–1.09)
Medicare	1.17 (0.69–1.98)	0.96 (0.62–1.48)
Medicaid	1.38 (0.67–2.82)	0.75 (0.46–1.21)
None	0.92 (0.53–1.61)	0.69 (0.43–1.13)
Distance to closest ACTG or CPCRA clinical-trial center‡		
0–1 mi	1.00	1.00
2–7 mi	0.50 (0.29–0.85)	0.65 (0.40–1.04)
8–74 mi	0.38 (0.18–0.78)	0.41 (0.26–0.64)
≥75 mi	0.61 (0.30–1.24)	0.50 (0.29–0.86)
No. of HIV patients cared for in the physician's practice		
≥500	1.00	1.00
100–499	1.88 (1.10–3.22)	1.68 (1.05–2.68)
10–99	0.62 (0.22–1.72)	0.64 (0.36–1.14)
1–9	0.81 (0.09–7.09)	2.91 (0.86–9.89)
Region		
Northeast	1.00	1.00
Midwest	1.60 (0.91–2.81)	1.63 (0.96–2.79)
South	0.77 (0.37–1.58)	1.39 (0.74–2.61)
West	2.56 (0.87–7.59)	1.58 (0.90–2.76)

\*The multivariate logistic-regression model was adjusted for differences in the stage of HIV disease (as assessed in terms of the nadir CD4+ lymphocyte count) and in the attitudes and beliefs about health listed in Table 3. The results were weighted to represent the total population of patients with HIV receiving care in the United States. CI denotes confidence interval, ACTG AIDS Clinical Trials Group, and CPCRA Community Programs for Clinical Research on AIDS.

†The “other” category in this analysis included American Indian, Alaskan Native, Asian or Pacific Islander, and mixed race, as well as any other single race.

‡To convert values for distance to kilometers, multiply by 1.6.

even within socioeconomic strata, remained apparent after multivariate adjustment for the level of education, and seemed to be present in all aspects of access to research.

We found that fewer than half as many black patients as white patients attempt to obtain experimental HIV medications, suggesting that there is less awareness and a more widespread negative attitude about research in minority communities. Suspicion about research has long been recognized among black persons and may date back to past injustices such as the Tuskegee Syphilis Study and to beliefs within urban minority communities that HIV itself could be a government plot or experiment.<sup>39,40</sup> Black persons may interpret informed-consent procedures as “liability waivers” for researchers that do little to protect patients.<sup>40,41</sup> Innovative and culturally sensitive methods of communicating the benefits and risks of research to minority-group patients could be helpful, and consideration should be given to expanding such efforts.<sup>42,43</sup>

Previous research on differences among racial or ethnic groups in recruitment for clinical trials has produced varied results, possibly because of differences in study design or because of disease-specific, time-specific, or situation-specific factors.<sup>16,18,38,44–46</sup> Disproportionately few black persons participated in 50 drug studies performed in the mid-1980s, but blacks were overrepresented, as compared with other groups, in a large multicenter study of schizophrenia,<sup>44,45</sup> and no differences among racial or ethnic groups were seen in rates of participation in major cancer and heart-disease trials.<sup>46</sup> In the light of increasing evidence that sex differences in health and medicine may be more pervasive than previously imagined, it is encouraging to find that women were well represented in HIV-related trials.<sup>18,47</sup>

Errors could have influenced our results. Although the patients we approached were randomly selected, those who agreed to participate in the survey may have been more likely to enroll in clinical-research trials than those who did not participate. Concern about this issue led us to incorporate adjustments for those who did not respond to the survey into our analytic weights, but the adequacy of these adjustments is difficult to assess. Assessments of research participation based on the answers to interview questions could be inaccurate, but there is little reason to suspect that those interviewed would exaggerate or minimize their participation in research to conform to social pressures or that they would have difficulty recalling participation in studies. Moreover, we used a number of survey procedures, such as careful construction of the questions, scripted probes to clarify responses when necessary, central training of interviewers, and on-call backup, to minimize the risk of error. Furthermore, the validity of the results

