Survival and Disease Progression According to Gender of Patients With HIV Infection

The Terry Beirn Community Programs for Clinical Research on AIDS

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Objective.—To compare disease progression and mortality between women and men infected with human immunodeficiency virus (HIV).

Design.—Multicenter cohort.

Setting.—Seventeen community-based centers participating in the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA).

Patients.—A total of 768 women and 3779 men enrolled in one or more of 11 protocols between September 7, 1990, and September 30, 1993.

Main Outcome Measures.—Survival and opportunistic events.

Results.—The median CD4⁺ cell count at enrollment into the cohort was 0.240 $\times 10^9$/L (240/μL) for women and 0.137 $\times 10^9$/L for men ($P<.001$). Compared with men, women were younger (36 vs 38 years), more likely to be African American or Hispanic (78% vs 44%), and more likely to have reported a history of injection drug use (49% vs 27%). Women had been followed up for a median of 14.5 months and men for 15.5 months. The adjusted relative risk (RR) for death among women compared with men was 1.33 (95% confidence interval [CI], 1.06 to 1.67; $P=.01$) and for disease progression (including death) was 0.97 (95% CI, 0.82 to 1.15; $P=.72$). Women were at increased risk for bacterial pneumonia (RR, 1.38; 95% CI, 1.05 to 1.92) and at reduced risk for the development of Kaposi's sarcoma (RR, 0.16; 95% CI, 0.04 to 0.65) and oral hairy leukoplakia (RR, 0.54; 95% CI, 0.31 to 0.94). The increased risk of death and bacterial pneumonia for women compared with men was primarily evident among those with a history of injection drug use (RR, 1.68 for death, 95% CI, 1.20 to 2.35, $P=.003$; RR, 1.53 for bacterial pneumonia, 95% CI, 1.03 to 2.29, $P=.04$). Among patients without a history of disease progression at entry, death was the first event reported for more women than men (27.5% vs 12.2%).

Conclusions.—Compared with men, HIV-infected women in the CPCRA were at increased risk of death but not disease progression. Risks of most incident opportunistic diseases were similar for women and men; however, women were at an increased risk of bacterial pneumonia. These findings may reflect differential access to health care and standard treatments or different socioeconomic status and social support for women compared with men.

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THE NUMBER of cases of the acquired immunodeficiency syndrome (AIDS) reported among US women has increased dramatically since 1985. Through September 1993, the Centers for Disease Control and Prevention (CDC) had received AIDS reports for 40 702 US women aged 13 years or older, accounting for 12% of 334 344 total cases.[1] The incidence of AIDS among women increased 20-fold between 1981 and 1990[2]; women and their infected offspring constitute the fastest growing groups of newly diagnosed cases.[3-6] More than 100 000 US women may be infected with the human immunodeficiency virus (HIV), but not yet diagnosed with AIDS.[3,4]

A shift has occurred in the worldwide pattern of AIDS incidence from a disease occurring primarily among men to a pattern of gender equity. Medical providers in the United States will be caring for increasing numbers of HIV-infected women, particularly in urban centers with epidemic drug use. Moreover, current recommendations for medical management of HIV disease are based largely on observations of disease progression among men.[7,8] Data regarding rates of occurrence of HIV-related clinical conditions among women relative to men are therefore of vital interest. However, most findings to date have been based on observations on small numbers of women, retrospective chart reviews, or surveillance data for which minimal information is available on prognostic factors, such as CD4⁺ T-lymphocyte count (CD4⁺) for the women and men under study.[9-20] One of the most comprehensive studies of women[10] did not have a concurrent cohort of men for comparison. A recent European study considered gender differences only among women and men with previously diagnosed AIDS.[21] The purpose of the current study is to compare mortality and disease progression rates at different

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stages of HIV disease between large groups of women and men who were enrolled in studies sponsored by the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA).

METHODS

CPCRA Patients

The Terry Beirn CPCRA is a consortium of 17 groups conducting randomized clinical trials and observational cohort studies. Established in 1989 and located in 13 US cities where HIV-infected persons live and receive their primary care, the CPCRA uses common disease and toxicity definitions and data collection forms for recording baseline demographic information, HIV-related treatments, and clinical diagnoses (history and incident events). A modular data collection form system and standard definitions for disease progression have facilitated the combination of information across CPCRA studies. From September 7, 1990, through September 30, 1993, 5651 patients were enrolled in one or more of 10 randomized clinical trials located at the 17 centers or in an observational database study undertaken by nine of the 17 centers. Baseline $CD4^+$ cell counts measured within 90 days of enrollment were available for 4547 of the 5651 patients. These 4547 patients became the basis for this report.

