

MINIREVIEW

The Women's Interagency HIV Study: an Observational Cohort Brings Clinical Sciences to the Bench

Melanie C. Bacon,^{1,*} Viktor von Wyl,² Christine Alden,³ Gerald Sharp,⁴ Esther Robison,⁵
 Nancy Hessel,⁶ Stephen Gange,³ Yvonne Barranday,⁷ Susan Holman,⁸
 Kathleen Weber,⁹ and Mary A. Young²

Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, Maryland¹; Georgetown University Medical Center, Washington, D.C.²; Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland³; Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland⁴; Montefiore Medical Center, Bronx, New York⁵; University of California, San Francisco, California⁶; University of Southern California Medical Center, Los Angeles, California⁷; Health Science Center at Brooklyn, State University of New York, Brooklyn, New York⁸; and John H. Stroger Hospital of Cook County, Chicago, Illinois⁹

The Women's Interagency HIV Study (WIHS) is an ongoing long-term observational study of 3,772 women who are either infected with human immunodeficiency virus (HIV) or considered to be at risk for acquiring HIV. Since 1994, the WIHS (pronounced like "wise") has developed a large database and specimen repository that serve as resources for WIHS investigators as well as for nonaffiliated researchers working on HIV-related or HIV coinfection issues. The purpose of this report is to update researchers on the progress of the WIHS and to provide information on WIHS resources, the methods by which they were obtained, and background for any new potential researchers interested in conducting collaborative research through shared use of these resources.

BACKGROUND

At the start of the HIV epidemic, research was focused on the male population known to be at highest risk for AIDS. In 1983, The Multicenter AIDS Cohort Study was initially funded by the National Institute of Allergy and Infectious Diseases (NIAID) and has subsequently enrolled 4,944 adult, urban, homosexual/bisexual men, 95% of whom were white (14). By the mid-1990s, however, there was a dramatic increase in new AIDS cases among women (89% increase among women and 29% among men between 1990 and 1994) (J. W. Ward, J. Karon, P. Fleming, and H. Gayle, Abstr. 11th Int. Conf. AIDS, abstr. 36, 1996). These new cases were primarily among women of color exposed through heterosexual partners or intravenous drug use (6).

In response, NIAID was joined by the National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute of Drug Abuse (NIDA), and the National Institute of Dental and Craniofacial Research (NIDCR) to fund six sites across the country to study the natural history of HIV in women. These

sites initially enrolled 2,059 HIV-positive women and 569 HIV-negative women between 1 October 1994 and 15 November 1995, making the WIHS the largest study in the United States to focus on HIV infection among women.

The proportion of AIDS cases occurring in women has continued to rise in the United States (7). Highly active antiretroviral therapy (HAART) became available in 1996, greatly increasing life expectancy and quality of life for those with HIV. By 2001, however, 554 women of the original cohort had died, and among the 1,618 (78%) survivors who remained active in the study, the median age was 42 years, and 23% of the cohort reported being postmenopausal. To ensure the ability of WIHS to study HIV and its therapies in the HAART era, recruitment was reopened from 1 October 2001 to 30 September 2002; the cohort was expanded by another 1,144 women to a total of 2,762 women with a median age of 32 years. The larger cohort enables the WIHS to better define the effects of infection and therapy across both reproductive and postmenopausal periods of women's lives.

STUDY ORGANIZATION AND COHORT DEVELOPMENT

Organizational Structure

There are six WIHS consortia, each made up of multiple clinical subsites, located in Bronx/Manhattan, NY; Brooklyn, NY; Los Angeles/Southern California/Hawaii; San Francisco/Bay Area, CA; Chicago, IL; and Washington, DC. Each consortium represents the population of HIV-infected women in its metropolitan area. An executive committee (EC) consists of investigators from each consortium, NIH program officers, and representatives of the study participants. EC members develop their specific areas of research and work with investigators outside the consortium who want to conduct research using WIHS resources. Study protocol and proposals for new research concepts for the cohort are reviewed and voted on by the EC.

Each WIHS consortium is supported by a community advisory board (CAB) comprised of study participants, and these local CAB members select representatives for the national

* Corresponding author. Mailing address: NIAID/DAIDS/BSP/Epidemiology Branch, 6700-B Rockledge Drive, Room 4221, Bethesda, MD 20817. Phone: (301) 451-2747. Fax: (301) 402-3211. E-mail: mbacon@niaid.nih.gov.

WIHS CAB (NCAB). Participating in WIHS EC meetings and working group conference calls, NCAB members review plans and rationales for protocol changes and assist researchers in understanding what new initiatives are likely to be supported by study participants and what questions are of importance to the HIV-infected community.

