Study Design

Characteristics of the MACS/WIHS Combined Cohort Study: Opportunities for Research on Aging With HIV in the Longest US Observational Study of HIV

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In 2019, the National Institutes of Health combined the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS) into the MACS/WIHS Combined Cohort Study (MWCCS). In this paper, participants who made a study visit during October 2018–September 2019 (targeted for MWCCS enrollment) are described by human immunodeficiency virus (HIV) serostatus and compared with people living with HIV (PLWH) in the United States. Participants include 2,115 women and 1,901 men with a median age of 56 years (interquartile range, 48–63); 62% are PLWH. Study sites encompass the South (18%), the Mid-Atlantic/Northeast (45%), the West Coast (22%), and the Midwest (15%). Participant race/ethnicity approximates that of PLWH throughout the United States. Longitudinal data and specimens collected for 35 years (men) and 25 years (women) were combined. Differences in data collection and coding were reviewed, and key risk factor and comorbidity data were harmonized. For example, recent use of alcohol (62%) and tobacco (28%) are common, as are dyslipidemia (64%), hypertension (56%), obesity (42%), mildly or severely impaired daily activities (31%), depressive symptoms (28%), and diabetes (22%). The MWCCS repository includes serum, plasma, peripheral blood mononuclear cells, cell pellets, urine, cervicovaginal lavage samples, oral samples, B-cell lines, stool, and semen specimens. Demographic differences between the MACS and WIHS can confound analyses by sex. The merged MWCCS is both an ongoing observational cohort study and a valuable resource for harmonized longitudinal data and specimens for HIV-related research.

biorepositories; cohort studies; collaborative research; comorbidity; HIV; Multicenter AIDS Cohort Study; MACS/WIHS Combined Cohort Study; Women's Interagency HIV Study

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; IQR, interquartile range; MACS, Multicenter AIDS Cohort Study; MSM, men who have sex with men; MWCCS, MACS/WIHS Combined Cohort Study; NIH, National Institutes of Health; PLWH, people living with HIV; WIHS, Women's Interagency HIV Study.

The Multicenter AIDS Cohort Study (MACS), established in 1983, and the Women's Interagency HIV Study (WIHS), established in 1993, were prospective observational cohort studies designed to characterize the US human immunodeficiency virus (HIV) epidemic, the natural history of HIV infection, and the pathogenesis of the disease in men and

women, respectively (1, 2). Both cohort studies were multicenter studies with a unified protocol, centralized testing, and multiple waves of enrollment. Both included people living with HIV (PLWH) and similar HIV-seronegative participants at risk of HIV infection for comparison.

Because of substantial improvements in the effectiveness of treatment, HIV infection is now a chronic disease. Nearly half of PLWH in the United States are aged 50 years or older (3), and they are increasingly subject to aging-associated non–acquired immunodeficiency syndrome (AIDS)-defining conditions. MACS and WIHS participants have contributed to a rich data set compiled over many years, including detailed information on HIV risk factors, and a large biospecimen repository that includes a diverse set of samples collected during in-person visits at 6-month intervals. These resources can be used to inform research on HIV and the pathogenesis and treatment of health conditions that differentially affect PLWH or that affect all populations.

PURPOSE OF MERGER

In April 2019 the MACS and WIHS, which were primarily funded by the National Institute of Allergy and Infectious Diseases, were merged to form the MACS/WIHS Combined Cohort Study (MWCCS) (4–6), with primary stewardship by the National Heart, Lung, and Blood Institute and cofunding provided by 13 additional institutes of the National Institutes of Health (NIH). At the time of this merger, they were the longest-running observational studies of PLWH in the United States. The MACS and the WIHS had similar study designs and visit schedules (every 6 months on the same October–March and April–September schedule), and both included HIV-seronegative participants who were demographically similar to participants living with HIV and had collaborated. However, while data collection protocols were similar, they were not identical, which complicated joint analyses and precluded others. Therefore, the NIH recommended combining the cohorts to harmonize protocols and to facilitate the exploration of relevant research questions within the evolving HIV epidemic, including an increased focus on aging and comorbidity. Further, the merger was expected to enable better sex comparisons, increase statistical power for analyses, and streamline the use of the studies' rich longitudinal data sets.

With the merger, the study's principal investigators developed a unified scientific agenda to advance understanding of the basic clinical, behavioral, and epidemiologic characteristics of HIV infection. This agenda addresses a wide range of conditions among aging PLWH and seronegative persons, including cardiovascular and pulmonary disease; sleep quality; neurocognitive ability; frailty and physical disability; cancer; HIV pathogenesis; psychosocial and behavioral conditions; metabolic, liver, and kidney dysfunction; and health disparities. It also provides a well-documented, reliable, valid, and standardized structural platform for collaborations with independently funded investigators, including early-stage investigators. Former MACS and WIHS participants described in this paper will be reenroll in the MWCCS with a harmonized baseline visit from October 2020 through

September 2021. In addition, the MWCCS will recruit up to 2,500 new participants to enrich the representation of the epidemic in the South and among Black and Hispanic men.