Measurements

At the time of enrollment, a medical history was obtained, current treatments were ascertained, and demographic data and HIV risk behaviors were recorded on standardized data collection forms. Drug use was defined as "any injectable drug use since 1977." Risk behaviors were collected in a nonhierarchical manner; however, with the data collected, hierarchical summaries similar to those used by the CDC could be made.[22,23] In hierarchical summaries, the first applicable risk behavior identified in the hierarchy is the one recorded; other potentially applicable risk behaviors that are lower in the hierarchical ranking are not recorded. $CD4^+$ cell counts were performed by the laboratory used by the patient's health care provider. No attempt was made to ensure standardization of $CD4^+$ cell counts by the laboratories. Using the same data forms for all CPCRA protocols facilitated combining information across protocols. Completed data collection forms were sent to a central statistical center for data processing and analysis.

The CPCRA used standardized clinical definitions across all protocols that corresponded closely to the CDC 1987 definition of AIDS-indicating events.[24,25] The presence of a history of one or more of the events at the time of enrollment constituted the diagnosis of disease progression at baseline.

Follow-up

Patient follow-up examinations and duration of follow-up were guided by the protocol(s) in which the patient participated. Data were collected every 6 months for observational database study participants and every 2 to 6 months for clinical trial participants, depending on the protocol requirements. Deaths, disease progression events, and vital status were reported on the same data collection forms for all protocols.

Data Analysis

All analyses were stratified by the CPCRA center of enrollment. Baseline differences between women and men were summarized with use of stratified analysis of variance and Mantel-Haenszel χ^2 statistics.[26] Baseline comparisons were made within three $CD4^+$ cell count groups ($<0.200\times10^9$/L [<200/μL], 0.200 to 0.499×10^9/L, and $\geq0.500\times10^9$/L).

Differences in death and disease progression rates for women and men were summarized with Kaplan-Meier estimates, log-rank statistics, and proportional hazards regression models stratified by CPCRA center.[27-29] Because these rates varied markedly by $CD4^+$ cell count, analyses were carried out for each of six $CD4^+$ cell count strata (<0.025, 0.025 to 0.049, 0.050 to 0.099, 0.100 to 0.199, 0.200 to 0.299, and $\geq0.300\times10^9$/L) and overall, to allow for finer control of confounding. For each stratum and overall, regression analyses were performed with the following covariates: $CD4^+$ cell count, age, race, history of injection drug use, Karnofsky score, disease progression history, and baseline use of antiretroviral treatments and *Pneumocystis carinii* pneumonia (PCP) prophylaxis.

For analyses of disease progression events, event times were computed as follows. For patients who experienced an incident disease progression event, time was measured from enrollment to the workup date of the first event. For patients with no reported incident opportunistic event, follow-up time was measured from the enrollment date to the date when the last diagnosis form was completed. For analyses in which death was part of the outcome, if no opportunistic diseases were reported before death, time was measured from enrollment to death.

RESULTS

Comparison of Women and Men at Enrollment

Between September 7, 1990, and September 30, 1993, a total of 3779 men and 768 women with $CD4^+$ cell counts obtained within 90 days of entry were enrolled in a CPCRA protocol(s). The baseline $CD4^+$ cell count distribution of women and men varied greatly (data not shown). The median $CD4^+$ cell count at enrollment into the cohort was 0.240×10^9/L among women and 0.137×10^9/L among men ($P<.001$). Among women, 44% had a $CD4^+$ count less than 0.200×10^9/L, 37% had a count between 0.200 and 0.499×10^9/L, and 19% had a count of 0.500×10^9/L or more. The corresponding percentages for men were 62.7% ($<0.200\times10^9$/L), 26.6% (0.200 to 0.499×10^9/L), and 10.7% ($\geq0.500\times10^9$/L).

Characteristics at entry for women and men by baseline $CD4^+$ cell count and overall are summarized in Table 1. Overall, 74% of men reported sex with another man, 27% reported injection drug use, and 9% reported both of these risk behaviors. Forty-nine percent of women reported injection drug use, 70% reported having sex with an injection drug user (IDU) or bisexual male, and 45% reported both. Although 10% of women reported sex with other women, less than 2% reported only same-sex partners; 47% of men reported only same-sex partners.

A hierarchical summary of risk exposure for women and men is shown in Table 2 for three racial/ethnic groups and overall. Fifty-five percent of the patients in the "Other heterosexual contact" category (103 women and 144 men) reported heterosexual contact with a person for whom injection drug use and/or bisexual status was unknown. The "Other/unknown" category includes patients with no other risk behaviors listed who received transfusions or had unknown risk behavior. Either injection drug use or heterosexual contact with an IDU was reported by 65% of African-American women, 79% of Hispanic women, and 64% of white/other women. Overall, 67% of women were in one of these two risk groups.