Protection of Human Subjects and Informed Consent

Despite 20 years of growing awareness about HIV and AIDS, there remains a stigma associated with the diagnosis and a fear of disclosure among many infected women. HIV-negative participants worry that they will be thought to be HIV positive if identified with an HIV study. Hence, confidentiality is carefully guarded in the WIHS. A certificate of confidentiality from the U.S. Department of Health and Human Services protects study staff from being required to respond to requests for information on participants from any persons or organizations unrelated to the study. Participants are assigned study identification numbers and names are not used on any WIHS documentation except consent and locator forms and medical record requests. Forms with identifying information are maintained separately from data files in a secured file cabinet.

WIHS participants provided written informed consent, in English or Spanish, both for screening and for enrollment. For those unable to read, the consent form is read to them and this is documented on the consent form prior to obtaining signatures. WIHS consent forms include information on current study procedures and on the storage of specimens in the repository for future studies as approved by the WIHS EC. Each subsite within the WIHS consortia has consent forms approved by its institutional review board. Significant changes in the protocol and new substudies are reviewed by institutional review boards prior to initiation; women may choose whether or not to participate in new substudies without jeopardizing their status as core WIHS participants.

Recruitment

At the time of the original WIHS recruitment, there were few inclusion and exclusion criteria. Adult women able and willing to consent to participation in the study, complete the interview in English or Spanish, travel to the research site for an interview and physical examination every six months, and have blood drawn for laboratory testing by venous or arterial access were enrolled into one of two groups: HIV positive or HIV negative. Prior to 1996, HAART exposure was limited to early clinical trials; therefore, most enrollees were naïve to highly active therapy and many had already been diagnosed with an AIDS-defining illness. A detailed description of the original recruitment was published by Barkan et al. in 1998 (4).

The goals of expansion in the period from 2001 to 2002 were to recruit a younger group with limited disease progression and to identify two groups related to treatment exposure—those who had been on HAART and those who had never been exposed to HAART—as well as a control group of HIV-negative women of similar ages and backgrounds. To obtain a representative sample of the population of HIV-infected women in the community, recruitment focused on African-American and Latina women. Eligibility criteria for the expansion cohort included the following:

(i) documented results from an HIV enzyme-linked immunosorbent assay and a confirmatory Western blot for each of those who were HIV positive or documented HIV-negative results obtained within 30 days prior to enrollment for HIV-negative women; (ii) no history of clinical AIDS-related conditions, confirmed by medical record abstraction; (iii) documentation of laboratory reports of HIV RNA levels and CD4 counts surrounding the period of HAART initiation for those enrolled as HAART exposed; and (iv) consent from the woman to have her specimens stored in the WIHS national repository.

To ensure comparability with the HIV-positive women, site recruitment targeted women who engaged in high-risk behaviors for enrollment in the HIV-negative group. High-risk behaviors were defined as reporting one or more of the following criteria within the past year: (i) injection drug use; (ii) having a sexually transmitted disease; (iii) having unprotected sex with three or more men or protected sex with more than five men; or (iv) having exchanged sex for drugs, money, or shelter.

Recruitment methods used in both the original and expansion cohorts emphasized face-to-face techniques. Infectious disease, internal medicine, and obstetric and gynecology offices throughout the community were contacted for referrals. Outreach to HIV community organizations, churches and HIV ministries, and social-service organizations was conducted. Women who were part of the original cohort recruited friends and family members, women with whom they shared support groups and counseling sessions, and friends of friends.

Loss to follow-up between baseline and the first follow-up visit was 10.3% among original enrollees. For this reason, five of the six sites chose a two-step enrollment process for the period from 2001 to 2002 which required an initial screening visit and then a second baseline study visit. Due to the high loss to follow-up at some consortia among those recruited from residential drug rehabilitation centers during the 1994-to-1995 period, many sites did not recruit at drug treatment centers but did enroll women in rehabilitation who were referred by a physician or friends. These changes resulted in a loss to follow-up between baseline and first follow-up visits of only 5.3% among the expansion cohort.

Retention

After the baseline visit, the new cohort was merged into the original cohort's protocol and visit schedule. One year after the expansion recruitment was completed, the retention rate for the combined cohort was 76% for seronegative and 83% for seropositive women. One-year retention rates for new recruits were 91% among HIV-negative women and 95% among those who were HIV positive. An analysis of the successful WIHS retention efforts from 1994 through 1999 was detailed in a paper by Hessol et al. (11).