In this paper, we describe the MACS and WIHS participants who are being targeted for MWCCS enrollment and their sociodemographic, behavioral, and clinical characteristics relative to PLWH in the United States. We review harmonized data that are now available for analysis. Our goal is to characterize the rich retrospective database (now harmonized) and biospecimen collection (now centralized) integrated into the MWCCS; to facilitate use and analysis of the data by all stakeholders, including policy-makers, PLWH, and investigators; and to share lessons learned.

METHODS

Study population

The MACS targeted enrollment of men who have sex with men (MSM), with initial enrollment during 1984–1985 in 4 cities across the United States (2) and additional enrollment waves in 1987–1990 and 2001–2003, and limited replenishment enrollment from 2010 to 2017. In 1995, the NIH administratively censored some seronegative participants to achieve an approximately 1:1 target ratio of PLWH to seronegative men for follow-up. WIHS enrollment targeted women living with HIV and similar seronegative women at a 3:1 ratio. WIHS initial enrollment took place in 1994–1995 in 6 cities across the United States (7), with additional enrollment in 2001–2002 and 2011–2012, the closing of the Los Angeles, California, site in 2013, and the addition of 4 new sites in the southern United States in 2013–2015 (1).

Study design and inclusion criteria

We performed a cross-sectional comparison of men and women living with HIV in the MACS and WIHS, respectively, with seronegative participants in these cohorts. We restricted the analysis to current participants, defined as those who participated in at least 1 of the last 2 MACS or WIHS visits (between October 2018 and September 2019). We excluded from this analysis 18 participants who were known to have died (12 women, 1 man) or withdrawn from the study (5 women) since attending their last MACS or WIHS visit.

Exposures and outcome definitions

Characteristics and behaviors from data collected at the most recent visit were used. Analysis explored sociodemographic variables (e.g., age, race/ethnicity, education), study follow-up, HIV-related variables (cluster of differentiation 4 (CD4) cell count, HIV viral RNA load, antiretroviral therapy (ART)), behavioral variables (sexual activity; alcohol, tobacco, and drug use), and comorbid conditions. Table 1 shows harmonized definitions of comorbidity and the available data used for these outcomes. Biospecimen collection is described in the Results section, and the number

Table 1. Harmonized Definitions for Risk Factors, Clinical Characteristics, and Comorbid Conditions Used in the MACS/WIHS Combined Cohort Study

Indicator	Summarized Data or Harmonized Definition
Summary files[a]	
dhbasesocdem	Baseline sociodemographic data from participant's first MACS or WIHS visit, including: visit number and date, enrollment wave, race and ethnicity, education, baseline HCV and HBV status, and lifetime behaviors (tobacco and drug use, sexual behavior) and sexually transmitted infections reported at baseline. Categories harmonized.
dhbehavior	Longitudinal data, by visit, on recent behaviors (tobacco, alcohol, and drug use and sexual behavior), income, and lifetime and recent sexually transmitted infections. Categories harmonized.
dhchronHlth	Longitudinal data, by visit, on chronic health conditions, including BMI, body measurements, CES-D score, cardiovascular and metabolic measures, diabetes, hypertension, and kidney and liver disease. Definitions and categories harmonized.
dhhivhist	Summarized data file (1 record per participant) on key HIV-related variables, including HIV status, CD4 cell count nadir, most recent CD4 cell count, HIV viral RNA load, date of first AIDS diagnosis, first use of ARV agents (ARVs), and dates of most recent study visit, medical events, and death (when applicable). Definitions and categories harmonized.
dhhivlabs	Longitudinal data, by visit, on HIV-related laboratory results, including HIV viral RNA load and CD3, CD4, and CD8 cell counts. Harmonized lower limits of quantitation and information on tests used over time.
dhvertdatebase	Longitudinal data, by visit, on study visit details, including visit number and date, clinical research site, HIV serostatus at visit, and age at visit. MACS/WIHS Combined Cohort Study site codes and harmonized visit windows based on calendar dates.
dhoutcome	Longitudinal data, by outcome, on AIDS, cancer, tuberculosis, neuropsychological status, CVD, and death events with ICD-9, ICD-10, and ICD-O codes and event dates as applicable. Harmonized study-specific event codes, type of event confirmation, and level of confidence in event.
dhaidsdrug	Longitudinal data, by visit, on medications used to treat HIV for Food and Drug Administration–approved ARVs, including classification (e.g., protease inhibitor) and use since last interview. Harmonized use of combination and single ARVs, length of use, use since visit (no use, current use, used but not currently), and ARV's effect on HIV suppression status (HIV viral RNA load undetectable/detectable).
Visit files[b]	
	Longitudinal visit files of study participant data across all visits for each study form. Harmonized and standardized, within each cohort, for changes in questions over time. (Not harmonized between cohorts, although some questions asked were the same and other variables differed by cohort or were assessed in one cohort but not the other.)
Comorbid conditions	
Hypertension	Having any of the following: 1) SBP $\geq$140 mg/dL, 2) DBP $\geq$90 mg/dL, 3) self-reported hypertension, or 4) self-reported use of antihypertensive medication (women only).
Diabetes mellitus	Having any of the following: 1) self-reported ever use of antidiabetic medication, 2) fasting glucose level $\geq$126 mg/dL, 3) hemoglobin A_{1c} concentration $\geq$6.5%, or 4) self-reported diabetes confirmed by one of the previous 3 conditions.
Metabolic syndrome	Having $\geq$3 of the following: 1) waist circumference $\geq$102 cm (men) or $\geq$88 cm (women), 2) fasting triglyceride level $\geq$150 mg/dL, 3) fasting glucose level $\geq$100 mg/dL (men) or $\geq$110 mg/dL (women) or current use of diabetic medication and a history of diabetes, 4) HDL cholesterol level <40 mg/dL (men) or <50 mg/dL (women), or 5) SBP $\geq$130 mg/dL or DBP $\geq$85 mg/dL or self-reported use of hypertension medication or history of hypertension.
Dyslipidemia	Any of the following diagnostic features: 1) low-density lipoprotein level $\geq$130 mg/dL, 2) HDL cholesterol level <40 mg/dL, 3) triglyceride level $\geq$150 mg/dL, 4) self-reported use of lipid-lowering medication (or clinical diagnosis in the past for men), and 5) fasting total cholesterol level $\geq$200 mg/dL (for men only).
CVD risk scores	American College of Cardiology/American Heart Association Pooled Cohort Equations: <5% risk of coronary death or nonfatal MI or fatal or nonfatal stroke within 10 years = low risk; 5.0%–7.5% risk = moderate risk; >7.5% risk = high risk. Framingham Risk Score: <10% estimated risk of MI and coronary death within 10 years = low risk; 10%–20% risk = moderate risk; >20% risk = high risk (49).
Cancer diagnosis	Confirmed diagnosis of invasive cancer from cancer registry match or medical record abstraction. Excluded: basal and squamous cell skin cancers, noninvasive tumors, and self-reported or next-of-kin–reported cancer.