**TABLE 3.** HEALTH-RELATED ATTITUDES AND BELIEFS ASSOCIATED WITH PARTICIPATION IN A CLINICAL TRIAL OR STUDY OF HIV MEDICATION.\*

ATTITUDE OR BELIEF	PATIENTS IN THE UNITED STATES RECEIVING HIV CARE AT BASE LINE	PATIENTS PARTICIPATING IN A MEDICATION TRIAL OR STUDY AT ANY INTERVIEW		ADJUSTED ODDS OF PARTICIPATING IN A MEDICATION TRIAL OR STUDY AT FOLLOW-UP INTERVIEW†
	weighted no.	%	P value	odds ratio (95% CI)
Are antiretrovirals worth taking?‡			<0.001	
Definitely	110,100	17±2		1.00
Probably	73,400	13±2		0.58 (0.40–0.82)
Probably not	20,900	8±2		0.64 (0.42–0.98)
Definitely not	20,500	11±3		0.55 (0.27–1.14)
Level of trust in the doctor or clinic			0.04	
High	112,000	16±2		1.00
Low	119,400	12±1		0.81 (0.58–1.12)
Level of desire for information about health and treatment			0.16	
High	130,900	15±2		1.00
Low	100,500	13±2		1.27 (0.78–2.05)
Level of desire for involvement in treatment decisions			0.07	
High	128,500	15±2		1.00
Low	102,900	12±2		1.14 (0.81–1.60)

\*Results were weighted to represent the estimated population of patients with HIV receiving care in the United States. Plus-minus values are proportions ±SE. The levels of trust, of desire for information, and of desire for involvement in treatment decisions were determined on the basis of ratings on a Likert scale in response to two questions for each variable; responses were then dichotomized on the basis of the median score. HIV denotes human immunodeficiency virus, and CI confidence interval.

†The multivariate logistic-regression model was adjusted for differences in the stage of HIV disease (as assessed in terms of the nadir CD4+ lymphocyte count) and the sociodemographic variables listed in Table 2.

‡Data were missing for 78 subjects, representing 6500 patients receiving care.

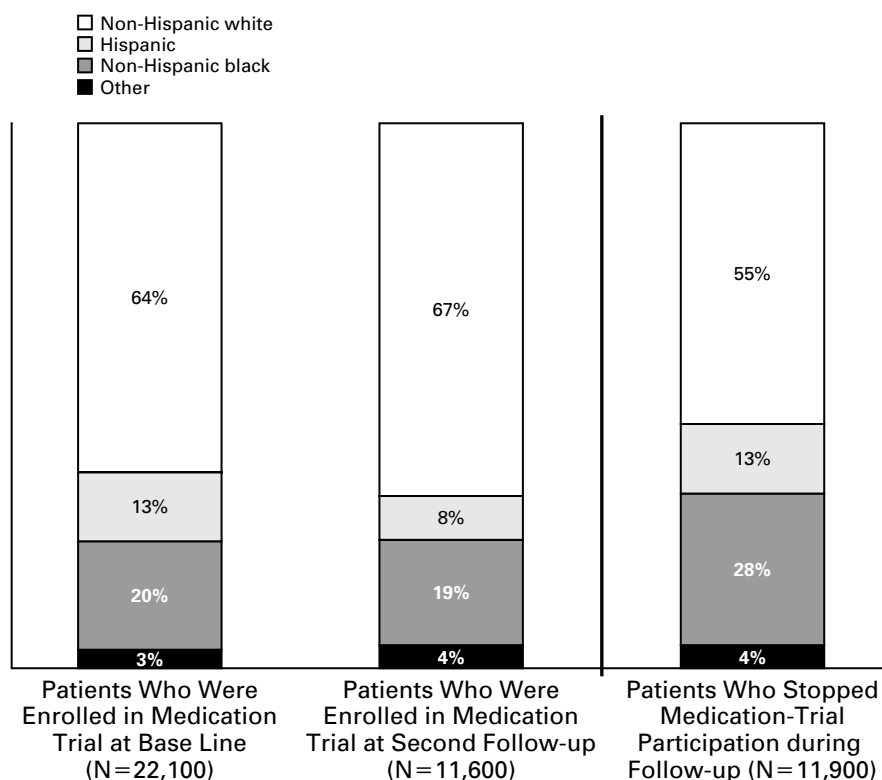
is supported by associations between self-reported participation in research and greater use of important HIV care services, such as CD4+ lymphocyte measurements and visits to the health care provider. These patterns are consistent with the receipt of protocol-driven care.