The WIHS is structured with a 6-calendar-month period for visit windows. For example, visit 16 occurred between 1 April 2002 and 30 September 2002. Ideally, visits are scheduled 6 months apart plus or minus 6 weeks. Because of the importance of identifying long-term outcomes, women are never withdrawn from the study due to missed visits. Those who move out of the area may remain active by transferring to a closer WIHS site, or long-distance transportation may be pro-

TABLE 1. WIHS laboratory testing

Specimen type collected	Test ^a	Frequency or time of testing	
		HIV+ specimen	HIV- specimen
Blood	Hepatitis B	Baseline only	Baseline only
	Hepatitis C	Baseline only	Baseline only
	HSV serology	Baseline only	Baseline only
	Toxoplasma serology	Baseline only	Baseline only
	Syphilis	Baseline only	Baseline only
	CBC differential and platelet count	Biannual	Biannual
	CD4, CD8	Biannual	Annual
	HIV ELISA and Western blot	Baseline only	Biannual
	Viral load	Biannual	Not done
	Chemistry (liver function, kidney function)	Biannual	Biannual
Vaginal	Papanicolaou smear	Biannual	Biannual
	Bacterial vaginosis smear	Biannual	Biannual
	<i>Candida</i> vaginal culture	Baseline only	Baseline only
	<i>Chlamydia</i> Gen-Probe smear	Baseline only	Baseline only
	Gonorrhea Gen-Probe	Baseline only	Baseline only
	<i>Trichomonas</i> saline mount	Biannual	Biannual
	HPV by PCR with CVL	Biannual	Biannual
	HPV by hybrid capture with CVL	Biannual	Biannual
Urine	Pregnancy test	Biannual	Biannual
	Urinalysis	When clinically indicated	When clinically indicated
	Urine culture	When clinically indicated	When clinically indicated
	Chlamydia confirmatory test	When indicated	When indicated

^a CBC, complete blood count; CVL, cervicovaginal lavage fluid; ELISA, enzyme-linked immunosorbent assay.

vided for annual visits. Abbreviated visits may be conducted over the phone for ill or incarcerated participants, with data collection limited to the participant’s medical and therapeutic history for the preceding 6 months.

Locator information. At each visit, WIHS participants are asked to provide the name and contact information of a friend or family member in addition to someone in their home along with instructions regarding the limit or extent of messages that can be left. This helps to track and retain those who may have unstable living situations.

WIHS PROTOCOL AND SPECIMEN REPOSITORY

The Study Visit

The core WIHS protocol has been described previously by Barkan et al. (4). The elements of a study visit are as follows.

Interview. Centrally scripted interviews were conducted at each 6-month WIHS visit. Self-reported data include general medical history; antiretroviral therapy; obstetric and gynecologic history; use of drugs, alcohol, and cigarettes; sexual behaviors; health care utilization; beliefs regarding HIV and treatments; and psychological status. Changes are submitted to the EC for approval and then are included in the protocol starting in the next visit window.

To ensure the highest-quality data, centralized training was conducted for all study interviewers at the start of the WIHS and again prior to its expansion. A designated interviewer from each consortium completed additional training that enabled them to orient new staff and evaluate all interviewers at their sites on an annual basis. Additionally, question-by-question guidance forms are distributed at the start of each visit to assist interviewers with new questions and their abilities to objectively prompt participants to clarify answers when needed.

Additional surveillance. All reports of AIDS-related diagnoses are followed up with medical record abstractions. State cancer registries, local and state tuberculosis registries, and the National Death Registry are utilized to add to and confirm the outcome data collected.

Clinical examination. Physical examinations conducted at each core visit include a standardized assessment of vital signs with blood pressure; anthropometric measures; a skin and oral examination; an examination of the breasts, lymph nodes, and abdomen; and a gynecological examination that includes a Pap test and the collection of specimens for testing and storage as described below. The WIHS protocol includes colposcopic examination and biopsy when indicated. Women needing further treatment are referred for care outside of the WIHS, and sites have referral mechanisms which take into account each participant’s insurance coverage and ability to pay.

Laboratory testing. All WIHS participants had blood, urine, and cervicovaginal swab and lavage fluid specimens taken for baseline laboratory tests; follow-up lab work is done at each 6-month visit. As the study evolves, new areas of testing are identified and included. The collection of fasting samples was added in 2000 to allow for cardiovascular and metabolic research. Table 1 details these tests.

National and local repositories. Additional specimens are collected at each visit and stored in central and local WIHS repositories. These samples are used both by WIHS investigators and by unaffiliated outside collaborators after approval by the WIHS EC. Table 2 details the types and amounts of specimens currently in the repository.