Table continues

Table 1. Continued

| Indicator	Summarized Data or Harmonized Definition
Kidney function	eGFR ≥60.0 mL/minute/1.73 m² = normal kidney function; eGFR 15.0–59.9 mL/minute/1.73 m² = kidney disease; eGFR <15.0 mL/minute/1.73 m² = kidney failure.
IADL	Assessment of IADL occurred at every other visit starting in 2008 for the men and at every visit for the women. Each question evaluated change in function from "best" to "current" score and classified functional status as: severe IADL impairment (major decline for ≥2 questions or major or minor declines in score for ≥4 questions), mild IADL impairment (minor decline for ≥2 questions or major or minor declines in score for 2 or more questions), or no impairment.
Aging-related measures	"Slower walker" if 4-m walking speed was ≤0.65 m/s for men with height ≤173 cm and women with height ≤159 cm or ≤0.76 m/s for men with height >173 cm and women with height >159 cm. "Weak" was based on how hard participants squeezed a dynamometer using their dominant hand. Men were defined as weak if grip strength was ≤29 kg (BMI ≤24.0), ≤30 kg (BMI 24.1–26.0), ≤31 kg (BMI 26.1–28.0), or ≤32 kg (if BMI >28.0). Women were defined as weak if grip strength was ≤17 kg (BMI ≤23.0), ≤17.3 kg (BMI 23.1–26.0), ≤18 kg (BMI 26.1–29.0), or ≤21 kg (BMI >29.0).
Frailty phenotype	MACS only: Using the 5 Fried frailty phenotype criteria, participants were classified as robust (not frail) if they met 0 criteria, prefrail if they met 1–2 criteria, and frail if they met ≥3 criteria. Fried frailty phenotype criteria are: unintentional weight loss, weakness, exhaustion, slowness, and low physical activity level.
Depressive symptoms	CES-D score ≥16.
Abnormal liver function	AST or alanine aminotransferase blood test result >40 IU/L.
Liver fibrosis	AST:platelet ratio index > 1.5 = significant fibrosis. FIB-4 score > 3.25 = significant fibrosis; FIB-4 score 1.45–3.25 = inconclusive; FIB-4 score < 1.45 = absence of fibrosis.
HBV	HBV status was classified as 1) negative (surface antibody-negative and core antibody-negative and surface antigen-negative *or* vaccinated), 2) resolved infection (surface antibody-positive and core antibody-positive and surface antigen-negative), 3) chronic/active infection (surface antigen-positive), or 4) unknown/inconclusive (missing some measures). HBV serological testing was done using antigen and antibody tests at or shortly after enrollment. For men only, updated HBV status was also measured (though not reported here), with men who remained uninfected during follow-up receiving anti-HBc tests 2 years after their most recent test; those positive for HBsAg received antibody and antigen tests at their next visit, those who seroconverted during follow-up received additional anti-HBc and HBsAg tests to determine when seroconversion occurred, and those with past or recovered HBV infection received HBsAg tests every 5 years to identify reactivation.
HCV	HCV status was classified as 1) not infected (antibody-negative, RNA-negative), 2) resolved infection (antibody-positive, RNA-negative), 3) chronic infection (active infection, RNA-positive), or 4) antibody-positive, RNA unknown. HCV serological testing was done using antibody testing at or shortly after enrollment. HCV-seropositive participants received a quantitative HCV RNA test to determine clearance or persistence of infection. Men who were uninfected received HCV antibody tests 2 years after their last negative test; those who seroconverted during follow-up received additional antibody tests to determine seroconversion, those prevalent at study entry received RNA tests once every 5 years to verify ongoing infection, and those who cleared their HCV infection received antibody and RNA tests once every 5 years to identify reinfection or reversions. Select longitudinal HCV testing was done for some women (project-specific).