Outreach programs and efforts by providers to educate patients about research and investigational treatments could improve trust in researchers and boost enrollment. However, such programs may not eliminate disparities in access to experimental drugs, since certain groups, such as blacks, were less likely to receive experimental treatments for HIV infection even when they tried, and they had higher rates of withdrawal from studies after they had enrolled. In our study, characteristics of the practice providing the patient's HIV care, such as a higher number of patients with HIV treated on site and close proximity to an NIH-funded HIV trial center, were independently associated with enrollment in research and use

of experimental medications. This finding suggests that we must examine critically such structural barriers as the entry criteria for trials, enrollment and tracking procedures, and the practical details of study-center operation, as well as the attitudes and practices of clinical researchers.<sup>48</sup>

New, innovative therapies for HIV have been successful in part because of impressive participation in the well-designed clinical research studies that have guided treatment and in expanded-access programs for persons with few other options. Nevertheless, as the demographic features of the epidemic have shifted toward patients with fewer resources, the disproportionately small number of disadvantaged patients who are enrolled in treatment trials or have early access to experimental therapies is of particular concern. The pace of therapeutic advances and the acceptance of new therapies in underserved communities may be slowed. Initiatives to increase access to and acceptance of clinical trials are needed for patients with

PARTICIPATION IN RESEARCH BY HIV-INFECTED PATIENTS



**Figure 2.** Changes in the Racial or Ethnic Mix of Trial Participants. Base-line interviews were conducted between January 1996 and April 1997, and second follow-up interviews were conducted between August 1997 and January 1998. Because of rounding, some percentages do not total 100. Numbers of patients are weighted.

HIV disease, as well as for patients with other conditions among whom participation in research is less common.

Supported by a cooperative agreement (HS08578) between RAND Health and the Agency for Healthcare Research and Quality, with additional funding from the Health Resources and Services Administration, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Institute on Aging, and the Office of the Assistant Secretary for Planning and Evaluation in the Department of Health and Human Services. Dr. Gifford is supported by an Advanced Research Career Development Award for Health Services Research and Development from the Department of Veterans Affairs, by the Generalist Physician Faculty Scholar Award of the Robert Wood Johnson Foundation and by grants (AI027670 and AI038858) from the Adult AIDS Clinical Trials Group. Dr. Cunningham is supported by a Clinical Scientist Development Award from the Doris Duke Charitable Foundation.

REFERENCES

1. National Institutes of Health. NIH guidelines on the inclusion of women and minorities as subjects in clinical research. *Fed Regist* 1994;59(59):14508-13. (Also available at <http://grants1.nih.gov/grants/guide/notice-files/not94-100.html>.)
2. Outreach notebook for the NIH guidelines on inclusion of women and minorities as subjects in clinical research. Bethesda, Md.: National Institutes of Health, 1994. (Also available at <http://www4.od.nih.gov/orwh/outreach.pdf>.)

