ORIGINAL CONTRIBUTIONS

Design and Baseline Participant Characteristics of the Human Immunodeficiency Virus Epidemiology Research (HER) Study: A Prospective Cohort Study of Human Immunodeficiency Virus Infection in US Women

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The prospective, multisite human immunodeficiency (HIV) Epidemiology Research Study was established to define the biologic, psychologic, and social effects of HIV infection on the health of US women. From 1993 to 1995, a total of 871 HIV-infected women and 439 demographically matched, uninfected women aged 16–55 years, half of whom reported injection drug use and half of whom reported only sexual risk behaviors, were recruited in four US cities. Two sites recruited primarily from medical/drug therapy care settings, and two recruited from community sources. Women consented to biannual interviews; physical examination; blood, urine, and cervicovaginal specimen collection and repository; laboratory assays; and abstraction of outpatient and inpatient medical records to document HIV and acquired immunodeficiency syndrome-related diagnoses. Retention was greater than 88% at the third 6-month follow-up. Lower retention was associated with currently injecting drugs, not having dependent children, and not being infected with HIV at enrollment. In addition to the core study, a variety of nested studies are under way, some in collaboration with other HIV cohorts and various Public Health Service agencies. This cohort is distinct from other HIV longitudinal cohorts in the diversity of its participants and the comprehensive range of measures to study prospectively the biomedical, social, and emotional effects of the HIV epidemic on infected women and those whose behavior puts them at high risk of infection. Am J Epidemiol 1997;146:459–69.

acquired immunodeficiency syndrome; cohort studies; disease progression; HIV; women

MATERIALS AND METHODS

From January 1 through December 31, 1995, 13,764 acquired immunodeficiency syndrome (AIDS) cases in women were reported to the Centers for Disease Control and Prevention (CDC); these cases accounted for 19 percent of all AIDS cases reported in 1995 (1) compared with 7 percent

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Abbreviations: AIDS, acquired immunodeficiency syndrome; CD4 cell count, CD4+ T-lymphocyte count; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; HER, HIV Epidemiology Research; HIV, human immunodeficiency virus; HPV, human papillomavirus; IDU, injection drug user; NERI, New England Research Institute.

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of the cases reported in 1982, the first full year of AIDS surveillance (2).

Before the inception of the Human Immunodeficiency Virus (HIV) Epidemiology Research (HER) Study, small, focused studies of select biomedical, psychosocial, and behavioral questions had been conducted, but no prospective studies had explored the effects of HIV on a large group of women over the course of their infection. Some questioned if and how women at high risk of HIV infection could be successfully recruited and retained in long-term prospective cohort studies (3). In turn, a lack of understanding of the spectrum and timing of HIV disease manifestations in women has caused uncertainties about the sensitivity of the pre-1993 AIDS surveillance case definition for monitoring the epidemic in women, has produced difficulty in anticipating the types and amounts of medical care required by HIV-infected women, and has contributed to the deficiencies in the full spectrum of mental health and drug abuse treatment services appropriate to the needs of HIV-infected women.

For these reasons, CDC and HER Study investigators began planning the first multisite women's "natural history" study in mid-1991, and it is now generating information useful to those providing, funding, or planning for the health care of HIV-infected women. The study was designed to yield epidemiologic, clinical, demographic, laboratory, behavioral, and psychosocial data useful for answering a variety of questions about the effects of HIV infection on women, such as: What are the incidence, response to treatment, and determinants of both for cervical dysplasia in HIV-infected and uninfected women? What are the immunologic effects of active or treated (e.g., with methadone) drug use in HIV-infected and uninfected women? What are the incidence and causes of mortality and hospitalization among HIV-infected compared with uninfected women? What social supports are available to and used by infected and uninfected women in response to stressful life events? Some of these questions are biologically gender specific (e.g., incidence of cervical dysplasia), and some are gender related (e.g., incidence of physical and sexual abuse) because of the social class, racial/ethnic, or risk behavior differences between women with or at risk for HIV infection and existing cohorts composed primarily of men. This paper describes the design and data collection methods of the HER Study and selected characteristics of HER Study women at their enrollment visit.

**Recruitment/eligibility**

The HER Study sites selected in mid-1991 were The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD; Montefiore Medical Center, Bronx, NY; Brown University, Providence, RI; and Wayne State University School of Medicine, Detroit, MI. Study protocols and materials were developed and implemented with the support and expertise of both new and experienced investigators from several universities, federal agencies, and other HIV/AIDS cohort studies. After selection, development, piloting, and revision of study instruments and protocols with the participation of Community Advisory Boards at each study site, study procedures and materials were cleared through Institutional Review Boards at each funded institution. Active recruitment, screening, and enrollment of women began in April 1993 and was completed in January 1995. A variety of recruitment modalities were used, including flyers posted in community gathering places; notices in community newspapers; letters to physicians at nearby HIV care, infectious disease, and drug treatment sites; information meetings with staff at drug treatment centers; invitations to participants in prior behavioral or clinical studies; and word of mouth through participants in other HIV studies (who were therefore ineligible for the HER Study) at the study institutions. Methods for recruitment were tailored to the resources of each study site. However, at all sites, HIV-uninfected women were recruited over the same time period and from the same or comparable sources as the HIV-infected women. For example, where HIV-infected women were recruited from HIV care clinics, uninfected women were recruited from general medicine or infectious disease clinics at the same facility.