Abbreviations: AIDS, acquired immunodeficiency syndrome; anti-HBc, hepatitis B core antibody; ARV, antiretroviral; AST, aspartate aminotransferase; BMI, body mass index; CD3, cluster of differentiation 3; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis 4; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IADL, instrumental activities of daily living; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, Tenth Revision*; ICD-O, *International Classification of Diseases for Oncology*; MACS, Multicenter AIDS Cohort Study; MI, myocardial infarction; SBP, systolic blood pressure; WIHS, Women's Interagency HIV Study.

[a] Summary files are analytical data files.
[b] Visit files are raw data files.

of person-visits with samples available for each biospecimen type in the national repository is reported. More details on historical data collection and new MWCCS data collection can be found on the study's website (https://statepi.jhsph.edu/mwccs/) (6).

If the value of a variable was missing (e.g., participants who had a telephone interview rather than an in-person visit), the most recent value of that variable was carried forward using data collected up to 2 years prior; otherwise the variable was coded as missing. While data in many domains
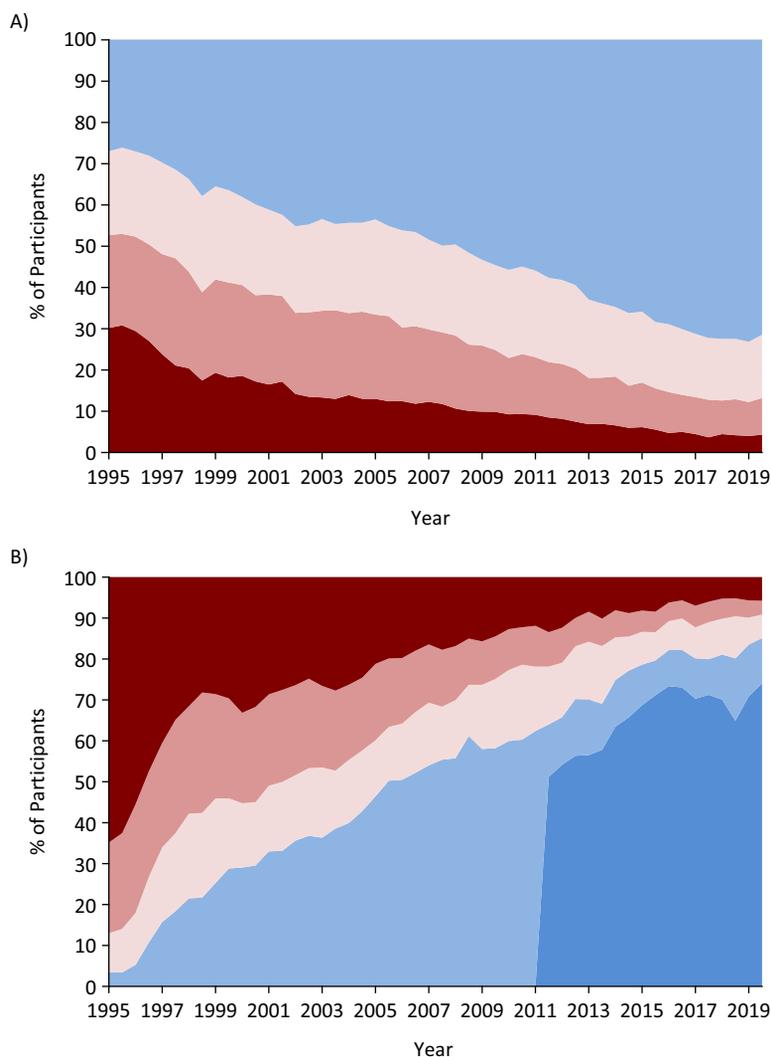
Figure 1. Distributions of cluster of differentiation 4 (CD4) cell counts (A) and plasma human immunodeficiency virus (HIV) viral RNA loads (B) among current Multicenter AIDS Cohort Study and Women's Interagency HIV Study participants living with HIV, by year, 1995–2019. Data were restricted to current participants, and we used semiannual CD4 cell counts and HIV viral RNA load measures to explore these trends. CD4 cell count categories, from top to bottom (A): blue, $\geq$500 cells/mm^3; lighter pink, 350–499 cells/mm^3; darker pink, 200–349 cells/mm^3; red, <200 cells/mm^3. HIV RNA viral load categories, from top left to bottom right (B): red, >10,000 copies/mL; darker pink, 1,001–10,000 copies/mL; lighter pink, 81–1,000 copies/mL; lighter blue, $\leq$80 copies/mL; darker blue, $\leq$20 copies/mL. AIDS, acquired immunodeficiency syndrome.