Data management. Since 1998, the WIHS Data Management & Analysis Center (WDMAC) has been maintained in the Department of Epidemiology of the Bloomberg School of

TABLE 2. WIHS repository specimens^a

No. of specimens stored		WIHS specimen type description ^b	Volume of specimen
HIV-	HIV+		
35,100	116,900	Serum	0.5- or 1.0-ml aliquots
106,100	352,300	Plasma	0.5- or 1.0-ml aliquots
31,600	91,200	Viable PBMC cells	≥6 million cells per aliquot
43,400	141,400	PBMC pellets	0.5 or 2 million cells per aliquot
6,400	24,500	Urine supernatant	1-ml aliquots
20,500	64,900	Urine	1- or 5-ml aliquots
1,100	3,900	Oral fungal culture (mouth scrapings)	1 swab
1,100	3,800	Vaginal fungal culture	1 swab
43,900	143,400	Whole CVL	1-ml aliquots
6,600	25,000	CVL supernatant	0.5- or 1.0-ml aliquots
8,700	33,000	CVL pellet (suspended)	2.5 million cells per tube
2,900	8,100	Cervical swab	1 swab

^a Serum, plasma, cells, and CVL samples were stored for every visit from 1994 to present, provided sufficient amounts were obtained (priority given to protocol testing); urine collected at each visit between 1994 and 1998; oral fungal cultures collected at baseline visit.

^b PBMC, cryopreserved peripheral blood mononuclear cells from cell preparation tubes; CVL, cervicovaginal lavage fluid.

Public Health at the Johns Hopkins University. Data collected at the sites using paper forms are entered at each consortium into a World Wide Web-based data system maintained by WDMAC. A data manager at each consortium oversees data entry and works with WDMAC to ensure that data are complete and methods of recording the data are comparable between locales.

A DECADE OF RESEARCH

In all, 2,796 HIV-positive women and 976 HIV-negative women have been enrolled in this continuing study, and 2,662 of these remain active participants. During the first 18 study visits of the WIHS, a total of 33,500 person visits was completed. Of these, only 1.8% (*n* = 594) were done as abbreviated visits. Remarkably, 834 women from the original cohort have never missed any part of a single visit. Ten years of data have been collected through extensive interviews and laboratory testing, and there are currently over 1.3 million specimens in the WIHS national repository.

Characteristics of the Cohort

The characteristics of the HIV-positive women in the WIHS cohort are similar to those seen in the national statistics on HIV maintained by the CDC. Table 3 shows the racial distribution and exposure categories for AIDS cases (the CDC did not report HIV infection in 1995) reported in the United

States in 1995 and for those women recruited into the WIHS in the original recruitment period. Table 4 shows the same breakdown for HIV-only cases (AIDS free) from areas with confidential HIV reporting through 2001 and for new WIHS recruits enrolled in 2001 and 2002. The higher percentage of Latina women in the WIHS relative to that shown in CDC statistics may reflect the fact that confidential HIV reporting was not required until 2002 in any jurisdictions where WIHS sites are located and where there tend to be larger Hispanic populations. In the expansion cohort, Latinas comprised 64% of those enrolled in Southern California and 42% in Bronx, NY.

The newly recruited HIV-positive members of the cohort have viral loads lower and CD4⁺ counts higher than the original group when they were enrolled. (Table 5) This is due in part to the exclusion of women with previous AIDS diagnoses from the expansion and also reflects effective treatment with antiretrovirals that were not available in 1995. Hepatitis was more common at enrollment in the original cohort (Table 6). At their baseline visits, 39% of the original cohort had hepatitis C antibodies, compared to 13% in the new cohort, which likely reflects the shift from intravenous drug use (IVDU) to heterosexual sex as the more common mode of transmission to U.S. women.

The WIHS cohort includes women who are rarely recruited into U.S. clinical trials for HIV and AIDS (10a); thus, it is more reflective of the population of U.S. women infected with

TABLE 3. Cumulative female adult/adolescent AIDS and HIV infection cases in the United States and WIHS through 1995

Exposure category	% HIV/AIDS cases from ^a :							
	CDC data				WIHS data for HIV+ only			
	w (24)	b (57)	h (18)	o (1)	w (18)	b (55)	h (24)	o (3)
IVDU	40.6	43.2	43.8	28.8	38.7	34.5	30.0	25.9
Sex	37.8	34	44	41	46.4	39.9	42.6	37.1
Other	8.1	2.2	3.2	12.8	2.6	3.9	4.8	7.4
Unreported	13.1	20.6	9	17.4	12.3	21.6	22.6	29.6

^a Percentages for race/ethnic distribution are shown in parentheses. w, white; b, black; h, Hispanic; o, other.