The history of opportunistic diseases differed for women and men by baseline $CD4^+$ cell count (data not shown). Within the lowest stratum ($<0.200\times10^9$/L), significantly more men than women reported a history of PCP (26.5% vs 17.5%; $P=.01$), invasive herpes simplex (1.5% vs 0.3%; $P=.01$), nonvisceral Kaposi's sarcoma (KS) (7.9% vs 0.3%; $P<.001$), and oral hairy leukoplakia (19.2% vs 9.5%; $P=.01$). More women than men reported a history of oral thrush (57.7% vs 54.3%) and progressive multifocal leukoencephalopathy (1.2% vs 0.1%). With consideration of the other $CD4^+$ cell count groups and the overall results, more women than men experienced bacterial pneumonia, progressive multifocal leukoencephalopathy, and oral thrush; more men than women had a history of KS,

Table 1.—Baseline Characteristics of Women and Men Enrolled in the CPCRA by CD4+ Count at Entry*

Characteristic	CD4+ T-Lymphocyte Count, Cells ×10⁹/L: <0.200 Women	<0.200 Men	0.200-0.499 Women	0.200-0.499 Men	≥0.500 Women	≥0.500 Men	Overall Women	Overall Men
Age, mean years	36.9	38.2†	36.4	37.7†	34.2	36.3†	36.2	37.9†
Race/ethnicity, %								
African American	60.9	29.3†	58.8	32.1†	54.8	36.2‡	59.0	30.8†
Hispanic	20.7	12.2†	18.3	13.6†	16.4	15.1‡	19.0	12.9†
White/other	18.3	58.5†	22.9	54.3†	28.8	48.6‡	22.0	56.4†
IDU, %	41.7	24.0‡	55.7	30.7†	50.3	33.1	48.5	26.8†
Hemophilia/blood transfusion, %	11.9	6.7†	13.1	6.3†	17.9	7.2†	13.4	6.7†
Sexual contacts, %								
Same-sex contact	8.2	75.9†	13.1	71.2†	6.7	70.1†	9.7	74.0†
Opposite-sex contact	95.5	47.4†	94.3	51.3†	99.3	57.5†	95.8	49.5†
With an IDU	63.1	10.9†	63.0	18.2†	62.3	20.0†	62.9	13.9†
With a bisexual	9.5	7.6	17.2	7.7†	9.5	10.4	12.4	7.9‡
CD4+ count, mean cells ×10⁹/L	0.083	0.073	0.328	0.320	0.761	0.695†	0.303	0.205†
Disease progression history, %	37.9	45.6†	13.4	14.8	8.9	7.4	23.3	33.3‡
Mean Karnofsky score	88.5	87.6	91.8	92.5	93.9	95.0	90.7	89.7
Antiretroviral drug use, %	71.0	69.9	68.7	70.2	21.2	31.8†	60.7	65.7
PCP prophylaxis, %	74.0	80.8	28.0	36.1	4.1	5.2	43.7	60.8
Enrolled in a clinical trial, %	84.6	81.3	65.1	55.7	44.5	37.7	69.8	69.8
No. of patients	338	2369	284	1007	146	403	768	3779

*CPCRA indicates Community Programs for Clinical Research on AIDS; IDU, injection drug user; and PCP, *Pneumocystis carinii* pneumonia.
†$P<.01$ based on analysis with stratification by CPCRA center for each CD4+ group and with stratification by center and CD4+ for overall.
‡$P<.05$ based on analysis with stratification by CPCRA center for each CD4+ group and with stratification by center and CD4+ for overall.

Table 2.—Hierarchical HIV Risk Exposure: Categories by Race for Women and Men Enrolled in the CPCRA*