were collected using similar or identical questions in the 2 cohorts, other domains were assessed differently. For this analysis, we present data on key characteristics for which comparable data were available across the 2 cohorts; some data presented were collected in similar but not identical ways and were harmonized in order to directly compare them (detailed information on criteria used is presented in Table 1). Certain data assessed in only 1 of the cohorts are also presented.

Statistical methods

The prevalences of demographic characteristics, behaviors, and comorbidity were compared between PLWH and seronegative participants. HIV-related characteristics were compared among men and women living with HIV using Wilcoxon 2-sample tests for continuous variables and χ^2 tests for categorical variables. Fisher's exact test was used if any group had fewer than 5 participants.

Trajectories of CD4 cell count (number of cells/mm^3), hereafter called CD4, and plasma HIV viral RNA load ([number of copies/mL) over time were explored visually (Figure 1). Each was categorized into a range from the most harmful levels (CD4 < 200 cells/mm^3 and HIV viral RNA load > 10,000 copies/mL; colored in red) to the most beneficial (CD4 $\geq$ 500 cells/mm^3 and HIV viral RNA load $\leq$ 20 copies/mL; colored in blue), and we explored how the proportions in each category changed over time.

Distributions of age and race/ethnicity among men and women living with HIV were compared with those in the overall US HIV epidemic using 2018 data from the Centers for Disease Control and Prevention (8).

RESULTS

There are 1,901 male participants, with an approximately 1:1 ratio of men living with HIV to seronegative men, and 2,115 female participants, with an approximately 2.5:1 ratio of women living with HIV to seronegative women (Table 2). The study includes sites throughout the United States, with 22% of participants on the West Coast, 15% in the Midwest, 45% in the Mid-Atlantic/Northeast, and 18% in the South. The 4,016 current participants represent 33% of the 12,340 participants who have ever participated in the studies; 31% of participants have died since enrollment, 14% have been lost to follow-up or have remained in contact but did not complete a study visit in the last year, 2% withdrew, and 20% were administratively censored by the NIH for budgetary reasons. Censored participants included 1,614 seronegative men from the MACS who were censored in 1995 and 282 seronegative women and 569 women living with HIV who were censored from the WIHS, primarily in 2013 (details are shown in Web Figure 1, available online at https://doi.org/10.1093/aje/kwab050).

As Table 2 shows, most men (72%) and women (86%) in the MWCCS are between 40 and 69 years of age. However, the median age is about 10 years higher in men than in women (61 years vs. 52 years; $P < 0.001$). Participants have been followed for a median of 17 years (interquartile range (IQR), 7–31), and 511 (13%), 701 (17%), 1,753 (44%), and 1,051 (26%) participants have had ≤5.00, 5.01–15.00, 15.01–25.00, and >25.00 years of follow-up, respectively (Table 2). Almost half of participants are non-Hispanic Black ($n = 1,970$; 49%), and over one-third are non-Hispanic White ($n = 1,402$; 35%), with 13% identifying as Hispanic of any race ($n = 527$). Significantly fewer men than women are Black (23% vs. 73%; $P < 0.001$) or Hispanic (12% vs. 14%; $P = 0.04$). Women are less likely to report having graduated from college (8% vs. 54%; $P < 0.001$) and more likely to report a low income (62% vs. 26%; $P < 0.001$) than men.

Sociodemographic characteristics (including age, race/ethnicity, income, and education) are similar between women who are living with HIV and seronegative women (Table 2). By contrast, men living with HIV are younger, less educated, and more likely to be a member of a racial minority group than the seronegative men; this difference is primarily due to high mortality from AIDS among men living with HIV early in the MACS (55% of HIV-seropositive men have died vs. 9% of seronegative men), as well as enriched recruitment of minority men in later waves of MACS enrollment (9–11).

HIV-related characteristics are described in Table 3. The study includes 2,492 PLWH, 2,236 of whom were HIV-seropositive at enrollment and 256 of whom acquired HIV during the study; these latter participants have been followed for a median of 23 years (IQR, 12–30) since seroconversion. One-quarter (24%) of PLWH have a history of clinically defined AIDS, including 11% of men and 33% of women.