Eligibility criteria for enrollment in the HER Study included documented HIV status within the previous 60 days or consenting to HIV testing as part of eligibility screening, fluency in either English or Spanish, age between 16 and 55 years, and reporting one or more HIV-risk behaviors. The risk behaviors assessed were chosen to facilitate recruitment of an uninfected cohort that was behaviorally comparable with the HIV-infected cohort. For purposes of monitoring comparability of the cohorts during enrollment, all women enrolled in the HER Study were categorized as having either drug-use risk or sexual risk. Drug-use risk was defined as having injected drugs at least once since 1985. Sexual risk was defined as either having sex with five or more partners in the previous 5 years or ever having sex with a male injection drug user (IDU), exchanging sex for money or drugs, or having sex with a man suspected or known to be infected with HIV.

Exclusion criteria were: no identified HIV risk behavior; risk only by transfusion history or birth to an HIV-infected woman (i.e., perinatally infected); not born female (i.e., transsexual); or not consenting to the
full protocol, including pelvic examination, phlebotomy, and repeated HIV counseling and testing (for seronegative women). In addition, because a primary study goal was to examine progression of HIV disease over time, women were considered to be late in HIV infection and thus ineligible for enrollment if they reported previously having selected AIDS-defining conditions for which self-report was believed to be sufficiently reliable for screening purposes— *Pneumocystis carinii* pneumonia, Kaposi’s sarcoma, cryptococcal meningitis, toxoplasma encephalitis, cytomegalovirus (CMV) retinitis, lymphoma, *Mycobacterium avium-intracellulare* complex, or candida esophagitis.

Enrollment goals were 230 HIV-infected and 115 HIV-uninfected women per site, with 50 percent reporting injection drug use and 50 percent reporting only sexual risk behavior in each comparison group (or cohort). These goals were chosen on the basis of sample size determinations for key study questions (e.g., incidence of cervical dysplasia) and to provide sufficient numbers for analyses stratified by the two primary modes of transmission for women. Key characteristics of the uninfected and infected cohorts were monitored monthly during the enrollment period by study epidemiologists, statisticians, and investigators. When imbalances were detected, site staff were advised to increase efforts to recruit women with specific underrepresented characteristics (e.g., uninfected IDUs).

**Core** visit protocol

Core visits for all women in the HER Study occur at 6-month intervals and include an extensive face-to-face interview; a general physical and pelvic examination; and blood, urine, cervicovaginal, and oral specimen collection. Study visits are scheduled in advance and are not performed if women come to the study site on a non-HER Study appointment day requesting evaluation or treatment of symptoms. At three sites, all study visits, including screening, occur in HER Study-dedicated space and with clinicians and interviewers not involved in their clinical care visits. At the fourth study site, HER Study visits are conducted in the care clinic by clinicians and interviewers, some of whom are clinical care providers for participants. At this site, study visits are scheduled separately from clinic visits, and clinical issues are not addressed during study visits. Whenever possible, study visits are conducted by study staff other than their care providers.

**Core interview.** During core visits, women participate in an interview lasting about 1 hour and composed of six modules. The first four cover the previous 6-month history of 1) medical symptoms, illnesses, procedures, and medication access and use; 2) reproductive events; contraceptive intentions and use; and gynecologic symptoms, illnesses, and procedures; 3) insurance status; and sources, perceived need for, and use of medical treatment, drug treatment, and social services; and 4) tobacco, alcohol, and drug use and sexual behaviors with male and female partners. The last two modules provide assessments of 1) current depressive symptoms, social support, beliefs about HIV/AIDS, life events, and loss and bereavement; and 2) current demographic factors, including marital status, living situation, source and amount of income, and religious participation.

Standardized interview forms are used at all sites. All interview forms were translated into Spanish (including back-translation to check for adequacy of translation) and reviewed by Spanish-speaking interviewers at the sites before being used with Spanish-speaking women in the HER Study.

**Core physical examination**

After the interview, women are given a focused physical examination to assess specific measures of potential importance to monitoring HIV disease progression and female-specific medical conditions. Assessment includes height and weight, dermatologic findings, oropharyngeal examination, breast examination, examination of lymph nodes, liver and spleen size, and a thorough pelvic examination that includes a Papanicolaou smear (see below).