Hierarchical Exposure Classification†	African American: No. (%) of Women	African American: No. (%) of Men	Hispanic: No. (%) of Women	Hispanic: No. (%) of Men	White/Other: No. (%) of Women	White/Other: No. (%) of Men	Total: No. (%) of Women	Total: No. (%) of Men
Men who have sex with men	...	519 (44.6)	...	200 (41.2)	...	1701 (79.9)	...	2420 (64.0)
IDUs	214 (47.2)	374 (32.2)	78 (53.4)	182 (37.4)	78 (46.2)	86 (4.0)	370 (48.2)	642 (17.0)
Men who have sex with men and IDUs	...	91 (7.8)	...	45 (9.3)	...	221 (10.4)	...	357 (9.4)
Hemophilia	3 (0.7)	2 (0.2)	0 (0.0)	0 (0.0)	2 (1.2)	20 (0.9)	5 (0.7)	22 (0.6)
Heterosexual contact with IDUs	79 (17.4)	31 (2.7)	38 (26.0)	11 (2.3)	30 (17.8)	7 (0.3)	147 (19.1)	49 (1.3)
Heterosexual contact with bisexual male	5 (1.1)	...	0 (0.0)	...	16 (9.5)	...	21 (2.7)	...
Other heterosexual contact	139 (30.7)	128 (11.0)	26 (17.8)	42 (8.6)	36 (21.3)	76 (2.6)	201 (26.2)	246 (6.5)
Other/unknown	13 (2.9)	18 (1.5)	4 (2.7)	6 (1.2)	7 (4.1)	19 (0.9)	24 (3.1)	43 (1.1)
Total	**453 (100.0)**	**1163 (100.0)**	**146 (100.0)**	**486 (100.0)**	**169 (100.0)**	**2130 (100.0)**	**768 (100.0)**	**3779 (100.0)**

*HIV indicates human immunodeficiency virus; CPCRA, Community Programs for Clinical Research on AIDS; IDU, injection drug user; and ellipses, not applicable.
†Patients are characterized by the first applicable category. The category "Other heterosexual contact" includes patients for whom none of the risk categories above apply, and who report heterosexual activity with partners who are not bisexual or IDUs, or heterosexual activity with partners for whom these behaviors are not known.

PCP, herpes simplex, and oral hairy leukoplakia. Eleven women reported a history of a cervical malignancy.

Disease Incidence and Survival

Median follow-up was 14.5 months (maximum, 36.5) for women and 15.5 months (maximum, 36.8) for men. For 10.7% of women, vital status was unknown as of September 30, 1993, the closing date for these analyses. Of the men enrolled, 9.1% were unavailable for follow-up for vital status. Disease progression follow-up was available for 696 women (90.6%) and 3522 men (93.2%). The median number of follow-up visits attended was five for both women and men.

To control for differences in CD4+ cell count distribution between women and men, mortality and disease progression rates were compared within six CD4+ cell count strata (Tables 3 and 4). Cumulative mortality and disease progression rate estimates after 12 and 24 months and relative risk (RR) (women:men) estimates were obtained from a proportional hazards regression model, adjusting for center, CD4+ cell count, age, race, history of injection drug use, Karnofsky score, disease progression history, and use of antiretroviral drugs and PCP prophylaxis. For each CD4+ cell count stratum, adjusted mortality RR estimates (women:men) were greater than 1.0. Overall, mortality was significantly greater ($P=.01$) for women than men. The adjusted RR of mortality (women:men) was 1.33 (95% confidence interval [CI], 1.06 to 1.67). For each CD4+ cell count stratum and overall, adjusted disease progression RR estimates (women:men) were close to 1.0. Overall, the adjusted disease progression RR (women:men) was 0.97 (95% CI, 0.82 to 1.15; $P=.72$).

Differences between women and men were explored further in subgroups defined by race, injection drug use, baseline history of disease progression (ie, AIDS at entry), and enrollment in clinical trials (Table 5). In each of these subgroup analyses, estimates were adjusted for the same variables as described for Tables 3 and 4, minus the variable for the relevant subgroup under study (eg, race for race subgroup analyses). Relative risks (women:men) for disease progression did not differ significantly from 1.0 in any subgroup, nor did any of the RRs differ from one another, ie, tests for gender-subgroup interactions were not significant. Women were at greater risk of death compared with men in several subgroups, including African Americans, IDUs, and those re-

Table 3.—Cumulative Mortality for Women and Men Enrolled in the CPCRA by CD4⁺ Level*

	Women				Men				
			Cumulative Mortality, %				Cumulative Mortality, %		Adjusted Relative Risk (95% CI)†
CD4⁺ Count, Cells ×10⁹/L	No. of Patients	No. of Deaths	12 mo	24 mo	No. of Patients	No. of Deaths	12 mo	24 mo	(Women:Men)
<0.025	88	36	43.2	71.2	690	292	38.5	69.8	1.29 (0.87-1.92)
0.025-0.049	41	12	23.0	49.7	404	119	22.0	62.1	1.45 (0.73-2.90)
0.050-0.099	66	17	7.6	44.4	506	119	14.6	44.7	1.09 (0.58-2.03)
0.100-0.199	143	17	6.3	26.6	769	102	5.7	23.8	1.40 (0.77-2.55)
0.200-0.299	131	10	4.9	12.3	482	38	1.7	11.8	1.57 (0.62-3.96)
≥0.300	299	13	2.5	4.7	928	30	1.0	3.1	1.58 (0.71-3.51)
Total	768	105	...	...	3779	700	...	...	...