TABLE 4. Cumulative reported HIV cases only (no AIDS) in the United States through 2001 and new WIHS HIV-positive recruits for 2001 and 2002

Exposure category	% HIV cases from ^a :							
	CDC data				WIHS data for HIV+			
	w (22)	b (66)	h (10)	o (1)	w (7)	b (56)	h (32)	o (5)
IVDU	26	15	15	19	27	9	9	12
Sex	41	39	36	40	40	39	46	38
Other	1	1	1	2	0	0	0	0
Unreported	31	45	49	39	33	51	46	50

^a Percentages for race/ethnic distribution are shown in parentheses. w, white; b, black; h, Hispanic; o, other.

TABLE 5. Clinical markers in the WIHS

HIV-positive cohort characteristic	Percentage showing characteristic in:		
	1994–1995 cohort at baseline (n = 2,059)	2001–2002 cohort at baseline (n = 738)	Combined cohort in 2002 (n = 1920)
Viral load (copies) ^a			
>4,000	72.2	34.1	34.8
2,001–4,000	17.8	6.1	6.6
80–2,000	7.7	22.9	22.3
<80	2.3	36.9	36.3
Not available	2.5	2.3	5.3
CD4 count			
<50	12.4	1.9	3.6
50–199	17.5	8.0	11.9
200–349	23.5	18.0	22.4
≥350	46.6	72.1	62.1
Not available	3.6	1.9	6.5
HAART use	0.2	65.6	76.4
AIDS ^b	33.6	3.3	36.3

^a 1994 and 1995 viral loads originally tested with a lower limit of 4,000 copies and retested with a lower limit of 80 copies with stored samples for 17% of the study cohort.

^b History of AIDS-defining illness; excludes AIDS diagnosed by CD4 count alone.

HIV. In addition to those with histories of substance abuse and unstable living situations, many WIHS participants have faced adversity throughout their lives, including physical and/or sexual abuse, limited education, unemployment, and poverty (Table 7). One-half of the women reported that their initial sexual contacts occurred by the age of 15; one in three of those was pregnant within 1 year of that event, including six women who reported that they were first pregnant by the age of 10 years. Nearly one-third of WIHS women are raising children without partners, while those infected are also managing the physical and emotional aspects of HIV and its complex therapy.

Given their high rate of poverty and unemployment, health insurance coverage for HIV-positive women is primarily through Medicaid (56%) and the AIDS Drug Assistance Program (14%). Nine percent of HIV-positive women and 36% of HIV-negative women in the study are uninsured.

TABLE 6. Comorbidity at baseline in the WIHS cohort

Parameter or condition ^a	% Comorbidity	
	Original cohort (1994–1995)	Expansion cohort (2001–2002)
HBV core antibodies	43	19
HBV surface antigen	2.6	1.4
HCV antibodies	39	13
SIL on Pap test ^a	13	8
Diabetes	4.4	4.6
Hypertension	17	12
Obesity	53	65
Smoking	58	42

^a HBV, hepatitis B virus; HCV, hepatitis C virus; SIL, squamous intraepithelial lesion. Low-grade SIL, high-grade SIL, or carcinomas were detected in situ on initial Pap smear. Obesity defined as a body mass index of >25.

Substudies and Collaborations

To address new research questions, the WIHS has actively recruited additional researchers to assist and/or lead in developing new substudies or modifications to the core study. Through one recent initiative, WIHS researchers are collecting data on and evaluating indicators of cardiovascular disease. The WIHS also serves as a platform for 34 NIH-funded projects developed by non-WIHS investigators who obtained agreement with the WIHS EC to include their protocols within the WIHS structure or to access WIHS cohort data and/or repository specimens. Once published by a collaborating researcher, new data are added to the WIHS database to further the research capabilities of the study. For example, the database has been augmented with results on antiretroviral pharmacokinetic levels, presence of GB virus type C, and HIV and human papillomavirus viral genetics. These collaborations have been timely and economically efficient, adding value to both the cohort and collaborating studies.

Examples of work by researchers working with the WIHS include the determination that, in contrast to findings in studies of male cohorts, there may be partial protection against HIV-1 associated with the CCR5Δ32 heterozygotes in women (20), the description of the presence of antibody-dependent cell-mediated cytotoxicity in cervicovaginal lavage fluids at levels that were unpredicted by serum titers and that can contribute to mucosal defense against HIV-1 (5), and the suggestion of the possible existence of a separate reservoir of HIV-1 replication in a small percentage of women who were found to have vaginal shedding of HIV-1 despite plasma HIV-1 RNA levels below 500 copies/ml (16).

