WOMEN'S INTERAGENCY HIV STUDY

SECTION 4: STUDY DESIGN

A. STUDY DESIGN

The Women's Interagency HIV Study (WIHS) is a multicenter longitudinal study funded by the National Institutes of Health (National Institute of Allergy and Infectious Diseases, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Drug Abuse, and National Cancer Institute) to investigate the progression of HIV disease in women.

The WIHS is conducted at six clinical sites, including a New York City Consortium; the State University of New York at Brooklyn; a Washington, D.C., Consortium; a Los Angeles, Southern California Consortium; a San Francisco/Bay Area Consortium, and a Chicago Consortium. The WIHS Data Management and Analysis Center (WDMAC) is located at the Johns Hopkins University Bloomberg School of Public Health, in Baltimore, Maryland.

All study participants undergo an initial screening to determine study eligibility. If the study participant is willing to take part in the study and gives informed consent, she will participate in an in-depth interview, physical exam, and specimen collection.

The data collected at each visit will include the following: medical and health history, obstetric/gynecological and contraceptive history, health care utilization, sexual behavior, usage of drugs and alcohol, psychosocial factors, sociodemographics, laboratory parameters and a physical and gynecological examination.

Initial enrollment into the WIHS occurred between October 1994 and November 1995. The total initial enrollment for the WIHS was 2,056 HIV-seropositve women and 569 HIV-seronegative women. The following chart reflects the numbers of HIV-seropositive and -seronegative women enrolled into the initial WIHS cohort at each site.

SITE	NUMBER OF POSITIVES	NUMBER OF NEGATIVES	**TOTAL ENROLLMENT**
Bronx	416	120	**536**
Brooklyn	312	86	**398**
Washington, D.C.	295	102	**397**
Los Angeles	421	112	**533**
San Francisco	338	90	**428**
Chicago	274	59	**333**
TOTALS	**2056**	**569**	**2625**

Between October 2001 and October 2002, the WIHS re-opened enrollment into the cohort. The following table shows the composition of the new WIHS recruits for each clinical site.

SITE	HIV +/AIDS-FREE/HAART-NAIVE	HIV +/AIDS-FREE/ HAART	HIV-	**TOTAL ENROLLMENT**
Bronx	37	92	104	**233**
Brooklyn	48	98	70	**216**
Washington, D.C.	42	80	49	**171**
Los Angeles	32	117	79	**228**
San Francisco	52	39	61	**152**
Chicago	44	57	40	**141**
TOTALS	**255**	**483**	**403**	**1141**

Total enrollment for both initial and new recruits is as follows:

SITE	NUMBER OF POSITIVES	NUMBER OF NEGATIVES	**TOTAL ENROLLMENT**
Bronx	545	224	**769**
Brooklyn	458	156	**614**
Washington, D.C.	417	151	**568**
Los Angeles	570	191	**761**
San Francisco	429	151	**580**
Chicago	375	99	**474**
TOTALS	**2794**	**972**	**3766**

Between January 2011 and December 2012, WIHS again opened enrollment, in order to replace those women who had died since the second enrollment (i.e., since October 1, 2002). Estimated target numbers for this enrollment are as follows:

SITE	**HIV+ TARGET**	**HIV- TARGET**	**TOTAL TARGET**
Bronx	67	28	95
Brooklyn	30	12	42
Washington, D.C.	36	15	51
Los Angeles	45	19	64
San Francisco	62	26	88
Chicago	53	22	75
TOTAL	**293**	**122**	**415**

For 2011/12 recruits, there are maximum targets allowed for both Latina/Hispanic women and for women with prior "clinical"AIDS diagnoses (this excludes women with only CD4 counts <200). Latina/Hispanic women should be kept to 10% of the maximum total target for all sites except LA, where the number of Latina/Hispanic women should be kept to 20% of the maximum total target. Women with prior clinical AIDS diagnoses should be kept to 10% of the HIV-positive target for each site. Sites may be allowed to exceed these targets if they trade with another WIHS site, for example if the Brooklyn site agrees to enroll fewer than their target number of Latina/Hispanic women then LA would be able to enroll over their target number of Latina/Hispanic women. These "trades" should be coordinated with the WIHS IV replenishment coordinating committee (Mardge Cohen, Nancy Hessol, and Christine Alden). Please check with your site PD prior to enrolling any new participant to ensure that targets are not exceeded.