*CPCRA indicates Community Programs for Clinical Research on AIDS; and CI, confidence interval. Cumulative mortality was based on Kaplan-Meier life table analysis.
†Obtained from a proportional hazards model with stratification by center and covariates corresponding to CD4⁺ count, age, race, injection drug use history, Karnofsky score, disease progression history, and use of antiretroviral drugs and *Pneumocystis carinii* pneumonia prophylaxis. The adjusted relative risk of disease progression for all strata was 1.33; 95% CI, 1.06 to 1.67; P=.01.

Table 4.—Cumulative Incidence of Disease Progression for Women and Men Enrolled in the CPCRA by CD4⁺ Level*

	Women				Men				
			Cumulative Incidence, %				Cumulative Incidence, %		Adjusted Relative Risk (95% CI)†
CD4⁺ Count, Cells ×10⁹/L	No. of Patients	No. of Events	12 mo	24 mo	No. of Patients	No. of Events	12 mo	24 mo	(Women:Men)
<0.025	88	50	70.6	82.9	690	418	71.5	90.7	1.05 (0.75-1.47)
0.025-0.049	41	19	50.9	71.4	404	203	56.0	87.3	0.97 (0.57-1.67)
0.050-0.099	66	26	30.5	65.0	506	219	44.9	76.2	0.82 (0.50-1.35)
0.100-0.199	143	34	20.8	48.0	769	211	22.9	53.1	0.99 (0.65-1.52)
0.200-0.299	131	25	12.7	38.0	482	103	13.6	31.5	0.99 (0.56-1.75)
≥0.300	299	28	5.9	13.4	928	103	6.0	13.6	0.80 (0.49-1.29)
Total	768	182	...	...	3779	1257	...	...	...

*CPCRA indicates Community Programs for Clinical Research on AIDS; and CI, confidence interval. Cumulative incidence of disease progression was based on Kaplan-Meier life table analysis.
†Obtained from a proportional hazards model with stratification by center and covariates corresponding to CD4⁺ count, age, race, injection drug use history, Karnofsky score, disease progression history, and use of antiretroviral drugs and *Pneumocystis carinii* pneumonia prophylaxis. The adjusted relative risk of disease progression for all strata was 0.97 (95% CI, 0.82 to 1.15; P=.72).

porting disease progression history at entry. For race/ethnicity the P value corresponding to a test for differences in relative risk estimates was .87; for IDUs the interaction P value was .15; for history of disease progression the interaction P value was .53; and for type of study (clinical trial vs observational) the P value corresponding to differences in RR estimates was .83.

Separate analyses were also carried out for the 17 CPCRA centers. For nine centers, the RR of death (women:men) was greater than 1.0; for five centers, less than 1.0; and for one center, 1.0. For two centers, the number of women was insufficient to estimate an RR.

The types of first disease progression events for women and men who did not report a disease progression history at baseline varied (data not shown). More women experienced death as a first event than men, ie, more women died during follow-up without experiencing one of the 19 opportunistic events constituting disease progression. Among the 102 women who developed their first event (disease progression or death) during follow-up, death was the first event for 28 (27.5%); in contrast, death was the first event for 72 (12.2%) of the 589 men who developed their first event during follow-up (adjusted RR, 2.25; 95% CI, 1.32 to 3.84; P=.003). The most common first events for women other than death were PCP (18.6%), invasive (esophageal or pulmonary) candidiasis (16.7%), and wasting (10.8%). Similarly, for men, PCP (22.4%), invasive candidiasis (13.2%), and wasting (11.7%) were the most common first events. Cytomegalovirus disease and *Mycobacterium avium* complex were also first events for approximately 10% of men.

Incidence rates for specific opportunistic events for women and men are summarized in Table 6. Crude rates per 100 person-years are shown as well as relative risk estimates (women:men) adjusted for baseline CD4⁺ cell count and adjusted for baseline CD4⁺ cell count plus other covariates mentioned above. Crude rates of bacterial pneumonia were greater in women (8.5 per 100 person-years) than men (5.8 per 100 person-years); with adjustment for baseline differences in CD4⁺ cell count, the RR was 1.42 (95% CI, 1.05 to 1.92). With adjustment for additional baseline variables, the RR was 1.38 (95% CI, 1.02 to 1.88; P=.04). Among IDUs, the adjusted RR (women:men) of bacterial pneumonia was 1.53 (95% CI, 1.03 to 2.29; P=.04); for non-IDUs the RR was 1.11 (95% CI, 0.65 to 1.91; P=.70) (data not shown).