Physical examinations are performed by study clinical staff and investigators who have undergone standardized training. The order of the physical examination and the variables measured are standard across the sites and are recorded on a common form.

**Core specimen collection and testing.** At core visits, several biologic specimens are collected and tested (table 1) or stored in repositories. Processing and storage of specimens have been standardized at all sites. Baseline laboratory measures done on site include confirmation of HIV infection status; antigen skin tests for tuberculosis and functional immune status; urinalysis; complete blood count with differential; lymphocyte immunophenotyping; chemistry profile; acute and confirmatory serology for syphilis; and fungal culture of oral, rectal, and vaginal swabs. Blood is sent to central laboratories at CDC for baseline evaluation of hepatitis, herpes simplex virus, and cytomegalovirus serology and for determination of $\beta_2$ microglobulin levels, and fungal isolates from local laboratories are sent to a central laboratory at Wayne State University for additional fungal studies. To provide for future laboratory studies of correlates of HIV disease pro-

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progression and manifestations, blood samples from each woman at each core visit are shipped overnight to the central repository at CDC for processing and storage of cells, serum, and plasma at $-70^\circ$C.

During the pelvic/rectal examination, clinical samples are collected for local testing to screen for sexually transmitted diseases and causes of vaginitis/vaginosis. Papaincopolou smears are performed at each visit and sent to a central pathology laboratory for reading (Kyto Diagnostics, New York, New York). Abnormal Papaincopolou smears trigger referral for colposcopy at three sites; at the fourth, all women have a colposcopy as part of the core pelvic examination. At the end of the pelvic examination, all women have a cervicovaginal lavage done for human papillomavirus (HPV) testing, assessment of leukocytosis, and sample repository at CDC.

At core visits after baseline, many of these laboratory measures are repeated to determine changes over time (e.g., in CD4+ T lymphocyte counts, HPV strains detected) and the incidence of clinical conditions (e.g., HIV seroconversion among initially uninfected women, cervical dysplasia).

Biannual measurement of HIV viral load by the Quantiplex branch DNA assay (Chiron Corp., Emeryville, California) was added to the laboratory protocol for infected women in April 1995.

Supplementary psychosocial interview. Each participant is given a comprehensive psychosocial interview within 2–4 weeks of her core medical visit. An advisory panel of behavioral scientists working with other populations of women and HIV-infected cohorts was convened to assist HER Study investigators in developing psychosocial research questions and se-

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**TABLE 1. Baseline laboratory measures for HER* Study women, United States, 1993–1995**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Assay(s)</th>
<th>Specimen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV*</td>
<td>Enzyme immunoassay</td>
<td>Serum</td>
</tr>
<tr>
<td>HIV infection status</td>
<td>Western blot (and bands)</td>
<td>Serum</td>
</tr>
<tr>
<td>Viral load</td>
<td>Branched DNA</td>
<td>Plasma</td>
</tr>
<tr>
<td>T cell subsets</td>
<td>Flow cytometry and CBC* with differential</td>
<td>Blood</td>
</tr>
<tr>
<td>Immune activation</td>
<td>$\beta_2$ microglobulin enzyme immunoassay</td>
<td>Serum</td>
</tr>
<tr>
<td></td>
<td>Anergy panel (mumps, Candida, and tetanus antigens)</td>
<td>Mantoux skin test</td>
</tr>
<tr>
<td>General health</td>
<td>CBC with differential</td>
<td>Blood</td>
</tr>
<tr>
<td>Anemia, granulocytopenia, or thrombocytopenia</td>
<td>Chemistry panel</td>
<td>Serum</td>
</tr>
<tr>
<td>Renal/liver function</td>
<td>CBC with differential</td>
<td>Serum</td>
</tr>
<tr>
<td>Prior/current systemic co-infection</td>
<td>Antibody and antigen tests</td>
<td>Serum</td>
</tr>
<tr>
<td>Hepatitis B, C, D</td>
<td>Western blot</td>
<td>Serum</td>
</tr>
<tr>
<td>HSV*</td>
<td>Culture (if ulcers)</td>
<td>Oral, vaginal, perineal swabs</td>
</tr>
<tr>
<td>CMV*</td>
<td>ELISA*</td>
<td>Serum</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Antibody and titer</td>
<td>Serum</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>White-cell esterase</td>
<td>Dipstick and urine</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Culture and sensitivity</td>
<td>Clean-catch urine</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>5 Todd-unit PPD* tuberculin</td>
<td>Mantoux skin test</td>
</tr>
<tr>
<td></td>
<td>Culture, speciation, typing, sensitivities</td>
<td>Oral, rectal, vaginal swabs</td>
</tr>
<tr>
<td></td>
<td>KOH* prep</td>
<td>Oral, vaginal swabs</td>
</tr>
<tr>
<td>Gynecologic health</td>
<td>HCG*-$\beta$ subunit antibody</td>
<td>Urine</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Gram stain</td>
<td>Vaginal swab</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>PCR*, culture</td>
<td>Vaginal swab</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>Saline preparation, culture</td>
<td>Vaginal swab</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>PCR, culture</td>
<td>Cervical swab</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>PCR, culture</td>
<td>Cervical swab</td>
</tr>
<tr>
<td>HPV*</td>
<td>PCR, Southern blot, and hybrid capture</td>
<td>Cervicovaginal lavege</td>
</tr>
<tr>
<td>Genital tract inflammation</td>
<td>Gram stain, cell count, and differential</td>
<td>Cervical swab</td>
</tr>
<tr>
<td>Cervical dysplasia/cancer</td>
<td>Papanicolaou smear, colposcopy</td>
<td>Cervix/vaginal cuff examination</td>
</tr>
<tr>
<td></td>
<td>Cervical biopsy</td>
<td>Abnormal colposcopies</td>
</tr>
</tbody>
</table>