3. el-Sadr W, Capps L. The challenge of minority recruitment in clinical trials for AIDS. *JAMA* 1992;267:954-7.
4. Hader SL, Smith DK, Moore JS, Holmberg SD. HIV infection in women in the United States: status at the Millennium. *JAMA* 2001;285:1186-92.
5. Johnson JA. Influence of race or ethnicity on pharmacokinetics of drugs. *Pharm Sci* 1997;86:1328-33.
6. Jacobson MA, Gundacker H, Hughes M, Fischl M, Volberding P. Zidovudine side effects as reported by black, Hispanic, and white/non-Hispanic patients with early HIV disease: combined analysis of two multi-center placebo-controlled trials. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996;11:45-52.
7. Smith MD. Zidovudine: does it work for everyone? *JAMA* 1991;266:2750-1.
8. Institute of Medicine, Committee on Understanding the Biology of Sex and Gender Differences. Exploring the biological contributions to human health: does sex matter? Washington, D.C.: National Academy Press, 2001.
9. Longford NT. Selection bias and treatment heterogeneity in clinical trials. *Stat Med* 1999;18:1467-74.
10. Beltangady M. Expanded access for HIV treatments: the VIDEX (ddI) experience and future plans. *Biometric Bull* 1993;10:7.
11. Keystone national policy dialogue on expanded access to promising therapeutic drugs for HIV infection and AIDS, with implications for other life-threatening diseases: final report. Keystone, Colo.: Keystone Center, 1993.
12. HIV/AIDS surveillance report: U.S. HIV and AIDS cases reported through June 2000. Vol. 12. No. 1. Atlanta: Centers for Disease Control and Prevention, 2000:1-44.
13. Annual population estimates by sex, race and Hispanic origin, 2000.