B. RECRUITMENT STRATEGIES

The procedures used for recruitment may vary by site. Regardless of methods used, however, sites recruited HIV-seronegative and seropositive women the same way to ensure comparability of the cohorts. Sites reviewed and monitored enrollment demographics (including age, race, IDU and sexual behavior) to make certain the cohorts were matched.

For the purpose of the 2001/02 and 2011/12 recruits, seronegative women enrollees must meet one of the below listed high-risk exposure criteria within the year prior to screening in order to enroll:

- Reported injection drug use, or use of crack, cocaine, heroin, or methamphetamine (2011/12 recruits only)
- Diagnosis by a health care provider with an STD
- Reported having unprotected sex with three or more men
- Reported having sex for drugs, money, or shelter

- Reported having sex with six or more men
- Reported having sex with known HIV-positive man

C. MONITORING OF NEW RECRUIT ENROLLMENT

WDMAC set up a report in Apollo (the web-based data management system) for tracking characteristics of new enrollees. The report utilizes data from the *Eligibility Form (EL)* and displays: (1) characteristics of women enrolled at the site (i.e., categories of IDU status and race/ethnicity, and distribution of ages) cross-tabulated with enrollment group (e.g., HIV-, HIV+), and (2) site-specific targets for enrollment.

Sites reviewed and monitored recruitment on the local site level to ensure comparability of the cohorts. For 2001/02 recruits, these reports were reviewed on a monthly basis by the Admin/Stat working group. For 2011/12 recruits, these reports were reviewed regularly by PDs to ensure that targets were being met but not exceeded.

For the 2011/12 enrollment, those recruits that need extra monitoring include those who are Latina/Hispanic and those with prior "clinical" AIDS diagnoses (excludes prior CD4 count <200). To ensure that sites do not overenroll in these categories, maximum targets have been established by site. For Latina/Hispanic women, no more than 10% of the maximum total target should be enrolled for all sites except LA, where the number of Latina/Hispanic women should be kept to 20% of the maximum total target. For women with prior "clinical" AIDS diagnoses, no more than 10% of the HIV-positive target for each site should be enrolled. Please check with your site PD prior to enrolling any new participant to ensure that targets are not exceeded in any category.

D. ELIGIBILITY CRITERIA

1. WIHS ELIGIBILITY CRITERIA FOR 1994/95 RECRUITS

   Women must meet the following criteria to be eligible to participate in the WIHS:

   - Women must be 13 years old or older. There is no restriction on the upper age limit. Individual sites may set their own (more restrictive) limits to satisfy local IRBs.
   - Women must be able and willing to give informed consent.
   - Women must agree to be re/tested for HIV for the WIHS.
   - Women must be able to complete the interview in English or Spanish.
   - Women must be able to travel to and from the site/clinic and participate in a baseline visit as an outpatient.
   - Women must be willing and able to have blood drawn for laboratory testing by venous or arterial access.

2. WIHS ELIGIBILITY CRITERIA FOR 2001/02 RECRUITS

   Women must meet all of the above criteria in addition to the following:

   - If HIV-positive, women must be free of clinical AIDS-related conditions evidenced through both self-report and any medical record abstractions that are performed. In screening, the women will not be asked to self report cervical cancer due to the large amount of over-reporting that occurs in the WIHS. Instead, participants will be asked about cervical cancer during their baseline interview. Additionally, if a woman self-reports an AIDS-defining condition during screening that sites can refute through medical record abstraction, the woman will still be eligible for enrollment.
   - Documented HAART and pre-HAART CD4 counts and HIV RNA quantification, if appropriate (i.e., HIV-positive, self-reported HAART).

- If hardcopy documentation of a positive result from both an HIV ELISA test and a confirmatory Western Blot are available, blood need not be drawn and women need not agree to be retested for HIV.
- Women must consent to have their specimens stored in the WIHS national repository.

Women who acquired HIV perinatally will not be eligible for enrollment.