* HIV, human immunodeficiency virus; HER, HIV Epidemiology Research; CBC, complete blood count; HSV, herpes simplex virus; CMV, cytomegalovirus; ELISA, enzyme-linked immunosorbent assay; PPD, protein-purified derivative tuberculin; KOH, potassium hydroxide; HCG, human chorionic gonadotropin; PCR, polymerase chain reaction; HPV, human papillomavirus.
lecting appropriate instruments. Because the psycho-
social interview addresses sensitive questions that may
require the interviewer to have special assessment and
counseling skills to respond appropriately to the par-
ticipant, this interview is conducted by specially qual-
ified and trained psychosocial interviewers. The inter-
view includes assessments of psychological well-
being, such as the Center for Epidemiologic Studies-
Depression Scale, mood, sexual functioning and satis-
faction, the effect of HIV on social roles, life events and concerns, coping style, social interaction and supports, relationship with current main partner, disclosure of HIV status, and attitudes/beliefs about HIV/AIDS.

Medical record abstraction
A signed medical release form to permit medical
record abstraction is obtained whenever hospitaliza-
tions, outpatient diagnostic procedures, or outpatient/
emergency room visits that generated HIV-related di-
agnoses are reported at any study visit.
HER Study medical record abstraction forms were
developed specifically to capture information to 1) de-
scribe causes of hospitalization; 2) document causes
of death; and 3) ascertain the occurrence of AIDS-
defining and HIV-related diagnoses. HER Study in-
vestigators defined a priori specific clinical data re-
quired to define diagnoses of interest that are
abstracted from medical records.

Midinterval visits for severely immunosuppressed
women
When women have a CD4+ T lymphocyte count
(CD4 cell count) of less than 100 cells/µl, midinterval
visits are added to the core visit protocol. Such women
are evaluated at more frequent intervals because they
may have more medical conditions and hospitaliza-
tions to report and are more likely to change residence
for financial or health reasons. In addition, research
questions specific to this population, such as the inci-
dence of early retinopathy associated with CMV in-
fection, can be studied better.
These interval visits are scheduled at the 3-month
midpoint between biannual core visits. A very brief
medical history, lasting approximately 15 minutes, is
obtained, focusing on hospitalizations, outpatient pro-
cedures, HIV/AIDS-related diagnoses and symptoms,
medications, illicit drug use, and performance of ac-
tivities of daily living. A limited physical examination
without a pelvic or rectal examination is performed.
Then a neuropsychologic screening battery is admin-
istered, consisting of Color Trails 1 and 2, Verbal
Fluency for first names, the Four Word Memory Task,
and the Grooved Pegboard. These measures were cho-
sen to test components required to diagnose HIV de-
mentia (4) and because they have been used success-
fully in minority populations and those with low
education levels. Centrally trained clinical staff ad-
minister these tests, and women who fail the screening
battery are referred for a full diagnostic evaluation. A
blood culture for atypical Mycobacterium infection is
obtained, and antibody titer to Toxoplasma gondii is
determined. Finally, women are referred to collaborat-
ing ophthalmologists for an eye examination (with pupils dilated), primarily to detect early asymptomatic
cytomegalovirus or HIV retinopathy.

Participant safety and confidentiality
Since provision of routine medical care is not part of
the study protocol, all sites have developed systems
for following up clinically significant interview re-
sponses, examination findings, and laboratory results.
In some cases, study investigators are also the care
providers of participants needing clinical follow-up; in
other cases, study participants have given consent for
notifying their care provider of findings indicating a
need for treatment; and in still others, appropriate
referrals are made in consultation with the participant.
All sites have obtained Public Health Service Certifi-
cates of Confidentiality to protect against access to
study data by any person or agency not part of the
HER Study. Study data are stored in locked cabinets in
locked rooms, and no personal identifiers are included
on data forms sent to the data management center or
CDC.

