Cohort Profile: The Women's Interagency HIV Study (WIHS)

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Why was the cohort set up?

The National Institutes of Health established the Women's Interagency HIV Study (WIHS) in 1993 to study the impact and progression of HIV infection among women in response to the rising number of AIDS cases and the relative paucity of clinical, behavioural and epidemiological data in this population. Women now comprise more than 50% of people with HIV (PWH) worldwide.[1] The WIHS is the largest and oldest ongoing prospective cohort study of women with and at risk for HIV infection in the world, and remains the leading study to document the experience of women with HIV (WWH) in the United States.

The cohort's scope of data collection and research has expanded considerably since the two previous publications that described the methodology and profile of the study in its early years.[2,3] Current areas of research include, but are not limited to: HIV-related comorbidities; epidemiological methods; genetics; frailty and ageing; behavioural and social determinants of health; pharmacology; and studies related to pursuit of an HIV cure. The purpose of this paper

is to update researchers on the substantial expansion of the cohort, its methods and the available data.

Who is in the cohort?

The six original cohort sites were in Brooklyn, NY; the Bronx/Manhattan, NY; Washington, DC; Chicago, IL; San Francisco, CA; and Los Angeles, CA. Since 1997, the WIHS Data Management and Analysis Center (WDMAC) has been located in Baltimore, MD. Four southern sites were added in 2013: Chapel Hill, NC; Atlanta, GA; Birmingham, AL/Jackson, MS; and Miami, FL. The Los Angeles site discontinued active follow-up in 2013.

The cohort enrolled 4982 women who at baseline were: either HIV-seropositive (3677); or HIV-seronegative (1305; 26 of them acquired HIV during follow-up) with a history of sexually transmitted infections (STIs) or behavioural or demographic characteristics that increased their risk of acquiring HIV. Enrolment occurred during four waves: 1994-95 (2054 HIV+; 569 HIV-); 2001–02 (737 HIV+, 406 HIV-), 2011-12 (276 HIV+; 95 HIV-); and 2013-15 (610 HIV+; 235 HIV-). Eligibility criteria were similar throughout the study, but varied from wave to wave to increase representativeness of the cohort.[2,3]

The most recent enrolment wave during 2013–15 (Wave 4) enrolled women between the ages of 25 and 60 years. WWH were required to have documentation of a reactive HIV serology and confirmatory test. Women who used anti-retroviral therapy (ART) were eligible only if all of their regimens met criteria for highly active antiretroviral therapy (HAART), as defined by the US consensus treatment recommendations.[4] Those who used non-HAART regimens were eligible only if use occurred during pregnancy or HIV pre- or post-exposure prophylaxis. Documentation of CD4+ T cell counts and HIV RNA quantification before initiation of HAART was required.

HIV-seronegative women were eligible for Wave 4 if they had at least one high-risk exposure in the preceding 5 years [e.g. STI diagnosis; sex without a condom with three or more men; sex with a condom with six or more men; trading sex; sex with an HIV-seropositive man; injection drug use (IDU) or use of crack cocaine, cocaine, heroin or methamphetamine; or any partner who had any of the previously mentioned risk characteristics]. Wave 3 enrolled women between the ages of 30 and 55 years, but eligibility criteria were otherwise similar to those of Wave 2.[3] During Wave 4, investigators used word of mouth and flyers to recruit participants from community-based organizations and medical, STI and family planning clinics.

Since the beginning of the study in 1993, 1268 participants have died, 130 have withdrawn from the study, 806 were discontinued for administrative reasons (such as termination of a site's participation or decreased funding that required sites to decrease enrolment), and 415 have been lost to follow-up. (Table 1) As of October 2016, the WIHS is actively following 2363 women.

A unique aspect of the WIHS is its enrolment of demographically similar HIV-seronegative women. The age and racial/ethnic distributions of seronegative participants are similar to those of WWH in the cohort (Black 72%, White 11%, Hispanic 14% and Other 3%) who, in turn, are generally representative by race/ethnicity of WWH in the USA (Black 59%, White 17%, Hispanic 19% and Other 5%). Tables 2 and 3 outline some key demographic, behavioural and clinical characteristics of active participants as of 2016 (visit 44). Most participants are poor; 64% of HIV-seropositive and 56% of HIV-seronegative participants report an annual household income of $18 000 or less.

Table 1. Disposition of participants in the Women's Interagency HIV Study, by enrolment wave and baseline HIV status[a]

	Wave 1		Wave 2		Wave 3		Wave 4		All Waves	
	HIV- $N = 569$	HIV+ $N = 2054$	HIV- $N = 406$	HIV+ $N = 737$	HIV- $N = 95$	HIV+ $N = 276$	HIV- $N = 235$	HIV+ $N = 610$	HIV- $N = 1305$	HIV+ $N = 3677$
Active[b]	207 (36)	508 (25)	217 (53)	354 (48)	78 (82)	209 (76)	214 (91)	576 (94)	716 (55)	1647 (45)
Deceased[c]	95 (17)	1016 (49)	16 (4)	113 (15)	2 (2)	13 (5)	5 (2)	8 (1)	118 (9)	1150 (31)
Withdrew from the study	26 (5)	62 (3)	15 (4)	21 (3)	3 (3)	1 (< 1)	1 (< 1)	1 (< 1)	45 (3)	85 (2)
Administrative disenrolment[d]	144 (25)	319 (16)	116 (29)	177 (24)	6 (6)	38 (14)	3 (1)	3 (< 1)	269 (21)	537 (15)
Lost to follow-up[e]	97 (17)	149 (7)	42 (10)	72 (10)	6 (6)	15 (5)	12 (5)	22 (4)	157 (12)	258 (7)

[a]Dates of enrolment were: Wave 1 = 1994–95; Wave 2 = 2001–02; Wave 3 = 2011–12; Wave 4 = 2013–15.