3. WIHS ELIGIBILITY CRITERIA FOR 2011/12 RECRUITS

Women must meet all of the above criteria, in addition to the following:

- HAART users must have started their first HAART regimen subsequent to December 31, 2004, unless the HAART use was during pregnancy or for PEP/PrEP only.
- Women must be between ages 30 through 55 for HIV-positive recruits; ages 35 through 60 for HIV-negative recruits.
- Women must not have ever used ddI (Videx, didanosine), ddC (Hivid, zalcitabine) or d4T (Zerit, stavudine) unless use was **only** during pregnancy or for PEP/PrEP.
- Women may not be on non-HAART ART at time of enrollment and must not have used ART before starting HAART, unless use was **only** during pregnancy or for PEP/PrEP.
- Women must be biologically female at birth.

NOTE: Participants with prior "clinical" AIDS diagnoses are eligible for enrollment in 2011/12 as long as the total number enrolled doesn't exceed 10% of the total HIV-positive target.

4. COENROLLMENT

For the 1994/95 recruits, women were ineligible for enrolling in the WIHS if they were currently participating in similar studies. These included:

- WITS (Women and Infant Transmission Study)
- HERS (HIV Epidemiology Research Study)
- Other studies that may be active at the site

Sites with other local studies that conflicted with full participation in the WIHS brought this to the attention of the WIHS Executive Committee. The Executive Committee decided whether participation in the other study deemed the participant ineligible for the WIHS.

These coenrollment exclusions are not pertinent to the new recruits. If a woman becomes pregnant while enrolled in the WIHS, she may co-enroll in the WITS.

However, a woman should not be enrolled as a new recruit in the WIHS if she is already enrolled in the WIHS through another site or subsite.

E. SCREENING AND ENROLLMENT PROTOCOL FOR NEW RECRUITS

Screening procedures vary from site to site. Some sites recruited participants primarily from their current clinic population, approaching women at the time of their care visits. Under this scenario, sites had complete access to medical records, allowing them schedule the screening "visit" on the same day as enrollment and administration of the baseline visit. Other sites recruited women from outreach centers and community populations, requiring those sites to request medical records for abstraction. Women recruited through these procedures needed to have a separate screening visit, followed by chart abstraction and an enrollment visit. While part of the reason for a separate screening and baseline visit was to ensure women remain committed to the study, women who would

be identified through clinic populations are not at as large a risk for loss to follow-up, while the women more at risk (i.e., recruited from the community) would be required to have separate visits.

For 2001/02 recruits, where possible, sites aimed for enrollment of 10-15% over the projected numbers. This over-enrollment was in anticipation of the loss to follow-up expected to occur between the first and second visits of the new recruits.

The procedures outlined in this section are meant to be flexible. Sites could accommodate the actual screening procedures to fit best with their site's enrollment plan. Whether on the same or separate days, screening and enrollment should contain the following and happen in the following order:

1. SCREENING VISIT
    a. Screening ID

        Assignment of unique Screening IDs will be the responsibility of the site. Sites may use characters and/or numbers for the Screening ID.

    b. Consent Forms

        - Screening consent forms
        - Medical record release forms (if indicated)
        - HIV antibody testing consent, including counseling (if indicated)

    c. *Screening Form (SCR)* (interview-administered or filled out by the site)

        The *Screening Form* will collect information on consent dates, race, age, AIDS-defining illnesses, antiretroviral medication history, and behavioral information on IDU and high-risk sexual behavior. Parts of this form will be data entered, but only if a participant is enrolled into the WIHS. If sites choose to obtain the information for this form without administering the form to the participant, they must be sure to obtain all required consents and to document the participant's language preference.

    d. Lab specimens / tests

        L01: HIV test. (See **Section 4F** for details on indications for this test.)

    e. Participant locator form (site-specific form)

2. Medical Record Abstraction (MRA)
    a. Indications for MRA
        i. Self-reported Highly Active Antiretroviral Therapy (HAART) user (HIV+ women only)
            1. If a participant reports in her screening interview that she has ever taken one of the following:
                - any protease inhibitor (PI);
                - any non-nucleoside reverse transcriptase inhibitor (NNRTI);
                - Ziagen (abacavir) or Viread (tenofovir) or Trizivir (ABC + AZT + 3TC) or Truvada (tenofovir + FTC);
                - HAART, cocktails, or three-drug combination therapy;
                - an entry or integrase inhibitor (i.e., Fuzeon, Selzentry or Isentress);

                then sites must verify the required therapy information on the *Retroactive Abstraction (RAB) Form* through MRA. Abstractionists should begin abstraction of

therapy information with medical records six months prior to the earliest reported date of any of the therapies listed above.