Quality control
Before data collection began, interviewers from all
sites received uniform, centralized training in admin-
istering the interviews, asking nondirective questions
to clarify responses, and reviewing of the interview
forms after the interview. Additionally, retraining and
problem solving are done on a regular basis. Inter-
viewers are observed during annual site visits, and
psychosocial interviewers are observed by a research
psychologist. The quality control staff at the data man-
agement center randomly assigns specific participant
visits for each interviewer at which interviews are audi-
taped (with participant consent) for central eval-
uation of interviewer proficiency. Physical examiners
also received common training to standardize sample
collection procedures and diagnosis of clinical condi-
tions, including the variations in dermatologic and oral
conditions that may occur in nonwhite persons. Sepa-
rate, regular clinician conference calls are held for
examiners. Medical record abstractors at the sites re-
ceived centralized training by a senior abstractor experienced in HIV/AIDS records. A committee of clinician-investigators hold monthly conference calls with the abstractors to resolve any difficult abstraction questions and communicate decisions to all abstractors so that standard procedures will be followed.

Data management

Most data in the HER study are now managed centrally at the New England Research Institute (NERI) in Watertown, Massachusetts. Printed copies of the data forms are stored locally, and the originals are mailed to NERI, where data are entered, data element edits are resolved with site staff, the database is cleaned, and analytic datasets are generated and documented. Selected central laboratory data are entered on site and electronically transferred to the data center. Data generated by substudies are managed at the sites or at CDC. Central data management will be transferred to CDC in late 1997.

Every 6 months, NERI provides an updated and documented SAS dataset (SAS Institute, Cary, North Carolina) for distribution to study sites. This dataset is used for analysis, internal review, presentation, and publication by study investigators.

RESULTS

Recruitment and retention

From April 1993 through February 1995, 1,994 women were screened, and 1,310 (66 percent) women were enrolled in the HER Study. Of the women screened, 199 (10 percent) were ineligible, and 16 (<1 percent) were eligible but decided not to enroll. Because more eligible uninfected women were identified than were needed, 77 percent of eligible, uninfected women screened were randomly selected for enrollment, and 23 percent were not enrolled.

Word of mouth was the most frequent response given by enrolled women (36.4 percent) when asked, “How did you find out about this study?” and was more commonly reported by HIV-uninfected (45.6 percent) than by HIV-infected (31.7 percent) women. The next most common response was referral by a woman’s health care provider (14.4 percent overall, 20.1 percent HIV+, 3.6 percent HIV−) or a social service organization (14.1 percent overall, 11.7 percent HIV+, 18.7 percent HIV−). Less commonly reported sources were: being contacted by the study team other than one’s own provider (11.0 percent overall, 12.4 percent HIV+, 8.2 percent HIV−), reading a newspaper notice or flyer (6.5 percent overall, 6.8 percent HIV+, 5.9 percent HIV−), and other sources. There were site-specific differences, however. The two sites that are also clinical care sites (Detroit Medical Center and Brown University) had high rates of referral from physicians and study clinic nurses (31.4 percent in Detroit and 24.7 percent at Brown University). The two study sites located in noncare research facilities (Montefiore Medical Center and The Johns Hopkins University) had few study participants referred by medical providers and high rates of community referral by word of mouth (48.5 percent at Montefiore Medical Center and 67.9 percent at The Johns Hopkins University).

Women were asked about their reasons for enrolling (or not enrolling) in the study. Their verbatim answers were independently classified into defined categories by two investigators. The most common first-mentioned reason for enrollment given by all enrolled women was to benefit their own health or to get regular physical examinations (33.0 percent of HIV-infected woman, 29.6 percent of HIV-uninfected women). Of HIV-infected women, 32.3 percent enrolled to help other women or to participate in research, and 21.2 percent enrolled to learn more about HIV/AIDS. Of women not infected with HIV, 28.1 percent enrolled to have access to HIV testing, 17.6 percent to help others or be involved in research, and 13.4 percent to increase their knowledge of HIV disease.

A total of 871 HIV-infected and 439 HIV-uninfected women were enrolled. Retention rates were calculated by deducting known deaths before each follow-up visit from all of those enrolled and counting as retained those women whose blood specimens had been received in the central repository for the relevant visit. This conservative method of assessing retention overestimates loss to follow-up since some women have died whose death has not yet been reported to the data center and because a small number of women may have had a study visit but had insufficient blood collected for a repository specimen. Of women who survived and returned for the second, third, and fourth study visits, retention rates were greater than 91 percent, greater than 88 percent, and greater than 84 percent of those enrolled, respectively. Higher losses to follow-up were associated with injecting drugs in the 6 months before enrollment, not having dependent children, and being HIV-uninfected at enrollment (table 2).