[b]Participants were considered 'active' if they attended at least one visit between October 2015 and September 2016. Among active participants who were HIV-seronegative at baseline, 14 seroconverted during WIHS follow-up (11 from Wave 1, two from Wave 2 and one from Wave 3).

[c]Among deceased participants who were HIV-seronegative at baseline, eight seroconverted during WIHS follow-up (six from Wave 1 and two from Wave 2) and two seroconverted after last WIHS visit (one from Wave 1 and one from Wave 2).

[d]Examples of reasons for administrative disenrollment include termination of a site's participation or decreased funding that required sites to decrease enrollment. Among administratively disenrolled participants who were HIV-seronegative at baseline, 1 seroconverted during WIHS follow-up (Wave 2).

[e]Among lost to follow-up participants who were HIV-seronegative at baseline, one seroconverted during WIHS follow-up Wave 1.

Table 2. Demographic and behavioural characteristics of currently active participants in the Women's Interagency HIV Study, by enrolment wave[a] and HIV status at last WIHS visit

	Wave 1		Wlave 2		Wave 3		Wave 4		All Waves	
	HIV- $N = 196$	HIV+ $N = 519$	HIV- $N = 215$	HIV+ $N = 356$	HIV- $N = 77$	HIV+ $N = 210$	HIV- $N = 214$	HIV+ $N = 576$	HIV- $N = 702$	HIV+ $N = 1661$
Demographics[b]										
Median age (IQR)	56 (49, 61)	56 (52, 61)	43 (37, 50)	48 (42, 52)	53 (47, 58)	49 (42, 53)	46 (37, 53)	47 (39, 53)	49 (41, 55)	51 (44, 56)
Race/ethnicity										
Black, non-Hispanic	128 (65)	308 (59)	135 (63)	245 (69)	65 (84)	163 (78)	178 (83)	477 (83)	506 (72)	1193 (72)
White, non-Hispanic	19 (10)	91 (18)	13 (6)	21 (6)	2 (3)	18 (9)	19 (9)	52 (9)	53 (8)	182 (11)
Hispanic/Latina	38 (19)	102 (20)	54 (25)	72 (20)	4 (5)	21 (10)	12 (6)	40 (7)	108 (15)	235 (14)
Other[c]	11 (6)	18 (3)	13 (6)	18 (5)	6 (8)	8 (3)	5 (2)	7 (1)	35 (5)	51 (3)
Heterosexual	163 (83)	452 (87)	170 (79)	320 (90)	66 (86)	184 (88)	178 (83)	536 (93)	577 (82)	1492 (90)
Less than high school education	61 (31)	170 (33)	75 (35)	120 (34)	21 (28)	77 (37)	62 (29)	178 (31)	219 (31)	545 (33)
Married or partnered	55 (28)	129 (25)	68 (32)	105 (29)	20 (26)	56 (27)	54 (25)	136 (24)	197 (28)	426 (26)
Unstable housing	6 (3)	16 (3)	5 (2)	12 (3)	8 (10)	8 (4)	14 (7)	29 (5)	33 (5)	65 (4)
Annual household income $\leq$ \$18 000	100 (51)	291 (56)	104 (48)	203 (57)	58 (75)	141 (67)	133 (62)	424 (74)	395 (56)	1059 (64)
Employed	67 (34)	145 (28)	92 (43)	152 (43)	25 (32)	68 (32)	87 (41)	208 (36)	271 (39)	573 (35)
Health insurance										
Any	169 (86)	490 (94)	185 (86)	341 (96)	73 (95)	201 (96)	131 (61)	544 (94)	558 (79)	1576 (95)
Medicaid	103 (53)	331 (64)	120 (56)	242 (68)	55 (71)	149 (71)	71 (33)	272 (47)	349 (50)	994 (60)
Medicare	47 (24)	159 (31)	17 (8)	57 (16)	15 (19)	33 (16)	24 (11)	99 (17)	103 (15)	348 (21)
Commercial/private	48 (24)	131 (25)	52 (24)	74 (21)	11 (14)	35 (17)	42 (20)	100 (17)	153 (22)	340 (20)
Military/student/other	68 (35)	174 (34)	86 (40)	114 (32)	20 (26)	70 (33)	24 (11)	29 (5)	198 (28)	387 (23)
AIDS Drug Assistance Program	0 (0)	85 (16)	0 (0)	68 (19)	0 (0)	39 (19)	0 (0)	273 (47)	0 (0)	465 (28)
Behavioural[b]										
Injection drug use										
Ever, reported at baseline	48 (24)	160 (31)	23 (11)	34 (10)	19 (25)	21 (10)	14 (7)	40 (7)	104 (15)	255 (15)
During WIHS follow-up	24 (12)	60 (12)	19 (9)	9 (3)	5 (6)	9 (4)	3 (1)	5 (1)	51 (7)	83 (5)
Past 6 months	3 (2)	3 (1)	3 (1)	4 (1)	2 (3)	3 (1)	0 (0)	1 (< 1)	8 (1)	11 (1)
Use of non-injection illicit drugs										
Ever, reported at baseline	136 (69)	390 (75)	160 (74)	224 (63)	68 (88)	148 (70)	157 (73)	370 (64)	521 (74)	1132 (68)
During WIHS follow-up	129 (66)	310 (60)	156 (73)	174 (49)	53 (69)	116 (55)	104 (49)	232 (40)	442 (63)	832 (50)
Past 6 months	45 (23)	87 (17)	68 (32)	71 (20)	32 (42)	63 (30)	69 (32)	127 (22)	214 (30)	348 (21)
Marijuana use										
Ever, reported at baseline	128 (65)	361 (70)	146 (68)	207 (58)	65 (84)	130 (62)	142 (66)	317 (55)	481 (69)	1015 (61)
During WIHS follow-up	113 (58)	272 (52)	137 (64)	150 (42)	47 (61)	94 (45)	92 (43)	194 (34)	389 (55)	710 (43)
Past 6 months	37 (19)	78 (15)	56 (26)	62 (17)	21 (27)	55 (26)	62 (29)	108 (19)	176 (25)	303 (18)