Other events for which incidence rates varied significantly between women and men included other mycobacterial infections, which were more frequent in women than men (although numbers were very small); oral hairy leukoplakia, which was less frequent in women than men; and KS, both nonvisceral and visceral, which, combined, occurred in only two women. In contrast, 137 men developed nonvisceral KS (3.6 per 100 person-years) and 48 developed visceral KS (1.2 per 100 person-years). The incidence of KS (visceral or nonvisceral) was substantially greater among men who reported same-sex contact (5.0 per 100 person-years) as compared with those who did not report same-sex contact (0.9 per 100 person-years) (data not shown). Crude rates of cytomegalovirus disease were lower in women than men, and the CD4⁺ cell count–adjusted RR (women:men) was significantly less than 1.0 (RR, 0.52; P=.04). When adjusted for other baseline predictors, the RR increased to 0.67 and was no longer significant (P=.21). Cervical malignancies occurred in four women during follow-up (0.5 event per 100 person-years).

Table 5.—Adjusted Relative Risk Estimates of Deaths and Disease Progression in Subgroups Defined by Race/Ethnicity, Injection Drug Use, Type of Protocol, and Disease Progression History in Which the Patient Was Enrolled*

	Death		Disease Progression	
Subgroup	Adjusted Relative Risk†	95% CI	Adjusted Relative Risk†	95% CI
African American	1.55‡	1.12-2.15	1.06	0.85-1.34
Hispanic	1.61	0.84-3.10	0.95	0.59-1.53
White/other	1.12	0.72-1.74	0.84	0.59-1.21
IDU	1.68‡	1.20-2.35	0.95	0.74-1.22
Non-IDU	1.18	0.84-1.65	1.01	0.79-1.30
Enrolled in clinical trial	1.24	0.92-1.67	0.93	0.76-1.15
Enrolled solely in ODB	1.59‡	1.10-2.32	1.10	0.80-1.53
History of disease progression	1.41§	1.04-1.91	0.97	0.75-1.25
No history of disease progression	1.23	0.87-1.79	0.92	0.72-1.17

*CI indicates confidence interval; IDU, injection drug user; and ODB, observational database study.
†Women:men, adjusted using a proportional hazards regression model with stratification by center and covariates corresponding to CD4+ cell count, age, race (except for race subgroups), injection drug use (except for IDU subgroups), history of disease progression (except for those subgroups), Karnofsky score, and use of antiretroviral drugs and *Pneumocystis carinii* pneumonia prophylaxis.
‡$P<.01$.
§$P<.05$.

COMMENT

The CPCRA has enrolled the largest cohort of women with HIV infection yet reported. The women enrolled and the men with whom they are compared represent a wide spectrum of HIV disease. Women enrolled in the CPCRA had a greater median CD4+ count than men. The principal finding of this report is that women had a poorer survival than men during a 15-month interval of observation, even though disease progression rates did not differ significantly between women and men. Analyses of specific opportunistic events revealed few differences. Bacterial pneumonia and mycobacterial infection rates were greater among women than among men; KS and oral hairy leukoplakia occurred less frequently among women than among men. Among those without an AIDS-defining illness at entry, death was the first event that occurred for more women than men.

Contradictory findings have emerged from previous investigations of differences in survival between women and men. In a study of 147 women and 4658 men, no survival differences were found 3 to 4 years after the start of zidovudine treatment.[13] Median survival of men and women whose cases of AIDS had been reported to the CDC through December 1990 was similar—9.8 months for men and 9.3 months for women.[14] However, because surveillance data include only persons with AIDS, they provide no information on asymptomatic or mildly symptomatic women and men. In another study, 133 women and 393 men with AIDS also had similar survival. However, survival was shorter for women younger than 35 years who had PCP as the AIDS-defining illness.[15] In New York City, survival was significantly shorter for 552 women with AIDS than for 5281 men: after 1 year, 59.8% of women and 50.3% of men were dead.[12] Among 118 women and 596 men with AIDS in Maryland, 1-year cumulative mortality was 54% for women and 41% for men; after adjustment for use of zidovudine (53% of men, 33% of women), the survival differences were no longer significant.[16] Although survival for 139 women and 7045 men with AIDS in San Francisco was found to improve over time, median survival was 11.1 months for women, 14.6 months for men.[17] Among 543 women and 3156 men reported with AIDS in New York State (excluding New York City), 51% of women and men died within 1 year.[18] In a recent study of AIDS patients, Phillips et al[21] reported a median survival of 18 months for 566 women and 16 months for 1988 men. The ability to adjust for CD4+ cell count in this investigation was hampered because counts were available for only 46% of subjects.[21]