WIHS STRENGTHS AND LIMITATIONS

As the focus of 250 publications thus far, the WIHS serves as a successful cohort for the study of HIV, its treatments, and related complications. The diverse multisite structure has resulted in a largely Latina population from Southern California along with predominantly African-American populations at other sites, allowing researchers to compare data from women of different ethnic minorities. Unlike clinical trials, participants in observational cohorts include those with more-complex life circumstances and who are treated by a wide range of health care providers with various treatment philosophies and regimens. Participants are not dropped from the study for lack of adherence or changes in care, nor is it dictated when therapy must begin or be changed. Hence, the WIHS cohort more closely reflects the real-world experience of HIV disease and treatment, allowing investigators to address the more complex clinical management questions of this chronic disease over time and to assess the effectiveness as well as the efficacy of interventions.

Due to the long-term nature of the study, the need to avoid overburdening participants prevents the WIHS from requesting more-frequent visits and specimen collection from the entire cohort. Because biannual visits may be insufficient to answer some research questions, short-term substudies have been utilized to gain more-frequent sampling from a limited portion of the cohort.

To date, WIHS publications have addressed HIV therapy

TABLE 7. Social demographic characteristics of study population

Characteristic	Quantification of characteristic for:					
	1994–1995 cohort at baseline		2001–2002 cohort at baseline		Combined cohort in 2002	
	HIV+	HIV–	HIV+	HIV–	HIV+	HIV–
No.	2,059	569	738	406	1,920	742
Median age in yr (range)	37 (17–73)	35 (17–62)	33 (18–62)	29 (18–53)	40 (19–80)	35 (18–69)
% Completed high school (no. missing)	62.8	63.0	59.6 (6)	64.7 (9)	62.3 (5)	64.5 (9)
% Unemployed (no. missing)	79.3 (6)	71.5 (1)	65.4 (1)	60.6	65.8 (74)	56.0 (34)
% Uninsured (no. missing)	17.6 (15)	40.3 (8)	15.5 (10)	38.8 (1)	9.0 (88)	36.0 (34)
% Single mothers	28.0	21.1	36.8	32.4	32.7	31.2
% Below poverty line (no. missing) ^a	45.9 (264)	53.8 (111)	52.3 (48)	51.0 (63)	48.9 (180)	50.8 (112)
% With unstable housing situation (no. missing) ^b	12.7 (3)	21.3	6.6	15.5	5.8 (74)	11.1 (33)
% Incarcerated ^c	NA	NA	NA	NA	11.5	10.6
% With history of abuse (no.) ^d	75.5 (981)	75.3 (275)	10.5 (52)	17 (45)	51.8 (648)	43.6 (212)

^a Poverty status determined by annual income and number of persons per household according to the U.S. government guidelines available at <http://aspe.hhs.gov/poverty/poverty.shtml>.

^b Defined as place of residence other than own apartment, parent's house, or someone else's house or apartment.

^c Only histories of incarceration while in study were available. NA, not applicable.

^d Numbers do not include California sites, where state law requiring reporting of any abuse conflicts with the WIHS guarantee of confidentiality. In other states, reporting was required only if the woman's life was in danger or she was considered a danger to those around her.

prescription and adherence patterns (8, 9, 10, 15, 19) as well as the effects of initiating HAART at different stages of HIV disease activity (1, 2). These studies could not have been done in the context of the controlled regimens and adherence requirements necessary for clinical trials. Collaborative work on coinfections such as hepatitis C (3) and human papillomavirus (21, 23, 18) in the HIV-positive cohort; on the risk of developing other comorbidities related to HIV and antiretroviral therapies, such as cancer (12), diabetes (13), and lipodystrophy (22); and on IVDU (17) and changes in sexual risk behaviors (24) have benefited largely by having a control group of HIV-negative women who match the infected cohort in sociodemographic and behavioral characteristics as well as by having both groups of HIV-positive women: those treated with HAART and those who are HAART naïve.

CONCLUSION

For 10 years, dedicated women participating in the WIHS have donated their time, personal histories, and specimens to further advance the knowledge of how HIV affects women over time, and they continue to do so. Drawn from all sectors of society, they form a unique and valuable cohort for studying the effects of HIV and its treatment.

As treatment options and outcomes change over time, the WIHS is the only study in the United States with the power of size and longevity to provide a more accurate picture of how these changes are affecting women's lives. There is significant value added for each investigator who chooses to collaborate with ongoing cohort studies, as there is the capacity to do both retrospective and prospective work utilizing the collected data, stored specimens, and the core visit structure with a proven, ongoing study population. As the course of HIV becomes increasingly complex, we believe that more of these types of collaborations will be required to answer the many questions that will need to be addressed. This cohort continues to accumulate a wealth of resources available for use by collaborating investigators and welcomes researchers who are dedicated to a better understanding of HIV infection in women.

Information and guidelines for researchers interested in utilizing these resources can be found on the WIHS website at <http://statepiaps.jhsph.edu/wihs/>.