(continued)

Table 2. Continued

	Wave 1		Wlave 2		Wave 3		Wave 4		All Waves	
	HIV- $N = 196$	HIV+ $N = 519$	HIV- $N = 215$	HIV+ $N = 356$	HIV- $N = 77$	HIV+ $N = 210$	HIV- $N = 214$	HIV+ $N = 576$	HIV- $N = 702$	HIV+ $N = 1661$
Crack, cocaine or heroin use										
Ever, reported at baseline	112 (57)	320 (62)	87 (40)	137 (38)	64 (83)	114 (54)	113 (53)	278 (48)	376 (54)	849 (51)
During WIHS follow-up	96 (49)	197 (38)	82 (38)	80 (22)	40 (52)	61 (29)	49 (23)	114 (20)	267 (38)	452 (27)
Past 6 months	16 (8)	25 (5)	17 (8)	19 (5)	20 (26)	16 (8)	19 (9)	46 (8)	72 (10)	106 (6)
Methamphetamines, past 6 months	0 (0)	1 (< 1)	3 (1)	3 (1)	3 (4)	4 (2)	0 (0)	2 (< 1)	6 (1)	10 (1)
Other drugs, past 6 months	4 (2)	0 (0)	4 (2)	5 (1)	1 (1)	2 (1)	4 (2)	2 (< 1)	13 (2)	9 (1)
Alcohol use, past 6 months										
Complete abstention	92 (47)	310 (60)	76 (35)	211 (59)	39 (51)	101 (48)	84 (39)	318 (55)	291 (41)	940 (57)
> 0–7 drinks/week	50 (26)	137 (26)	91 (42)	23 (26)	22 (29)	71 (34)	82 (38)	199 (35)	245 (35)	500 (30)
> 7–12 drinks/week	15 (8)	15 (3)	15 (7)	15 (4)	5 (6)	8 (4)	11 (5)	17 (3)	46 (7)	55 (3)
> 12 drinks/week	22 (11)	26 (5)	17 (8)	29 (8)	10 (13)	20 (10)	35 (16)	39 (7)	84 (12)	114 (7)
Current smoker	74 (38)	160 (31)	87 (40)	113 (32)	44 (57)	99 (47)	102 (48)	253 (44)	307 (44)	625 (38)
Male sex partners										
Median lifetime, reported at baseline (IQR)	10 (5, 30)	12 (5, 50)	10 (5, 40)	10 (5, 25)	15 (8, 50)	12 (5, 30)	17 (10, 52)	10 (5, 30)	12 (6, 40)	10 (5, 30)
At least one, past 6 months	75 (38)	195 (38)	135 (63)	219 (62)	43 (56)	121 (58)	166 (78)	366 (64)	419 (60)	901 (54)
More than one, past 6 months	3 (2)	13 (3)	29 (13)	20 (6)	11 (14)	15 (7)	57 (27)	43 (7)	100 (14)	91 (5)
Any female sex partners										
Ever	48 (24)	115 (22)	67 (31)	71 (20)	27 (35)	58 (28)	82 (38)	139 (24)	224 (32)	383 (23)
Past 6 months	6 (3)	11 (2)	13 (6)	10 (3)	3 (4)	5 (2)	12 (6)	10 (2)	34 (5)	36 (2)
Vaginal sex										
Past 6 months	71 (36)	189 (36)	134 (62)	219 (62)	42 (55)	119 (57)	165 (77)	360 (63)	412 (59)	887 (53)
Always used condoms	17 (24)	121 (64)	26 (19)	126 (58)	5 (12)	66 (55)	42 (25)	197 (55)	90 (22)	510 (58)
Anal sex										
Past 6 months	4 (2)	8 (2)	11 (5)	13 (4)	2 (3)	11 (5)	9 (4)	20 (3)	26 (4)	52 (3)
Always used condoms	3 (75)	5 (63)	3 (27)	6 (46)	0 (0)	3 (27)	2 (22)	5 (25)	8 (31)	19 (37)
Sex with known HIV+ partner										
During WIHS follow-up[d]	23 (12)	187 (36)	49 (23)	160 (45)	14 (18)	87 (41)	28 (13)	206 (36)	114 (16)	640 (39)
Past 6 months	2 (1)	41 (8)	7 (3)	54 (15)	3 (4)	32 (15)	16 (7)	110 (19)	28 (4)	237 (14)
Transactional sex										
Ever	54 (28)	187 (36)	60 (28)	108 (30)	44 (57)	75 (36)	105 (49)	183 (32)	263 (37)	553 (33)
Past 6 months	3 (2)	2 (< 1)	6 (3)	1 (< 1)	3 (4)	4 (2)	8 (4)	10 (2)	20 (3)	17 (1)
Ever experienced sexual abuse	86 (44)	257 (50)	63 (29)	89 (25)	36(47)	89 (42)	94 (44)	197 (34)	279 (40)	632 (38)
Ever experienced physical violence	111 (57)	309 (60)	95 (44)	146 (41)	51 (66)	130 (62)	127 (59)	260 (45)	384 (55)	845 (51)