2. If a participant reports use of HAART only during a pregnancy and is HAART naïve otherwise, this woman should be classified as "HIV+/HAART," and sites must verify the required therapy information on the *RAB Form* through MRA. An appropriate note of this information should be recorded on the *RAB Form* in the question that asks specifically about pregnancy and HAART use.
3. If a participant was prescribed HAART according to the medical records, took HAART for a very short time, and then stopped HAART almost immediately, this woman should be categorized in the HIV+/HAART enrollment category, and date of first HAART prescription should be noted on the *RAB Form*. A note can be made in the additional comment field documenting the short-term use of HAART.
4. If a participant reports that she has never taken any of the therapies listed in (1) above, then sites do not have to verify this report through MRA. These women should be put in the "HIV+/HAART naïve" category if they are otherwise eligible for enrollment.

NOTE: As of December 3, 2001, medical record abstraction must be performed on all participants who report that they are HAART naïve. For those women who have already been enrolled into the study, retrospective medical record abstraction must be performed. The review on these participants is limited to the medical record charts held by the participant's current primary care provider (PCP). If a participant does not have a PCP, no review is required.

If use of HAART is found during medical record abstraction, sites should classify the participant as HAART-experienced on the *Eligibility Form (EL)* and a *RAB Form* should be completed. If a participant was already enrolled as HAART naïve, but abstraction shows that HAART was taken, edit her *Eligibility Form* so that she is reclassified as HAART-experienced, and complete a *RAB Form*. If she was enrolled as HAART naïve and her current primary care chart confirms this, no further action is needed.

5. If a participant reports taking antiretroviral medications (in general or a specific ART class) but cannot remember the exact name of the medication(s), sites must review the medical records to abstract the date of HAART initiation. This information must be recorded on the *RAB Form*. If the participant is unable to provide enough information to enable chart review (place and approximate date) or if records cannot be obtained or if the records do not accurately document her as HAART naïve or her first HAART date, then the participant is ineligible for enrollment.

ii. Self-reported AIDS-defining conditions (HIV+ women only)

1. No abstraction is required for self-reported AIDS-defining conditions.
2. If a 2001/02 enrollment candidate reports ever having had a clinical AIDS-defining illness, she is initially not eligible for enrollment. Sites have the following options:
   - Sites can perform chart abstraction to refute this report. If sites can document through MRA that the report was false, then a note should be made in the "Additional Comments" section of the *RAB Form* and the woman will be eligible for enrollment.

- If sites do not perform chart abstraction to refute the reported AIDS-defining illness, the woman is permanently ineligible for enrollment.

There are a few potentially problematic conditions that a woman may say "YES" to that are, in fact, not AIDS-defining illnesses. Conditions that might be erroneously reported, and that might warrant further review through record abstraction, include oral versus candida esophagitis, candida in the lungs/airways, herpes simplex virus or HSV (cutaneous x 30 days, lungs or esophagus; the AIDS-defining herpes is the chronic presence, without remission of a single ulceration), wasting, non-PCP pneumonia, the diarrheas, tuberculosis, and salmonella. If a participant reports "YES' to any of these conditions, a designated person at the site (with a reasonable amount of clinical experience) should determine whether this participant is eligible or ineligible for enrollment. Provider reports should be used for verification where necessary.

NOTE: If a 2011/12 enrollment candidate reports a prior "clinical" AIDS diagnosis, she will be eligible for enrollment as long as the total number enrolled doesn't exceed 10% of the total HIV-positive target.

b. Retrospective Abstraction Form (RAB)

This form will capture the antiretroviral therapy data that is abstracted from the medical records. This form will be data entered for all women enrolled in the WIHS who are indicated for MRA at the screening/enrollment visit.