Most men (96%) and women (92%) report use of ART, with 90% reporting at least 95% adherence to ART. One-quarter (26%) of PLWH had a detectable HIV viral RNA load (≥20 copies/mL) at their last study visit (Table 3).

CD4 cell count at the last visit (in 2018–2019) was high among both men and women living with HIV (median values were 644 cells/mm^3 and 689 cells/mm^3, respectively); 13% have a current CD4 count less than 350 cells/mm^3. Participants have initiated ART at a wide range of CD4 counts. CD4 nadir is less than 200 cells/mm^3 in 40% of participants, with 33%, 17%, and 11% having a CD4 nadir of 200–349 cells/mm^3, 350–499 cells/mm^3, and ≥500 cells/mm^3, respectively. Male participants are less likely than women to have a CD4 nadir less than 200 cells/mm^3 (33% vs. 44%; $P < 0.001$); however, the prevalence of a current CD4 count less than 350 cells/mm^3 is similar between men and women (12% vs. 14%; $P < 0.13$).

Figure 1A explores the trajectory of CD4 count between October 1994 and September 2019 among the 2,492 PLWH. The proportion of participants with CD4 <200 cells/mm^3 decreased from 30% in 1995 to 10% in 2009 to 4% in 2019, and conversely, the proportion with CD4 ≥500 cells/mm^3 increased from 27% to 55% to 71%, respectively (P for trend < 0.001). HIV viral RNA loads also changed dramatically (Figure 1B). The proportion of participants with a viral RNA load greater than 10,000 copies/mL decreased from 65% in 1995 to 14% in 2009 to 6% in 2019 (P for trend < 0.001); the proportion with an undetectable viral RNA load (defined as <80 copies/mL for consistency in assay detection limits across time) increased from 3% to 58% to 85%, respectively.

Comparison with US statistics

Figure 2 shows the geographic distribution of participating research sites against the map of overall US HIV incidence. The geographic representation is broad and overlaps with high-prevalence areas in the Northeast, Southeast, Midwest, and West (12).

Current MACS and WIHS participants are 24–94 years of age, and 56% are aged 55 years or older, as compared with 32% of current US PLWH (Figure 3A). Another 40% of current participants are 35–54 years of age, as compared with 45% of US PLWH. Only 4% of participants are under 35 years of age, compared with 22% in national data, as expected, given the long study follow-up. The participant age distribution is compared with sex-stratified US data on MSM living with HIV and women living with HIV in Web Figure 2A.

The overall racial and ethnic distribution (49% Black, 13% Hispanic (all races), and 35% White) is comparable to that of US PLWH (41% Black, 23% Hispanic, and 29% White; Figure 3B). There are differences in race/ethnicity among men and women in the cohort, with a higher proportion of White participants among men living with HIV than among women living with HIV (54% vs. 10%) and a higher proportion of Black participants among women living with HIV than among men living with HIV (73% vs. 28%); these partly reflect differences in the race/ethnicity of MSM and women living with HIV in the United States (Web Figure 2B).

Table 2. Demographic Characteristics of Men in the MACS and Women in WIHS at Their 2018–2019 Study Visit, by HIV Status

Characteristic at Most Recent Study Visit	Total (n = 4,016)		Prevalence, %					
			Men[a]			Women[b]		
	No.	%	All Men (n = 1,901)	PLWH (n = 1,004)	HIV-SN (n = 897)	All Women (n = 2,115)	PLWH (n = 1,488)	HIV-SN (n = 627)
Geographic region								
West Coast	876	22	32	30	33	13	13	14
Midwest	614	15	19	24	14	12	12	11
Mid-Atlantic and Northeast	1,790	45	49	46	52	41	40	43
South	736	18	0	0	0	35	36	32
Duration of study follow-up, years[c]	17 (7–31)		32 (16–35)	17 (16–35)	35 (17–35)	17 (5–24)	17 (5–24)	17 (5–24)
≤5.00	511	13	3	4	2	21	23	19
5.01–15.00	701	17	10	17	2	24	25	23
15.01–25.00	1,753	44	32	36	28	54	52	58
>25.00	1,051	26	55	43	68	0	0	0
Age, years[c]	56 (48–63)		61 (54–68)	59 (51–65)	64 (58–71)	52 (45–58)	53 (46–59)	51 (43–57)
Age group, years								
24–39	389	10	7	9	6	12	10	16
40–49	738	18	10	12	7	26	25	28
50–59	1,370	34	26	33	19	41	43	36
60–69	1,088	27	36	35	38	19	19	17
70–94	431	11	20	11	30	2	2	2
Race/ethnicity								
Black (non-Hispanic)	1,970	49	23	28	16	73	73	73
Hispanic (any race)	527	13	12	16	8	14	14	15
White (non-Hispanic)	1,402	35	64	54	74	9	10	6
Other race	117	3	2	2	2	4	3	5
Education								
Less than high school	777	19	5	7	3	32	33	30
High school graduate/some college	2,037	51	41	47	34	60	59	61
College graduate or higher	1,200	30	54	46	63	8	8	8
Low income[d]	1,738	45	26	33	18	62	62	60
Currently employed	1,790	45	52	51	53	39	37	44

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; MACS, Multicenter AIDS Cohort Study; PLWH, people living with HIV; SN, seronegative; WIHS, Women's Interagency HIV Study.