- Washington, D.C.: Census Bureau, 2002. (Accessed March 28, 2002, at <http://cencensus.gov/popest/data/national.php>.)
14. Falloon J. Salvage antiretroviral therapy. *AIDS* 2000;14:Suppl 3:S209-S217.
  15. Fauci AS. AIDS — challenges to basic and clinical biomedical research. *Acad Med* 1989;64:115-9.
  16. Diaz T, Chu SY, Sorvillo F, et al. Differences in participation in experimental drug trials among persons with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;10:562-8.
  17. Hankins C, Lapointe N, Walmsley S. Participation in clinical trials among women living with HIV in Canada. *CMAJ* 1998;159:1359-65.
  18. 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.
  19. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. Belmont, Calif.: Lifetime Learning, 1982.
  20. Carter SK. Clinical research and drug development of antivirals in HIV: an industry perspective. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;10:Suppl 2:S107-S113.
  21. Pike IM, Daniels M, Wirtz CJ, Stout JJ, Quigley JJ. Expanded distribution of an investigational drug in parallel with ongoing controlled clinical trials: the didanosine model. *Clin Infect Dis* 1994;19:1071-5.
  22. Bozette SA, Berry SH, Duan N, et al. The care of HIV-infected adults in the United States. *N Engl J Med* 1998;339:1897-904.
  23. Frankel MR, Shapiro MF, Duan N, et al. National probability samples in studies of low-prevalence diseases. II. Designing and implementing the HIV Cost and Services Utilization Study sample. *Health Serv Res* 1999;34:969-92.
  24. 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.
  25. Shapiro MF, Berk ML, Berry SH, et al. National probability samples in studies of low-prevalence diseases. I. Perspectives and lessons from the HIV Cost and Services Utilization Study. *Health Serv Res* 1999;34:951-68.
  26. Berry SH, Brown JA, Athey L, et al. HCSUS patient questionnaires. Santa Monica, Calif.: RAND Health, 2002. (Accessed March 28, 2002, at <http://www.rand.org/health/hcsus/quest.html>.)
  27. Technical notes. In: HIV/AIDS surveillance report: U.S. HIV and AIDS cases reported through December 2000. Vol. 12. No. 2. Atlanta: Centers for Disease Control and Prevention, 2000:40-4.
  28. Rossi PH, Wright JD, Anderson AB, eds. *Handbook of survey research*. San Diego, Calif.: Academic Press, 1983.
  29. Kao AC, Green DC, Zaslavsky AM, Koplan JP, Cleary PD. The relationship between method of physician payment and patient trust. *JAMA* 1998;280:1708-14.
  30. Mahler HI, Kulik JA. Health care involvement preferences and social-emotional recovery of male coronary-artery-bypass patients. *Health Psychol* 1991;10:399-408.
  31. Krantz DS, Baum A, Wideman MV. Assessment of preferences for self-treatment and information in health care. *J Pers Soc Psychol* 1980;39:977-90.
  32. Division of AIDS Resource Materials. Demographic summary of ACTG study entries from beginning to 11/27/98. Bethesda, Md.: National Institute of Allergy and Infectious Diseases, 2000.
  33. AIDS cases by sex, age at diagnosis, and race/ethnicity, reported through December 1999, United States. In: HIV/AIDS surveillance report: U.S. HIV and AIDS cases reported through December 1999. Vol. 11. No. 2. Atlanta: Centers for Disease Control and Prevention, 1999:16.
  34. Kish L, Frankel MR. Inference from complex samples. *J R Stat Soc [B]* 1974;36:1-37.
  35. Kalton G. Compensating for missing survey data. Ann Arbor: Survey Research Center, Institute for Social Research, University of Michigan, 1983.
  36. Pike IM, Nicaise C. The didanosine Expanded Access Program: safety analysis. *Clin Infect Dis* 1993;16:Suppl 1:S63-S68.
  37. Patients' Bill of Rights Act of 2001: coverage for individuals participating in approved clinical trials. U.S. House of Representatives, 109:2315. (Accessed April 8, 2002, at [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107\\_cong\\_bills&docid=f:s889is.txt.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107_cong_bills&docid=f:s889is.txt.pdf).)
  38. Tejeda HA, Green SB, Trimble EL, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. *J Natl Cancer Inst* 1996;88:812-6.
  39. Klonoff EA, Landrine H. Do blacks believe that HIV/AIDS is a government conspiracy against them? *Prev Med* 1999;28:451-7.
  40. Corbie-Smith G, Thomas SB, Williams MV, Moody-Ayers S. Attitudes and beliefs of African Americans toward participation in medical research. *J Gen Intern Med* 1999;14:537-46.
  41. Sengupta S, Strauss RP, DeVellis R, Quinn SC, DeVellis B, Ware WB. Factors affecting African-American participation in AIDS research. *J Acquir Immune Defic Syndr* 2000;24:275-84.
  42. Fureman I, Meyers K, McLellan AT, Metzger D, Woody G. Evaluation of a video-supplement to informed consent: injection drug users and preventive HIV vaccine efficacy trials. *AIDS Educ Prev* 1997;9:330-41.
  43. Tindall B, Forde S, Ross MW, Goldstein D, Barker S, Cooper DA. Effects of two formats of informed consent on knowledge amongst persons with advanced HIV disease in a clinical trial of didanosine. *Patient Educ Couns* 1994;24:261-6.
  44. Svensson CK. Representation of American blacks in clinical trials of new drugs. *JAMA* 1989;261:263-5.
  45. Robinson D, Woerner MG, Pollack S, Lerner G. Subject selection biases in clinical trials: data from a multicenter schizophrenia treatment study. *J Clin Psychopharmacol* 1996;16:170-6.
  46. Gorkin L, Schron EB, Handshaw K, et al. Clinical trial enrollers vs. nonenrollers: the Cardiac Arrhythmia Suppression Trial (CAST) Recruitment and Enrollment Assessment in Clinical Trials (REACT) project. *Control Clin Trials* 1996;17:46-59.
  47. Gesensway D. Reasons for sex-specific and gender-specific study of health topics. *Ann Intern Med* 2001;135:935-8.
  48. Stone VE, Mauch MY, Steger KA. Provider attitudes regarding participation of women and persons of color in AIDS clinical trials. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19:245-53.

Copyright © 2002 Massachusetts Medical Society.