A major limitation of published studies is the lack of control of confounding by CD4+ count and other established predictors of survival and disease progression. In our investigation, we were able to assess men and women at various stages of HIV infection and to control for other baseline differences between men and women that could potentially confound survival and disease progression comparisons. For example, women had higher CD4+ cell counts at entry compared with men, and fewer women than men had a history of disease progression. Although CPCRA women and men differed with respect to prior injection drug use and race/ethnicity, neither of these variables was found to be a predictor of survival or disease progression in multivariate analysis. Our results indicate that for patients both with and without a history of disease progression at entry, death rates were higher in women than men after adjustment for baseline differences.

Reasons for the poorer survival in women in our investigation are unclear. Since many HIV patients die outside hospital settings, information on causes of death is difficult to obtain. Causes of death were either unavailable or unknown for 46% of 105 women who died and 36% of 700 men who died. An increased mortality for women was found in subgroup analysis among those with a history of injection drug use (adjusted RR for women vs men for the IDU subgroup was 1.68). Also, for IDUs, a 53% greater risk of bacterial pneumonia was evident for women compared with men. However, because the definition of injection drug use in this study was "any injectable drug use since 1977," the data must be interpreted cautiously. The current behavior of IDUs may differ between the men and women studied. Because death was the first disease progression event for more women than men in our study, observed survival difference may reflect a differential access to or utilization of health care resources by gender.

Our analyses were stratified by CPCRA center; therefore, differences in survival between men and women were unlikely to have been confounded by different baseline treatment patterns among CPCRA centers, eg, antiretroviral treatment or PCP prophylaxis. The lower limit of the CI for the RR (women: men) of death was close to 1.0 (1.06); thus, it will be important to continue the follow-up of the women and men in this cohort to determine whether the mortality difference persists. It will also be important to carry out similar analyses of survival in other studies that have adequate baseline data to compare stage of disease for the women and men being studied, as well as all-cause mortality. Factors not assessed in our study, such as pregnancy, socioeconomic status, support systems, homelessness, domestic violence, and access to health care, also should be evaluated.[30-41]

We are aware of few reports on the development of opportunistic diseases in women and men.[19-21] Farizo et al[19] abstracted medical charts of 626 women and 7008 men for a 12-month period prior to enrollment in the Adult and Adolescent Spectrum of HIV Disease Project. Using the lowest CD4+ cell count reported during this 12-month period as a measure of immunologic status, they concluded that similar proportions of women and men at comparable CD4+ cell counts developed an AIDS-indicator disease during the period. Munoz et al[20] reported that the RR for developing AIDS for women vs men was 1.77 (95%

Table 6.—Incident Events Indicative of HIV Disease Progression for CPCRA Men and Women*

Incident Event	Women No.	Women Rate†	Men No.	Men Rate†	CD4⁺-Adjusted Relative Risk‡ (Women:Men)	Fully Adjusted Relative Risk§ (Women:Men)
Parasitic						
Cryptosporidiosis‖	1	0.1	28	0.7	0.42	0.41
Isosporiasis‖	0	0.0	0	0.0	...	...
PCP‖	37	4.5	342	8.7	0.75	0.79
Toxoplasmosis‖	5	0.6	56	1.4	0.70	0.72
Bacterial						
MAC‖	24	2.9	235	6.0	1.11	1.11
Other mycobacterial infection‖	4	0.5	18	0.4	2.65	3.67#
TB‖	12	1.5	54	1.4	0.68	0.73
Salmonella‖	0	0.0	3	0.1	...	...
Bacterial pneumonia	67	8.5	230	5.8	1.46¶	1.38¶
Fungal						
Candidiasis, invasive‖	39	4.8	208	5.2	1.36	1.23
Candidiasis, thrush‖	198	28.4	1010	30.1	1.10	1.14
Candidiasis, vaginal‖#	128	17.2	...	...	...	...
Cryptococcosis‖	2	0.2	34	0.8	0.48	0.42
Histoplasmosis‖	3	0.4	12	0.3	1.55	1.18
Viral						
CMV‖	11	0.3	239	6.1	0.50¶	0.67
Herpes simplex, invasive‖	13	1.6	22	0.5	2.06	2.04
Herpes zoster, disseminated‖	10	1.2	28	0.7	1.85	1.58
Malignancies						
KS, nonvisceral	2	0.2	137	3.6	0.12**	0.16¶
KS, visceral‖	0	0.0	48	1.2	...	...
Lymphoma‖	3	0.4	58	1.4	0.53	0.72
Cervical#	4	0.5	...	...	...	...
Other						
ADC‖	11	1.3	88	2.2	1.20	1.43
PML‖	4	0.5	17	0.4	2.12	1.86
Wasting‖	23	2.9	190	5.0	0.77	0.76
Oral hairy leukoplakia	15	1.9	208	6.4	0.43**	0.54¶
Total patients	**768**		**3779**			