[a] Includes 1,899 cisgender men and 3 transgender women who participated in the MACS.

[b] Includes 2,114 cisgender women and 1 transgender man who participated in the WIHS.

[c] Values are expressed as median (interquartile range).

[d] Low income was defined differently by study among participants with known current income (n = 3,855): as household income ≤$18,000/year in the WIHS and as individual income <$20,000/year in the MACS.

Harmonized data

The merged MWCCS will collect new data under a unified protocol from October 2020 through September 2021, and data from that first MWCCS visit will be cleaned and available for analysis in 2022. The longitudinal data previously collected over 35 years are currently available, and key variables have been harmonized to facilitate utilization and analysis. Table 4 gives the characteristics of harmonized summary files (which utilize longitudinal data to define key

Table 3.   HIV-Related Characteristics of MACS Men and WIHS Women Living With HIV at Their 2018–2019 Study Visit

HIV Characteristic at Most Recent Study Visit	All PLWH (n = 2,492)		Prevalence Among PLWH, %		P Value
	No.	%	Men (n = 1,004)	Women (n = 1,488)	
HIV serostatus					<0.001
HIV-seroprevalent	2,236	90	76	99	
HIV-seroincident (seroconversion since enrollment in study)	256	10	24	1	
CD4 cell count nadir, cells/mm^3					<0.001
≥500	263	11	12	10	
350–499	427	17	21	15	
200–349	813	33	35	31	
<200	989	40	33	44	
Current CD4 cell count, cells/mm^3 [a]					
<350	315	13	12	14	0.13
<200	107	5	3	5	0.01
Current HIV viral RNA load[b]					0.06
Not detected (<20 copies/mL)	1,765	74	77	73	
Detected (≥20 copies/mL)	606	26	23	27	
Ever use of ART					0.98
Never used	47	2	2	2	
Ever used	2,445	98	98	98	
Current use of ART	2,328	93	96	92	<0.001
ART adherence among those currently receiving treatment					
100% adherent	1,185	51	49	52	0.14
≥95% adherent	2,088	90	92	88	0.003
History of clinical AIDS	607	24	11	33	<0.001
Time from estimated HIV seroconversion to most recent visit[c], years[d]	23 (12–30)		24 (12–30)	17 (11–20)	0.02
CD4 cell count nadir, cells/mm^3 [d]	241 (125–366)		273 (159–393)	223 (106–346)	<0.001
Current CD4 cell count, cells/mm^3 [d]	669 (470–903)		644 (476–850)	689 (463–930)	0.01
HIV viral RNA load, log$_{10}$ copies/mL (among those detected)[d]	2.1 (1.6–3.5)		1.8 (1.6–2.5)	2.2 (1.6–3.9)	<0.001
Years since ART initiation (among current users)[d]	16.9 (8.6–23.2)		20.3 (9.9–27.7)	13.3 (8.3–22.3)	<0.001

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; MACS, Multicenter AIDS Cohort Study; PLWH, people living with HIV; WIHS, Women's Interagency HIV Study.

[a] Among participants with a known current CD4 cell count (n = 2,372).

[b] Among participants with a known current HIV viral RNA load (n = 2,371). HIV viral RNA load in the past 2 years was unknown (not measured) among 10% of men (these were primarily men who completed a telephone visit only) and 1% of women.

[c] Calculated among the 256 participants with known HIV seroconversion ("seroincident") during study follow-up.

[d] Values are presented as median (interquartile range).