Characteristics of enrolled women

Demographics. Recruitment goals were met (table 3), and the uninfected cohort is behaviorally and demographically well matched to the infected cohort.
The median age at enrollment was 35 years; 9 percent of the women were aged 16–25 years, 71 percent were aged 26–45, and 20 percent were aged 46–55. Slightly more than half (58 percent) of the enrolled women are African American, 24 percent are white, 17 percent are Hispanic, and less than 1 percent each are Native American, Asian, or of undetermined race/ethnicity. HIV-infected women were somewhat more likely to be African American or Hispanic than were uninfected women.

Fifty-four percent of the HIV-infected women compared with 63 percent of the HIV-uninfected women had graduated from high school or received a graduation equivalency diploma. The financial poverty of these women is reflected in both their reported median annual household income ($9,000) and their per capita income ($3,000). Only 16 percent of the HIV-infected women received their income from employment, while a quarter of the HIV-uninfected women were employed.

**Baseline drug use behavior.** More than half the participants (58 percent) reported ever injecting drugs, and a quarter (26 percent) had done so in the 6 months before they enrolled in the HER Study (table 3). The infected cohort had a similar proportion who had injected drugs since 1985 (52.7 percent), as had HIV-uninfected women (50.1 percent). Recent noninjection use of illicit drugs, including illicit methadone, was reported by approximately half of all HER Study participants and was more common among uninfected (62 percent) than infected (48 percent) women.

**Baseline sexual behavior.** While the proportion of women enrolled with sexual risk factors only (i.e., no IDU history) was equivalent between HIV-infected (47.3 percent) and HIV-uninfected (49.9 percent) women, the type of past sexual risk behavior reported differed somewhat between the groups (table 3). HIV-infected women were more likely to report prior sex with a partner they knew or suspected to be HIV infected; women not infected with HIV were more likely to report sex with five or more partners (male or female) in the previous 5 years, while both groups...
TABLE 3. Selected baseline characteristics of HER* Study women, United States, 1993–1995

<table>
<thead>
<tr>
<th>Demographics</th>
<th>HIV*-positive women (n = 871)</th>
<th>HIV-negative women (n = 439)</th>
<th>Statistical difference‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>35.0</td>
<td>34.5</td>
<td>NS</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>60.3</td>
<td>53.7</td>
<td>NS</td>
</tr>
<tr>
<td>White</td>
<td>20.8</td>
<td>30.7</td>
<td>NS</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17.4</td>
<td>14.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Native American/Asian/other</td>
<td>1.5</td>
<td>1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Education (% less than high school graduate)</td>
<td>46</td>
<td>37</td>
<td>0.03</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median household (dollars)</td>
<td>$9,000</td>
<td>$9,000</td>
<td>NS</td>
</tr>
<tr>
<td>Median per capita (dollars)</td>
<td>$3,000</td>
<td>$3,000</td>
<td>NS</td>
</tr>
<tr>
<td>% with household income &lt;$12,000</td>
<td>74</td>
<td>69</td>
<td>NS</td>
</tr>
<tr>
<td>% employed</td>
<td>16</td>
<td>25</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sexual and drug use behaviors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDU* since 1985 (%)</td>
<td>52.7</td>
<td>50.1</td>
<td>NS</td>
</tr>
<tr>
<td>IDU in previous 6 months (%)</td>
<td>25.1</td>
<td>26.4</td>
<td>NS</td>
</tr>
<tr>
<td>Other drug use in previous 6 months (%)</td>
<td>47.8</td>
<td>61.6</td>
<td>0.001</td>
</tr>
<tr>
<td>≥5 sex partners in previous 5 years (%)</td>
<td>28.1</td>
<td>45.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ever had sex with male IDU (%)</td>
<td>75.2</td>
<td>74.7</td>
<td>NS</td>
</tr>
<tr>
<td>Ever had sex with partner known/suspected HIV* positive (%)</td>
<td>62.6</td>
<td>38.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ever had sex for money or drugs (%)</td>
<td>44.0</td>
<td>49.4</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex partners in previous 6 months (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27.1</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>1–10</td>
<td>71.4</td>
<td>79.5</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1.4</td>
<td>4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Ever had sex with a female (%)</td>
<td>24.5</td>
<td>26.6</td>
<td>NS</td>
</tr>
<tr>
<td>Female sex partner (previous 6 months) (%)</td>
<td>5.9</td>
<td>10.0</td>
<td>NS</td>
</tr>
<tr>
<td>Psychosocial (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D*§ score &gt;16</td>
<td>61.8</td>
<td>59.7</td>
<td>NS</td>
</tr>
<tr>
<td>No safe place to live (previous year)</td>
<td>19.3</td>
<td>22.8</td>
<td>NS</td>
</tr>
<tr>
<td>Physically attacked/raped (previous year)</td>
<td>9.5</td>
<td>13.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Physically attacked/raped (previous 6 months)</td>
<td>7.5</td>
<td>8.0</td>
<td>NS</td>
</tr>
<tr>
<td>Children taken away (previous year)</td>
<td>5.4</td>
<td>10.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>HIV-positive parent</td>
<td>1.8</td>
<td>2.3</td>
<td>NS</td>
</tr>
<tr>
<td>HIV-positive sibling</td>
<td>13.5</td>
<td>10.7</td>
<td>NS</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>17.1</td>
<td>0.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>200–499</td>
<td>50.7</td>
<td>1.7</td>
<td>NS</td>
</tr>
<tr>
<td>≥500</td>
<td>32.2</td>
<td>98.3</td>
<td></td>
</tr>
<tr>
<td>Mean β2-microglobulin</td>
<td>3.4</td>
<td>2.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>% syphilis serology reactive</td>
<td>8.5</td>
<td>5.7</td>
<td>0.03</td>
</tr>
<tr>
<td>% hepatitis B core Ab positive</td>
<td>58.9</td>
<td>42.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Health care indicators (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgically sterilized</td>
<td>39.7</td>
<td>31.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Same doctor for at least 2 years</td>
<td>47.7</td>
<td>37.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Routine pelvic examination In previous 12 months</td>
<td>70.6</td>
<td>55.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Teeth cleaned In previous 12 months</td>
<td>36.3</td>
<td>35.1</td>
<td>NS</td>
</tr>
<tr>
<td>Ever used antiretroviral§</td>
<td>70.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Now using antiretroviral§</td>
<td>36.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever used Pneumocystis carinii prophylaxis#</td>
<td>79.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Using P. carinii prophylaxis now#</td>
<td>52.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* HIV, human immunodeficiency virus; HER, HIV Epidemiology Research; IDU, Injection drug user; CES-D, Center for Epidemiologic Studies Depression Scale.
† Denominators vary slightly with missing data points from individual women.
‡ Statistical differences assessed by t test for continuous variables and chi-square for categorical variables. Nonsignificant (NS) = p > 0.05.
§ CES-D score greater than 16 indicates depressed mood.
¶ Of women with CD4 count less than 500.
# Of women with CD4 count less than 200.