*HIV indicates human immunodeficiency virus; CPCRA, Community Programs for Clinical Research on AIDS; PCP, *Pneumocystis carinii* pneumonia; MAC, *Mycobacterium avium* complex; TB, tuberculosis; CMV, cytomegalovirus disease; KS, Kaposi's sarcoma; ADC, AIDS dementia complex; and PML, progressive multifocal leukoencephalopathy.

†Rate per 100 person-years.

‡Obtained from a proportional hazards model with stratification by center and a covariate corresponding to CD4⁺ count.

§Obtained from a proportional hazards model with stratification by center and covariates corresponding to age, race, history of injection drug use, CD4⁺ count, Karnofsky score, disease progression history, and use of antiretroviral drugs and PCP prophylaxis.

‖Indicates CPCRA disease progression events.

¶$P<.05$.

#Women only.

**$P<.01$.

CI, 0.93 to 3.37; $P=.09$) after adjusting for CD4⁺ cell count. This investigation was restricted to 590 IDUs, of whom 21% were women. The relatively small number of women and the small number of events (only 41 total) explain the wide CIs for the estimated RR. Phillips et al[21] reported that women were at an increased risk of toxoplasmosis and herpes simplex viral ulceration than were men, but did not differ substantially for other opportunistic diseases. We also noted a twofold increase of herpes simplex infection in women compared with men and a lower rate of toxoplasmosis in women than in men. However, neither of these findings was statistically significant in our data.

Although overall disease progression rates were similar for women and men in our investigation, the incidence of certain opportunistic diseases varied by gender. Women were significantly more likely to develop bacterial pneumonia than men. This was also noted in a study by Greenberg et al.[42] We hypothesized that the increased incidence of bacterial pneumonia in women compared with men was due to a greater use of injection drugs by women than men[43,44]; however, this was not the case. When the analysis was restricted to men and women who reported a history of injection drug use, women still had a 53% greater risk of bacterial pneumonia than men.

Few women developed KS. As in the report by Fineberg and Schinella,[11] the incidence of KS in women was similar to that for heterosexual men. Few CPCRA women reported cervical malignancies. Because screening for cervical cancer was not assessed in this report, these data cannot be used to predict the impact on the number of women who will be reported as having a surveillance diagnosis of AIDS due to cervical malignancy.[45,46]

The gender distribution of patients enrolled by CPCRA centers is similar to that for cases of AIDS reported to the CDC. For example, 12% of AIDS cases reported to the CDC through September 30, 1993, were women; between October 1, 1992, and September 30, 1993, 15% were women. In the CPCRA, 17% of all patients were women. The percentages of female patients among those with CD4⁺ cell counts less than 0.200×10^9/L, 0.200 to 0.499×10^9/L, and 0.500×10^9/L or greater were 12%, 22%, and 27%, respectively.

A hierarchical summary of risk behavior categorizes an individual's risk according to the first applicable category in a series. With the hierarchical summary of risk behavior used by the CDC, and in this report, some information may be lost; in particular, the impact of heterosexual activity on HIV transmission to women may be underestimated. For example, according to the nonhierarchical summary of risk behavior reported in the CPCRA (Table 1), 63% of women reported sex with an IDU and 12% reported sex with a bisexual man; however, in the hierarchical summary in our study, only 19% and 3% of women are in these categories, because a large fraction of women who reported having sex with an IDU or a bisexual man also reported using injection drugs.

In summary, this is, to our knowledge, the largest prospective study to date that compares disease progression and survival between men and women while controlling for differences in baseline predictors of HIV disease. A major advantage of this investigation is the diversity of centers, and therefore patient characteristics, that were studied. In this cohort, we found that HIV-infected women had a poorer survival rate than men, even though rates of disease progression did not differ by gender. We cannot discern definitively the reasons for the poorer survival of women. It is possible that some of these deaths may have resulted from differential access to or utilization of health care resources, including antiretroviral and PCP prophylaxes. Other reasons for excess mortality in HIV-infected women compared with men might include lower socioeconomic status, homelessness, domestic violence, substance abuse, and lack of social support.[30-41] Further study of the relative contributions of diverse social factors, in addition to the availability of accurate information on causes of death, would enhance our understand-

ing of the complex patterns of HIV disease progression and survival in women and men.

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