[a]Dates of enrolment were: Wave 1 = 1994–95; Wave 2 = 2001–02; Wave 3 = 2011–12; Wave 4 = 2013–15.

[b]*N* (column %), unless otherwise noted.

[c]Includes: American Indian, Alaskan Native, Asian, Native Hawaiian, Pacific Islander and multiple races/ethnicities.

[d]Data are available since 1 October 2005.

Table 3. Clinical characteristics of participants in the Women's Interagency HIV Study, by enrolment wave[a] and HIV status at latest WIHS visit

	Wave 1		Wave 2		Wave 3		Wave 4		Overall	
	HIV- $N = 196$	HIV+ $N = 519$	HIV- $N = 215$	HIV+ $N = 356$	HIV- $N = 77$	HIV+ $N = 210$	HIV- $N = 214$	HIV+ $N = 576$	HIV- $N = 702$	HIV+ $N = 1661$
Clinical[b]										
Median CD4 cells/mm^3 (IQR)	1049 (832, 1293)	619 (393, 850)	1018 (785, 1280)	604 (411, 797)	1000 (798, 1259)	683 (515, 934)	991 (816, 1267)	635 (436, 865)	1011 (815, 1280)	628 (435, 853)
HIV RNA										
Not detected: < 20 copies/ml	N/A	351 (68)	N/A	238 (67)	N/A	143 (68)	N/A	420 (73)	N/A	1152 (69)
Median copies/ml among detected (IQR)	N/A	142 (42, 2760)	N/A	545 (74, 23000)	N/A	309 (49, 3030)	N/A	383 (51, 9540)	N/A	265 (53, 7000)
Antiretroviral drug use										
Ever	N/A	510 (98)	N/A	347 (97)	N/A	198 (94)	N/A	555 (96)	N/A	1610 (97)
At last visit	N/A	478 (92)	N/A	308 (87)	N/A	178 (85)	N/A	522 (91)	N/A	1486 (89)
100% adherent	N/A	231 (48)	N/A	140 (45)	N/A	96 (54)	N/A	260 (50)	N/A	727 (49)
≥ 95% adherent	N/A	417 (87)	N/A	261 (85)	N/A	155 (87)	N/A	445 (85)	N/A	1278 (86)
Body mass index (IQR)	32 (27, 38)	29 (24, 34)	31 (26, 37)	30 (25, 35)	30 (26, 36)	30 (25, 37)	34 (28, 38)	32 (27, 40)	32 (27, 37)	30 (25, 36)
Blood pressure (IQR)										
Systolic	128 (116, 144)	120 (111, 135)	122 (111, 136)	120 (110, 131)	122 (111, 134)	119 (110, 134)	122 (112, 137)	120 (110, 136)	124 (112, 138)	120 (110, 134)
Diastolic	76 (70, 84)	74 (68, 81)	76 (69, 84)	74 (68, 81)	75 (69, 83)	76 (70, 83)	74 (69, 83)	75 (69, 82)	75 (69, 84)	75 (69, 82)
Hypertension[c]	118 (60)	298 (57)	82 (38)	142 (40)	43 (56)	92 (44)	97 (45)	304 (53)	340 (48)	836 (50)
LDL cholesterol										
Unknown	28 (14)	79 (15)	27 (13)	50 (14)	9 (12)	24 (11)	8 (4)	23 (4)	72 (10)	176 (11)
≤ 3.36 mmol/l	126 (64)	356 (69)	159 (74)	261 (73)	61 (79)	156 (74)	178 (83)	461 (80)	524 (75)	1234 (74)
> 3.36 mmol/l	42 (21)	84 (16)	29 (13)	45 (13)	7 (9)	30 (14)	28 (13)	92 (16)	106 (15)	251 (15)
HDL cholesterol										
Unknown	28 (14)	79 (15)	27 (13)	50 (14)	9 (12)	24 (11)	8 (4)	23 (4)	72 (10)	176 (11)
< 1.03 mmol/l	24 (12)	52 (10)	26 (12)	59 (17)	8 (10)	25 (12)	36 (17)	104 (18)	536 (76)	1245 (75)
≥ 1.03 mmol/l	144 (73)	388 (75)	162 (75)	247 (69)	60 (78)	161 (77)	170 (79)	449 (78)	94 (13)	240 (14)
Estimated GFR: MDRD	88 (75, 103)	80 (64, 99)	98 (85, 111)	94 (77, 109)	87 (75, 104)	89 (74, 104)	100 (84, 117)	94 (76, 111)	95 (81, 111)	89 (72, 106)
Diabetes mellitus	64 (33)	147 (28)	36 (17)	66 (19)	19 (25)	38 (18)	39 (18)	89 (15)	158 (23)	340 (20)
History of adverse cardiovascular event[d]	47 (24)	129 (25)	20 (9)	37 (10)	17 (22)	19 (9)	24 (11)	58 (10)	108 (15)	243 (15)
History of cancer	16 (8)	47 (9)	6 (3)	21 (6)	2 (3)	5 (2)	2 (1)	10 (2)	26 (4)	83 (5)