were equally likely to report sex with a male IDU or sex for money or drugs. In terms of self-identified sexual orientation, 89 percent of HIV-infected women were identified as heterosexual/straight, 5 percent as
biseexual, and 6 percent as lesbian. Similar percentages were reported by uninfected women. Nearly one-fifth of participants (18 percent) had been abstinent during the 6 months before enrollment; HIV-infected women were more likely than uninfected women to report abstinence. Sex with large numbers of male partners was infrequent for both groups of women.

**Baseline behavioral and psychosocial status.** High levels of social stress and emotional distress were found among both the HIV-infected and the uninfected, at-risk women (table 3). Mean scores on the Center for Epidemiologic Studies-Depression Scale were approximately 20 for both HIV-infected and uninfected women, and more than half of both groups scored 16 or above, the cutoff score for clinically significant depressive disorder (5). On measures of stressful life events in the year before the baseline interview, 19.3 percent of infected women and 22.8 percent of uninfected women reported having no safe place to live, 9.5 and 13.7 percent, respectively, reported being physically attacked or raped in the previous year (7.5 and 8.0 percent in the previous 6 months), and 5.4 and 10.3 percent, respectively, had their children removed from their home.

**Baseline clinical status.** At enrollment, the median CD4 cell count of HIV-infected women was 350 cells/μl; 17.1 percent of infected women had CD4 cell counts of less than 200 cells/μl, 50.7 percent had counts of 200–499 cells/μl, and 32.2 percent had counts of greater than 500 cells/μl (table 3). Half of the women also had laboratory evidence of past hepatitis B infection. The median number of children born to HER Study women was two. More than a third of the study participants had undergone a hysterectomy or been surgically sterilized by tubal ligation. Almost half of the HIV-infected women had had the same doctor for the 2 years before enrollment; nearly three quarters had had a routine pelvic examination in the previous year, and more than one third had had routine dental care. Fewer HIV-uninfected than HIV-infected women reported having the same physician providing care for the previous 2 years or a pelvic examination in the previous year, but an equivalent proportion reported receiving routine dental care (table 3). Across all sites, more than two thirds of infected women with CD4-cell counts of less than 500 cells/μl had ever taken zidovudine, didanosine, or zalcitabine, and more than a third were taking an antiretroviral drug when they enrolled in the HER Study. Of infected women with CD4 cell counts of less than 200 cells/μl, 79.2 percent had ever used *P. carinii* pneumonia prophylaxis, and only 52.8 percent were taking prophylactic medication at the time of the interview.