ACKNOWLEDGMENTS

We are grateful for the guidance provided by Carolyn Williams and members of the Epidemiology Branch of DAIDS/NIAID and to the WIHS women who have given so much of themselves over the years as participants in this study.

Data presented in this work were collected by the WIHS Collaborative Study Group with centers (principal investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington, D.C., Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); and Data Coordinating Center (Alvaro Munoz).

The WIHS is funded by the National Institute of Allergy and Infectious Diseases with supplemental funding from the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute of Dental and Craniofacial Research (grants U01-AI-35004, U01-AI-31834, U01-AI-34994, U01-AI-34989, U01-AI-34993, and U01-AI-42590). Funding is also provided by the National Institute of Child Health and Human Development (grant U01-CH-32632) and the National Center for Research Resources (grants MO1-RR-00071, MO1-RR-00079, and MO1-RR-00083).

REFERENCES

- Anastos, K., Y. Barron, M. H. Cohen, R. M. Greenblatt, H. Minkoff, A. Levine, M. Young, and S. J. Gange. 2004. The prognostic importance of changes in CD4+ cell count and HIV-1 RNA level in women after initiating highly active antiretroviral therapy. *Ann. Intern. Med.* **140**:256–264.
- Anastos, K., Y. Barron, P. Miotti, B. Weisser, M. Young, N. Hessel, R. M. Greenblatt, M. Cohen, M. Augenbraun, A. Levine, A. Munoz, et al. 2002. Risk of progression to AIDS and death in women infected with HIV-1 initiating highly active antiretroviral treatment at different stages of disease. *Arch. Intern. Med.* **162**:1973–1980.
- Augenbraun, M., J. J. Goedert, D. Thomas, J. Feldman, E. C. Seaberg, A. L. French, E. Robison, M. Nowicki, and N. Terrault. 2003. Incident hepatitis C virus in women with human immunodeficiency virus infection. *Clin. Infect. Dis.* **37**:1357–1364.
- Barkan, S. E., S. L. Melnick, S. Preston-Martin, K. Weber, L. A. Kalish, P. Miotti, M. Young, R. Greenblatt, H. Sacks, and J. Feldman. 1998. The Women's Interagency HIV Study. *Epidemiology* **9**:117–125.
- Battle-Miller, K., C. A. Eby, A. L. Landay, M. H. Cohen, B. E. Sha, and L. L. Baum. 2002. Antibody-dependent cell-mediated cytotoxicity in cervical lavage fluids of human immunodeficiency virus type 1-infected women. *J. Infect. Dis.* **185**:439–447.