(continued)

Table 3. Continued

	Wave 1		Wave 2		Wave 3		Wave 4		Overall	
	HIV- $N = 196$	HIV+ $N = 519$	HIV- $N = 215$	HIV+ $N = 356$	HIV- $N = 77$	HIV+ $N = 210$	HIV- $N = 214$	HIV+ $N = 576$	HIV- $N = 702$	HIV+ $N = 1661$
Baseline HCV infection status										
Negative	151 (77)	335 (65)	194 (90)	309 (87)	65 (84)	172 (82)	187 (87)	504 (88)	597 (85)	1320 (79)
Resolved infection, Ab + RNA-	10 (5)	51 (10)	8 (4)	13 (4)	0 (0)	2 (1)	0 (0)	0 (0)	18 (3)	66 (4)
Ab + RNA unknown	1 (1)	6 (1)	0 (0)	2 (1)	11 (14)	33 (16)	27 (13)	70 (12)	39 (6)	111 (7)
Active infection, RNA+	33 (17)	126 (24)	13 (6)	32 (9)	1 (1)	2 (1)	0 (0)	0 (0)	47 (7)	160 (10)
History of clinical AIDS	N/A	295 (57)	N/A	108 (30)	N/A	37 (18)	N/A	82 (14)	N/A	522 (31)
Results of last Pap smear										
Normal or unspecified ASCUS	179 (91)	457 (88)	195 (91)	322 (90)	74 (96)	197 (94)	203 (95)	536 (93)	651 (93)	1512 (91)
LSIL	0 (0)	15 (3)	2 (1)	16 (4)	2 (3)	5 (2)	1 (< 1)	25 (4)	5 (1)	61 (4)
HSIL or carcinoma in situ	2 (1)	8 (2)	1 (< 1)	5 (1)	1 (1)	3 (1)	2 (1)	13 (2)	6 (1)	29 (2)
High risk HPV during WIHS follow-up[e]	15 (8)	93 (18)	11 (5)	27 (8)	N/A	N/A	N/A	N/A	26 (6)	120 (14)
Sexually transmitted infection[f]										
Baseline	108 (55)	359 (69)	124 (58)	217 (61)	56 (73)	144 (69)	153 (72)	397 (69)	441 (63)	1117 (67)
During WIHS follow-up	91 (46)	352 (68)	98 (46)	189 (53)	26 (34)	59 (28)	65 (30)	156 (27)	280 (40)	756 (46)
Past 6 months	1 (1)	13 (3)	3 (1)	9 (3)	3 (4)	6 (3)	13 (6)	30 (5)	20 (3)	58 (3)
Pregnancy										
Ever during WIHS	74 (38)	135 (26)	118 (55)	122 (34)	3 (4)	14 (7)	13 (6)	20 (3)	208 (30)	291 (18)
Hormonal contraceptive use	2 (1)	8 (2)	15 (7)	24 (7)	3 (4)	11 (5)	18 (8)	36 (6)	38 (5)	79 (5)
Menopause status at last visit[g]										
Premenopausal	26 (13)	47 (9)	108 (50)	122 (34)	18 (23)	72 (34)	97 (45)	214 (37)	249 (35)	455 (27)
Early perimenopause	16 (8)	31 (6)	24 (11)	38 (11)	8 (10)	26 (12)	22 (10)	52 (9)	70 (10)	147 (9)
Late perimenopause	7 (4)	19 (4)	12 (6)	26 (7)	4 (5)	8 (4)	7 (3)	30 (5)	30 (4)	83 (5)
Postmenopausal (natural or surgical)	129 (66)	392 (76)	56 (26)	160 (45)	46 (60)	94 (45)	84 (39)	277 (48)	315 (45)	923 (56)
At risk for depression[h]	53 (27)	145 (28)	50 (23)	80 (22)	27 (35)	70 (33)	80 (37)	195 (34)	210 (30)	490 (30)

LDL, low-density lipoprotein; HDL, high-density lipoprotein; ASCUS, atypical squamous cells of uncertain significance; GFR, glomerular filtration rate (ml/min/1.73 m^2); HSIL, high-grade squamous epithelial lesions; MDRD, modified diet in renal disease; LSIL, low-grade squamous epithelial lesions; NA, not available.

[a]Dates of enrolment were: Wave 1 = 1994-95; Wave 2 = 2001-02; Wave 3 = 2011-12; Wave 4 = 2013-15.

[b]*N* (column %), unless otherwise noted.

[c]Confirmed through self-report: on medication or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.

[d]Myocardial infarction, stroke or transient ischaemic attack, hospitalization for congestive heart failure or chest pain/angina, or surgery on heart vessels.

[e]High-risk HPV types 16, 18, 31, 45.

[f]Self report of gonorrhoea, syphilis, chlamydia, pelvic inflammatory disease, genital herpes, genital warts, or trichomonal vaginitis.