**Early findings**

From 1994 to 1996, interim analyses were done for some questions using the portion of baseline visit data that had then been collected (approximately three quarters of the entire baseline visit data). These biomedical, behavioral, and psychosocial findings have been presented at several recent conferences (6–25).

**DISCUSSION**

The design and population features of the HER Study provide a unique and comprehensive approach to the study of HIV infection in women. The HER Study has identified and enrolled a large number of HIV-infected women as well as a cohort of uninfected women who were behaviorally and demographically well matched. The 1,310 women enrolled in the four cities represent a wide age range and were selected without regard to their fertility or pregnancy status. The HER Study participants report a variety of behaviors associated with the risk of HIV acquisition, and the study includes those who did not use drugs, users in treatment/recovery, and both injection and noninjection drug users. Sufficient numbers of African-American, Hispanic, and white women are included to permit valid subanalyses of racial, ethnic, and cultural factors that may be related to HIV disease manifestations and/or progression. Study women are being monitored prospectively with extensive measures of psychologic, social, and biologic factors, including documentation of clinical outcomes by extensive medical record abstraction as well as participant reports. Data collection from the eighth biannual follow-up visits began in April 1997.

Earlier HIV longitudinal cohort studies focused on more narrowly defined populations such as (primarily white) homosexual and bisexual men (26–28) and drug users (29, 30), often in a single city. These earlier studies provided much of the available information about fundamental aspects of the progression of HIV disease over time and its determinants. The HER Study is unique in allowing multivariate analysis of the interactions of risk behavior, race/ethnicity, social class, geographic differences, and psychosocial factors with biomedical factors and their relations to HIV disease progression in women.

Questions have been raised about effective methods of recruiting and retaining significant number of women in longitudinal, HIV-related studies. An analysis of factors related to recruitment of women into the AIDS Clinical Trials Group protocols found that the involvement of female investigators in leadership positions was associated with enrollment of higher numbers of women into their trials (3). Another analysis of persons with HIV infection or AIDS found lower rates...
of enrollment in AIDS Clinical Trial Group trials among African Americans, women, injection drug users, and persons with low income or less than a high school education, all characteristics of HER Study participants (31). In the HER Study, variation in retention rates by study site may reflect differences in tracking methods employed, particularly among active drug users (e.g., use of community workers for street tracking). In addition to supportive services provided to study women (e.g., reimbursement for child care and travel, compensation for interview time and examination/phlebotomy discomfort, a newsletter for participants, and birthday and holiday cards), the involvement of female as well as male researchers at all study sites may have contributed to both study enrollment and retention.

The maintenance of a longitudinal cohort with such an extensive data-collection protocol is logistically complicated. However, in addition to providing prospectively collected information on the long-term impact of HIV disease, this design facilitates the conduct of smaller, short-term studies that can result in considerable time and cost efficiencies. HERs investigators and collaborators at other Public Health Service agencies are using this nested study mechanism to examine several areas, including immune responses in uninfected women with frequent sexual and/or IDU exposure to HIV, human leukocyte antigen class I and class II genotypes, chemokine receptor genetics, the predictive value of several measures of CMV viral load for the development of retinitis or gastrointestinal disease, surface activation markers on CD8+ T lymphocytes from HIV-infected women, cytokine production, vitamin and micronutrient status, menstrual cycling (in collaboration with the National Institutes of Health Office for Women's Research), cervical HIV shedding throughout the menstrual cycle, sexual and reproductive decision-making, determinants of condom use, women's reported legal needs and access to legal services, and a study of outpatient health care utilization (in collaboration with the Agency for Health Care Policy and Research). A series of sub-studies are being done in collaboration with the National Institute on Drug Abuse, including an assessment of the impact of illicit drug use on virologic correlates of HIV disease progression, measures of the immunologic consequences of drug use, and a study of potential biomarkers for measuring antiretroviral compliance, evaluation of new sweat patch tests for recent drug use, and jointly with the National Institutes of Health-funded Women's Interagency HIV Study, an evaluation of the effects of drug use on health care utilization.

The challenges of recruiting and retaining a multi-site research cohort composed largely of participants from populations often considered difficult to study (i.e., drug users, economically disadvantaged persons, racial/ethnic minority women) have been met. This cohort is distinct from other HIV-infected longitudinal cohorts in the diversity of its participants and the comprehensive range of its measures. The broad spectrum of demographic, behavioral, and clinical characteristics of HER Study participants at multiple sites provides investigators with an important resource to prospectively study and more fully understand the biomedical, social, and emotional effects of the HIV epidemic on infected women and those engaged in behaviors that put them at high risk of infection.

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REFERENCES