6. **Centers for Disease Control and Prevention.** 1996. HIV/AIDS Surveillance Report 8:2–39.
7. **Centers for Disease Control and Prevention.** 2002. HIV/AIDS Surveillance Report 13:21.
8. **Cohen, M. H., J. A. Cook, D. Grey, M. Young, L. H. Hanau, P. Tien, A. M. Levine, and T. E. Wilson.** 2004. Medically eligible women who do not use HAART: the importance of abuse, drug use, and race. *Am. J. Public Health* 94:1147–1151.
9. **Cole, S. R., M. A. Hernan, J. M. Robins, K. Anastos, J. Chmiel, R. Detels, C. Ervin, J. Feldman, R. Greenblatt, L. Kingsley, S. Lai, M. Young, M. Cohen, and A. Munoz.** 2003. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. *Am. J. Epidemiol.* 158:687–694.
10. **Cook, J. A., M. H. Cohen, D. Grey, L. Kirstein, J. Burke, K. Anastos, H. Palacio, J. Richardson, T. E. Wilson, and M. Youn.** 2002. Use of highly active antiretroviral therapy in a cohort of HIV-seropositive women. *Am. J. Public Health* 92:82–87.
- 10a. **Gandhi, M., N. Ameli, P. Bacchetti, G. B. Sharp, A. L. French, M. Young, S. J. Gange, K. Anastos, S. Holman, A. Levine, and R. M. Greenblatt.** Eligibility criteria for HIV clinical trials and generalizability of results: the gap between published reports and study protocols. *AIDS*, in press.
11. **Hessol, N. A., M. Schneider, R. M. Greenblatt, M. Bacon, Y. Barrantay, S. Holman, E. Robison, C. Williams, M. Cohen, and K. Weber.** 2001. Retention of women enrolled in a prospective study of human immunodeficiency virus infection: impact of race, unstable housing, and use of human immunodeficiency virus therapy. *Am. J. Epidemiol.* 154:563–573.
12. **Hessol, N., E. Seaberg, S. Preston-Martin, L. S. Massad, H. S. Sacks, S. Silver, S. Melnick, O. Abulafia, and A. M. Levine for the WIHS Collaborative Study Group.** 2004. Cancer risk among participants in the Women's Interagency HIV Study. *J. Acquir. Immune Defic. Syndr.* 36:978–985.
13. **Justman, J. E., L. Benning, A. Danoff, H. Minkoff, A. Levine, R. M. Greenblatt, K. Weber, E. Piessens, E. Robison, and K. Anastos.** 2003. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J. Acquir. Immune Defic. Syndr.* 32:298–302.
14. **Kaslow, R. A., D. G. Ostrow, R. Detels, J. P. Phair, B. F. Polk, and C. R. Rinaldo, Jr.** 1987. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am. J. Epidemiol.* 126:310–318.
15. **Kirstein, L. M., R. M. Greenblatt, K. Anastos, A. Levine, A. L. French, H. Minkoff, S. Silver, S. J. Gange, et al.** 2002. Prevalence and correlates of highly active antiretroviral therapy switching in the Women's Interagency HIV Study. *J. Acquir. Immune Defic. Syndr.* 29:495–503.
16. **Kovacs, A., S. S. Wasserman, D. Burns, D. J. Wright, J. Cohn, A. Landay, K. Weber, M. Cohen, A. Levine, H. Minkoff, P. Miotti, J. Palefsky, M. Young, P. Reichelderfer, and the DATRI Study Group.** 2001. Determinants of HIV-1 shedding in the genital tract of women. *Lancet* 358:1593–1601.
17. **Landay, A., L. Benning, J. Bremer, B. Weiser, H. Burger, M. Nowicki, and A. Kovacs.** 2003. Correlates of immune activation marker changes in human immunodeficiency virus (HIV)-seropositive and high-risk HIV seronegative women who use illicit drugs. *J. Infect. Dis.* 188:209–218.
18. **Massad, L. S., M. J. Silverberg, G. Springer, H. Minkoff, N. Hessol, J. M. Palefsky, H. D. Strickler, A. M. Levine, H. S. Sacks, M. Moxley, and H. D. Watts.** 2004. Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus. *Am. J. Obstet. Gynecol.* 190:1241–1248.
19. **Palacio, H., X. Li, T. E. Wilson, H. Sacks, M. H. Cohen, J. Richardson, M. Young, A. Munoz, and the Women's Interagency HIV Study (WIHS).** 2004. Healthcare use by varied highly active antiretroviral therapy (HAART) strata: HAART use, discontinuation, and naivety. *AIDS* 18:621–630.
20. **Philpott, S., B. Weiser, P. Tarwater, S. H. Vermund, C. A. Kleeberger, S. J. Gange, K. Anastos, M. Cohen, R. M. Greenblatt, A. Kovacs, H. Minkoff, M. A. Young, P. Miotti, M. Dupuis, C. H. Chen, and H. Burger.** 2003. CC chemokine receptor 5 genotype and susceptibility to transmission of human immunodeficiency virus type 1 in women. *J. Infect. Dis.* 187:569–575.
21. **Strickler, H. D., J. M. Palefsky, K. V. Shah, K. Anastos, R. S. Klein, H. Minkoff, A. Duerr, L. S. Massad, D. D. Celentano, C. Hall, M. Fazzari, S. Cu-Uvin, M. Bacon, P. Schuman, A. M. Levine, A. J. Durante, S. Gange, S. Melnick, and R. D. Burke.** 2003. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. *J. Natl. Cancer Inst.* 95:1062–1071.
22. **Tien, P. C., S. R. Cole, C. M. Williams, R. Li, J. E. Justman, M. H. Cohen, M. Young, N. Rubin, M. Augenbraun, and C. Grunfeld.** 2003. Incidence of lipoatrophy and lipohypertrophy in the Women's Interagency HIV Study. *J. Acquir. Immune Defic. Syndr.* 34:461–466.
23. **Viscidi, R. P., L. Ahdieh-Grant, B. Clayman, K. Fox, L. S. Massad, S. Cu-Uvin, K. V. Shah, K. M. Anastos, K. E. Squires, A. Duerr, D. J. Jameison, R. D. Burke, R. S. Klein, H. Minkoff, J. Palefsky, H. Strickler, P. Schuman, E. Piessens, and P. Miotti.** 2003. Serum immunoglobulin G response to human papillomavirus type 16 virus-like particles in human immunodeficiency virus (HIV)-positive and risk-matched negative women. *J. Infect. Dis.* 187:194–205.
24. **Wilson, T. E., M. E. Gore, R. Greenblatt, M. Cohen, H. Minkoff, S. Silver, E. Robison, A. Levine, and S. J. Gange.** 2004. Changes in sexual behavior among HIV-infected women after initiation of HAART. *Am. J. Public Health* 94:1141–1146.