[g]Stages of Reproductive Aging Workshop (STRAW) + 10 criteria.

[h]Centers for Epidemiologic Studies – Depression (CESD) score of 16 or greater.

About one-third (33% and 31%, respectively, of HIV+ and HIV- participants) have attained less than a high school education. Almost one-third (31%) of HIV+ participants have reported a history of clinical AIDS; as expected, women enrolled earlier are more likely to have had an AIDS condition than those enrolled later (57%, 30%, 18% and 14%, respectively, for Waves 1, 2, 3 and 4). Almost all (97%) of WWH have received some antiretroviral therapy (ART), and 89% reported taking ART at the most recent visit. Nevertheless, a substantial minority (31%) continue to have unsuppressed HIV viral loads, reflecting recognized deficiencies in the continuum of HIV care.[5]

Despite the high prevalence of IDU reported by participants at study entry, current IDU is less common; only 1% reported IDU in the 6 months preceding their most recent study visit. By contrast, higher proportions (6% HIV+, 10% HIV-) reported smoking or snorting crack cocaine, cocaine or heroin in the past 6 months. Almost one-third of women (30% HIV+, 30% HIV-) screened positive for risk of depression at their last visit, and 38% of HIV+ and 40% of HIV- women reported a history of sexual abuse. Cigarette smoking is common (38%, HIV+, 44% HIV-), as is obesity, with median body mass index (BMI) of 30 (HIV+) and 32 (HIV-). Substantial proportions of women have diabetes (20% HIV+, 23% HIV-), hypertension (50% HIV+, 48% HIV-) and a history of cardiovascular disease (15% HIV+, 15% HIV-).

How often have they been followed up? What has been measured?

Participants attend WIHS visits every 6 months for data collection. Each of these visits includes a scripted interview that covers general medical and medication history, substance use, sexual history, health care use and psychosocial/behavioural data. A physical examination, including standardized blood pressure assessment, anthropometric measures and gynaecological examination with cervical cytology, is conducted. Frailty assessments and ankle-brachial index measures to determine the extent of peripheral arterial disease are performed annually or every 2 years, respectively, on women 40 years of age or older. Colposcopy and biopsy are performed, as clinically indicated. Women who need additional evaluation and/or treatment of health conditions are referred to appropriate providers. In addition to clinical data, the WIHS collects haematological, metabolic, immunological, genetic and virological data. The following sections describe several special study modules that operate at varying intervals.

Neurocognition

Incorporation of neurocognitive testing has facilitated HIV-associated neurocognitive disorder (HAND) research.[6] Every 2 years since April 2009, all English-speaking participants have performed neurological and neurocognitive function tests, including: psychomotor speed and attention (Symbol Digit Substitution Test), gross motor speed (timed gait), fine motor speed and coordination (Grooved Pegboard), visuo-motor speed and executive function (Trail Making Test Part A and B), working memory/executive function (Letter Number Sequencing), executive function (Stroop, Letter Fluency; FAS), semantic fluency (animals) and verbal memory (Hopkins Verbal Memory Test-Revised and Brief Visual Memory Test). Participants who speak only Spanish undergo more limited testing. The Wide Range Achievement Test-3 (WRAT-3) was administered once during each participant's first neurocognitive test.

Geocoding

Because neighbourhood characteristics affect health,[7] the WIHS has used ArcGIS^{TM} (Esri, US) to geocode the residence of consenting participants annually since 2013. ArcGIS matches each participant's geocoded location to a Federal Information Processing Standard (FIPS) code that identifies geographical locations. Each site creates a limited dataset that contains only the participants' FIPS codes (at the census block group level) and WIHS identification (ID) numbers. The WIHS links the FIPS codes to census-linked datasets, such as the American Community Survey, to create group-level variables that describe neighbourhood characteristics. The WIHS creates individualized contextual datasets for investigators which only contain the WIHS ID and the value of the specific group-level variables requested by the investigator (e.g. percentage of individuals under the federal poverty line). Residences of 89% of HIV-seropositive and 92% of HIV-seronegative active participants have been geocoded.

Host genetics

Several WIHS studies have examined the genetic characteristics of cohort participants and their association with key study outcomes. These include candidate gene analyses and whole-exome studies of selected participant subsets, as well as WIHS-wide genotyping (Haemoglobin S, Haemoglobin C, CCR5Δ32, APOE). Viable cells are available in the WIHS specimen repository for epigenetics research. Genome-wide data have also complemented clinical, imaging, biochemical, biological and sociodemographic studies. WIHS benefits from considerable genetic diversity. A total of 74% of all 4982 WIHS participants (63% of 2363 active WIHS participants) consented to and have undergone genome-wide association study (GWAS) testing; genome-wide data from 4789 participants are

Table 4. Summary of Women's Interagency HIV Study specimen repository

Type of specimen	Volume of specimen	No. of specimens stored	
		HIV+ $N = 3677$	HIV- $N = 1305$
Serum	0.5, 1.0 or 1.8 ml aliquots	251584	94539
Plasma	0.5, 1.0 or 1.8 ml aliquots	332191	125460
Viable PBMC cells	> 5 million cells per aliquot	126106	52449
PBMC pellets	0.5 or 2 million cells per aliquot	284118	103761
Urine (clean void)	1.0 or 5.0 ml aliquots	37992	13305
Urine supernatant	1.0 ml aliquots	37404	15587
Whole CVL	1.0 or 1.5 ml aliquots	266442	104093
CVL supernatant	0.5 or 1.0 ml aliquots	16017	4847
CVL pellet (suspended)	> 2.5 million cells per aliquot	5187	6586
Cervical swab	1 swab	38075	15609
Oral fungal culture (mouth scrapings)	1 swab	2165	650
Vaginal fungal culture	1 swab	1763	629