There is a section of the form that captures abstraction data that is <u>required</u> for an individual to be eligible for the study, and a section that captures abstraction data that is <u>supplemental</u> information and not required for an individual to be eligible for the study. ALL abstraction information in the required section must be complete for a participant to be eligible for enrollment into the WIHS, with the exception of (1) prescribed dosages for first HAART regimen, and (2) CD3 and CD8 cell counts and percentages.

i. Required MRA information

1. Information indicating whether the participant was ever on HAART
2. Date that HAART was first prescribed
3. Drugs that comprised first HAART regimen (and start date of each)
4. At least one blood draw at, or within six months prior to, initial HAART date for which both a HIV RNA result and a T-cell count are available.

ii. Supplemental MRA information (sites have the option of gathering or not gathering these data based on their access to medical records and abstractionists)

1. Participant's use of ART prior to first HAART date
2. Additional HAART regimens participant was prescribed after her initial HAART regimen
3. Additional HIV RNA results and T-cell counts prior to the required markers listed above and within six months of HAART initiation
4. All available HIV RNA results and T-cell counts post HAART initiation.

3. ENROLLMENT VISIT

   a. WIHSID

      All women enrolled into the WIHS will be assigned an 8-digit WIHSID of the form S-**2**B-PPPP-C for 2001/02 recruits, or S-**3**B-PPPP-C for 2011/12 recruits. All sites adding new subsites should use the "B" digit to identify the new subsites. Assignment of the WIHSID will be the responsibility of the site.

   b. *Eligibility Form (EL)*

      This form is filled out by site personnel to determine whether or not a screening candidate is eligible for enrollment into the WIHS. Much of this information can be obtained from the *Screening Form (SCR)*. To be deemed eligible for enrollment, women should have a completed *SCR Form* and a completed *EL Form* that indicate the participant is eligible and has agreed to enroll into the WIHS.

   c. Consent Forms for enrollment into the WIHS

   d. Interview Forms / Medical Exams / Laboratory specimens and tests

      See **MOO, Section 6** (*Overview of the Baseline Visit for New Recruits*).

   e. Substudy recruitment

      Substudy recruitment should follow the same procedures outlined for the original recruits in **MOO, Section 7**.

   f. Post-test HIV counseling (if indicated)

F. HIV TESTING

1. HIV TESTING FOR 1994/95 RECRUITS

   HIV testing (or retesting) is required of all women participating in the WIHS. The testing may be done either at the time of screening, between screening and the first baseline visit, or at the time of the baseline visit.

   Results from HIV testing that occurred prior to screening may be used to provide provisional HIV serostatus for the *Screening Form*. These results, however, are only provisional; <u>all women, regardless of known serostatus</u> will need to be retested before enrollment into the WIHS. Once the WIHS HIV test is done and the appropriate laboratory form completed and data entered, it is these results which will trigger the woman's classification. No other results will be acceptable for actual HIV status and classification.

   If a woman tests HIV-seronegative at screening or between screening and the baseline visit, she must have her baseline visit within 30 days (and no longer than 60 days) of the seronegative test. The reason for this window is to minimize the possibility that the woman will seroconvert by the time baseline study visit data are collected on her.

   Please note that sites should use their judgment to determine if it is appropriate to proceed immediately into the baseline visit on the same day a woman is told about her HIV test results, particularly if it is the first time she has been tested for HIV.

2. HIV TESTING FOR NEW (2001/02 and 2011/12) RECRUITS

   HIV testing is required for all women participating in the WIHS who report that they are HIV-negative. HIV-positive women are not required to be retested for HIV if there is hardcopy documentation of a positive ELISA test with a confirmatory Western Blot. <u>Hardcopy results of this test must be transferred to a WIHS *Form L01 (HIV 1/2 ELISA and Western Blot Results)* and</u>

data entered into the WIHS database. If sites are unable to provide this documentation, self-reporting HIV-positive women must be retested.

If a woman tests HIV-seronegative at screening or between screening and the baseline visit, she must have her baseline visit within 30 days (and no longer than 60 days) of the seronegative test. The reason for this window is to minimize the possibility that the woman will seroconvert by the time baseline study visit data are collected on her.

Please note that sites should use their judgment to determine if it is appropriate to proceed immediately into the baseline visit on the same day a woman is told about her HIV test results, particularly if it is the first time she has been tested for HIV.