PBMC, peripheral blood mononuclear cells; CVL, cervico-vaginal lavage.

available for analysis. Investigators have genotyped DNA isolated from peripheral blood mononuclear cells, which are maintained in the WIHS DNA Repository. About 2.5 million common single nucleotide polymorphisms (SNPs) and 2.5 million rare SNPs have been identified. The WIHS GWAS analytical support group performs quality control of WIHS genomic data and provides analytical and bioinformatics support to investigators.

Liver disease

Participants underwent hepatitis C virus (HCV) antibody testing at or shortly after enrolment and, among HCV-seropositive participants, HCV RNA testing was performed to determine clearance or persistence of infection. HCV RNA quantification is also performed at least 12 weeks after HCV treatment to determine achievement of cure. Periodic HCV antibody and HCV RNA testing has detected incident HCV infections. WIHS has documented HCV infection in 29% of the cohort, and over 400 women have cleared HCV infection (either spontaneously or through treatment).

The cohort represents a unique opportunity to evaluate the effects of HCV mono- and co-infection and HCV treatment, substance use and obesity on liver disease among women. WIHS measures serum biomarkers [aspartate aminotransferase-to-platelet ratio index (APRI) and Fibrosis-4 (FIB4) score] to estimate the severity of liver fibrosis. In addition, WIHS participants undergo transient elastography [via FibroScan® 502 Touch device with CAPTM software (Echosens, Paris)] to evaluate extent of liver fibrosis and steatosis according to standardized protocols, which are performed by trained and certified WIHS staff. These data allow longitudinal analysis of the progression of liver fibrosis and steatosis.

Antiretroviral pharmacology

WIHS supports one of the largest and most diverse datasets focused on antiretroviral pharmacology, with intensive pharmacokinetic data for a number of antiretroviral drugs and a database that includes 2000 measurements of antiretroviral drugs in scalp hair and individual plasma samples.

Specimen repository

In addition to data that are accessible to researchers, the study maintains a repository of biological specimens, including serum, plasma, urine, peripheral blood mononuclear cells, oral fungal cultures, hair, cervico-vaginal lavage and cervical swabs that are collected at each visit for all participants. Also available are plasma anti-Müllerian hormone levels, a biomarker of ovarian reserve that estimates the time of onset of menopause. Table 4 outlines the type and quantity of each specimen collected and the number of specimens available in the repository.

Key findings

The WIHS has yielded more than 800 publications to date, see [http://statepi.jhsph.edu/wihs/wordpress/wp-content/uploads/2015/12/wihs_archives.pdf]. Below we outline a few of the study's major findings.

The WIHS has documented the dramatic changes in mortality and its contributing factors among WWH since the early years of the epidemic. After the advent of HAART, the age- and sex-specific standardized mortality ratio of 24.7 in 1996 fell to a mean of about 10.3 in 2001-04, and causes of mortality shifted from a predominance of AIDS to non-AIDS causes, such as overdose, trauma,

cancer, liver disease and heart disease by 2003.[8] Although survival increased with improvements in ART, PWH continued to die earlier; in both the WIHS and the Multicenter AIDS Cohort Study (MACS) (a prospective cohort of men with and at risk for HIV infection), PWH died a median 7.6 years earlier than their HIV-seronegative counterparts. Whereas the proportion of non-AIDS causes of death was similar between women and men with HIV after HAART's introduction (47% vs 50%), among PWH who died of non-AIDS causes, women have had substantially lower life expectancies than men (median age at death 55.9 vs 66.0 years).[9] An earlier study of WIHS and MACS participants revealed higher death rates due to accident or injury among women (2.96 deaths per 1000 person-years among both HIV+ and HIV-) than men (0.79 for HIV+ and 0.63 for HIV-), with differing risk factors for death among men (higher education, symptoms of depression and more sex partners) and women (lower CD4+ T cell count, unemployment, increased alcohol use and injection drug use).[10] WIHS mortality analyses also demonstrated that among WWH, Black women died at nearly double the rate of White women, even after adjusting for confounders known to be associated with death due to HIV infection.[11] WIHS participants also contributed to an early landmark study of patients in care between 1996 and 2005, which demonstrated the survival benefits of early initiation of ART at CD4+ T cell counts above the previously recommended threshold.[12]

Cardiovascular disease has emerged as a significant cause of morbidity among PWH. A cross-sectional analysis of carotid ultrasound examinations among MACS and WIHS participants established low CD4+ T cell count (< 200 cells/ml) as a major risk factor for atherosclerosis among PWH.[13] A prospective evaluation using carotid ultrasonography of men and women in the MACS and WIHS demonstrated an association of HIV infection with progression of subclinical carotid atherosclerosis, as evidenced by a 1.6-fold greater risk of new plaque formation after adjusting for cardiac and metabolic risk factors.[14]

WIHS has enhanced our understanding of the natural history of HPV infection among women with HIV. WIHS studies have documented the increased prevalence of human papillomavirus (HPV) infection, including oncogenic HPV types,[15] abnormal Pap tests[16] and cervical precancerous lesions.[17] Despite the higher prevalence of HPV among WWH, the risk of invasive cervical cancer is only modestly increased among WWH who undergo regular screening,[18] a finding that has informed cervical cancer screening guidelines for this population.

Assessment of severity of liver disease is important in counselling women with HIV-hepatitis C virus (HCV) co-infection. Studies of HIV-HCV co-infected WIHS participants revealed that although Black women are less likely to spontaneously clear HCV infection than Hispanic or Caucasian women,[19] they are also less likely than Caucasian and Hispanic women to die of liver disease, a finding that had not previously been reported in women.[20] Non-invasive assessment of liver disease severity has become increasingly important in evaluation of HCV infection. The WIHS has demonstrated the utility of non-invasive serum markers, such as APRI, FIB-4 and enhanced liver fibrosis (ELF), for assessing liver fibrosis severity and predicting mortality among women with HCV.[21–23]

HIV's impact on neurocognitive function among men has been well described, but neurocognitive function among WWH has received relatively little research attention. Early studies among WIHS WWH revealed deficits in episodic verbal memory which correlated with neuroimaging evidence of hippocampal dysfunction, suggesting an effect of HIV on the neurological systems that govern verbal memory.[24] Neurocognitive testing in another WIHS study identified an interaction between HIV infection and recent cocaine or heroin use on verbal learning and memory, with recent illicit drug use affecting only WWH.[25] Despite the worse performance of WWH on tests of verbal learning, delayed recall and recognition and psychomotor speed and attention, the effect of HIV on cognition was small; other factors such as reading level, age and years of education had a greater effect than HIV infection on cognitive performance.[6]

Intensive drug pharmacokinetic studies have revealed factors associated with elevated anti-retroviral drug levels among Black and Hispanic women, groups that are often poorly represented in pre-marketing studies.[26] The WIHS has evaluated antiretroviral drug concentrations in hair, as a non-invasive measure of long-term drug exposure. The WIHS has demonstrated a relationship between concentrations of antiretroviral drugs in hair and HIV suppression,[27,28] and has also shown a relationship between genetic markers associated with decreased metabolism of some antiretrovirals and increased drug concentrations in hair.[29]

Strengths and limitations

The cohort's strengths have made it a major platform for women's HIV research: a large sample size, collection of rich clinical, behavioural and laboratory data at 6-month intervals and a large diverse biospecimen repository that spans more than 20 years. The control group is well matched to WWH with respect to demographic, behavioural and other risk characteristics. The cohort is especially unique in its racial/ethnic diversity and inclusion of large numbers of women of colour and women of lower

socioeconomic status, who mirror the HIV epidemic among US women. The interval cohort design of the WIHS, with data collection at specified time points, has several advantages over the clinical cohort design; interval data collection renders the data more uniform and complete than is typically afforded by clinical cohorts. WIHS recruited women from both clinical and non-clinical settings. Although study staff facilitate participants' care by referring them for clinical, social and other services, some participants struggle to maintain access to care. Inclusion of participants from outside clinical settings allows more accurate reflection of WWH, including those who do not receive consistent HIV care.

A major challenge of the WIHS is intrinsic to observational cohorts: potential confounding restricts ability to make causal inferences. Randomized controlled trials permit causal inferences between exposures and outcomes, but their generalizability is often limited. The success of the WIHS is due in large part to the dedication of its participants, many of whom have remained in the study for decades, but this very characteristic likely limits the study's generalizability to the entire population of WWH in the USA. In addition, participants in clinical trials and other studies sometimes experience improved outcomes compared with non-participants—due to better care, behavioural changes and/or possibly other unknown factors.[30,31] Nevertheless, enrolment of new participants over four enrolment periods during the greater than 20-year span of the study has helped to ensure the cohort's continued reflection of US women who are affected by HIV.

Can I get hold of the data? Where can I find out more?

The WIHS welcomes collaborations with investigators. Information on proposing new studies and analyses, data and specimens is available at [wihshealth.org]. The WIHS also provides de-identified data in its Public Use Dataset, which is updated annually and may be obtained by submitting a data request form.

Profile in a nutshell

- The Women's Interagency HIV Study (WIHS) investigates the impact and progression of HIV infection among women in the USA.
- The cohort consists of 4982 women at nine sites in the USA, who are either living with HIV (3677) or are HIV-seronegative (1305) but have characteristics that increase their risk of acquiring HIV.
- A total of 2623 participants were enrolled at baseline in 1993; three subsequent waves have expanded the study's enrolment. Since the beginning of the study, 1268 participants have died, 130 have withdrawn, 806 have been dis-enrolled for administrative reasons, and 415 have been lost to follow-up. Current median age of the 2363 actively followed participants is 49 years [HIV-seronegative; interquartile range (IQR) 41, 55) and 51 years (HIV+; 44, 56).
- Participants attend bi-annual study visits. Data collection includes: clinical, medication and behavioral history; general physical, gynaecological and neurocognitive examination; and laboratory data including haematological, metabolic, immunological and virological testing, as well as cervical cytology, genetic testing and transient liver elastography. The specimen repository contains blood, urine, cervico-vaginal lavage and cervical swab specimens.
- The WIHS welcomes collaborations; information on collaboration can be found at [wihshealth.org].

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