risk factors and outcomes) that have recently been created, as well as harmonized comorbidity definitions utilized in this paper, which are all now available for investigator use (upon concept sheet approval—see the investigators' "Work With Us" section of the website) (6). The data harmonization process involved detailed review of areas of research between the MACS and the WIHS. Study definitions, question wording, and data categorization were compared by the data management team and vetted by scientific collaborators when criteria differed between the studies in order to create combined variables with comparable criteria and maintain clinically or behaviorally appropriate cutoffs by sex.
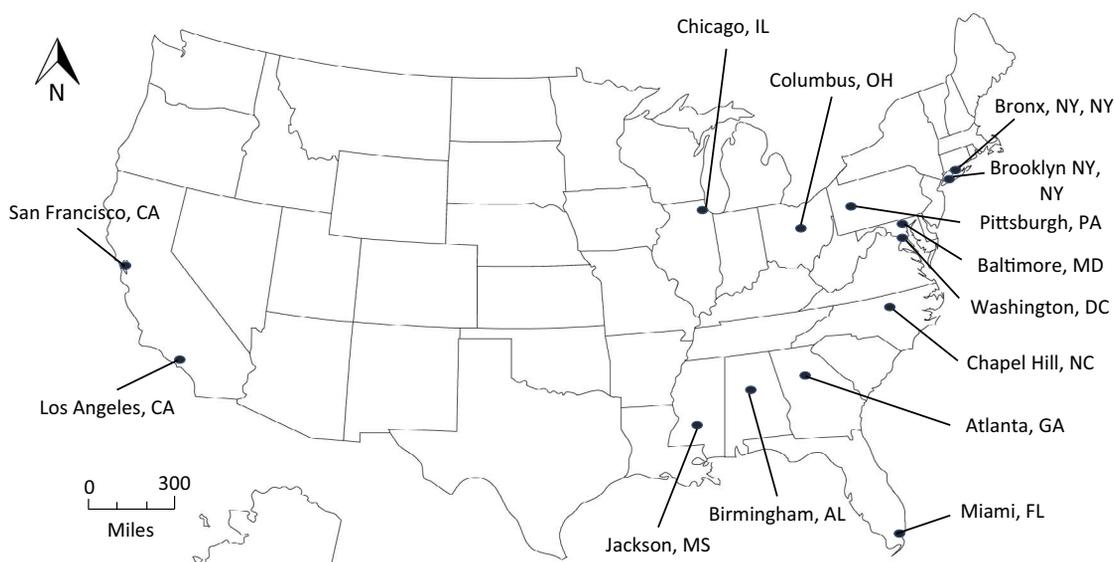
Figure 2. Geographic locations of MACS/WIHS Combined Cohort Study sites across the United States, 2020. AIDS, acquired immunodeficiency syndrome; AL, Alabama; CA, California; DC, District of Columbia; FL, Florida; GA, Georgia; HIV, human immunodeficiency virus; IL, Illinois; MACS, Multicenter AIDS Cohort Study; MD, Maryland; MS, Mississippi; NC, North Carolina; NY, New York; OH, Ohio; PA, Pennsylvania; WIHS, Women's Interagency HIV Study.

Health behavior profile

The behavioral characteristics of current MACS and WIHS participants are presented in Table 4. Because men and women were enrolled within 2 previously independent cohorts, some of their lifestyle characteristics are known to differ, while others are similar. Current use of alcohol (62%) and tobacco (28%) is common. These include binge drinking (7%) and more than 20 pack-years of smoking (20%).

While ever use of drugs and tobacco is similar in MACS and WIHS participants, current use differs significantly. Most participants smoked in the past (68%), and current smoking is more common in women than in men (36% vs. 18%; $P < 0.001$). Recent (past 6 months) marijuana use (29%) is common, and medical marijuana use is more common in men than in women (14% vs. 3%; $P < 0.001$). Recent use of "poppers" (sexual enhancement drugs containing alkyl nitrites) is common among male participants (21%). Conversely, recent opioid use is more common among women than among men (15% vs. 7%; $P < 0.001$), though use of opioids is similar among PLWH and HIV-seronegative persons of each sex (Table 4). More than half (55%) of participants have reported ever using "crack" cocaine, other forms of cocaine, or heroin, and 8% of participants have reported current use of at least 1 of these substances. Current injection drug use is rare (1%), though past use is more common (14%).

Most male participants are MSM (by design at enrollment in the MACS) and report having had sex with another man (97%); however, 67% of men report ever having had sex with a woman (Table 4). Most female participants are heterosexual, with 100% reporting ever having sex with a man but 32% also reporting ever having sex with a woman.

Most participants report having had sex in the past 6 months, including with a recent male partner (61% of men, 53% of women), a recent female partner (7% of men, 3% of women), and recent male and female partners (2% of men, 1% of women). The median number of recent sexual partners is the same among men (median, 1; IQR, 0–3) and women (median, 1; IQR, 0–1).

Comorbidity profile

Data on comorbidity and on treatment of some chronic conditions (e.g., lipid-lowering medication, hypertension medication) are routinely collected. Data were compared and harmonized for several key comorbid conditions (Table 1), and prevalence was explored (Table 5). Common comorbid conditions among participants include dyslipidemia (64%), hypertension (56%), obesity (42%), depressive symptoms (28%), diabetes (22%), and severely impaired instrumental activities of daily living (21%). Some participants have kidney disease (11%), frailty (7% of men), and a history of cancer (7%) (Table 5). Participants living with HIV have a higher prevalence than seronegative participants of several comorbid conditions, including diabetes, the metabolic syndrome, kidney disease, liver fibrosis, impaired instrumental activities of daily living, depressive symptoms, and chronic hepatitis B virus and hepatitis C virus infection. The 2 groups have similar prevalences of obesity, hypertension, dyslipidemia, and frailty. Among PLWH, men are less likely than women to be obese (23% vs. 55%; $P < 0.001$), to have the metabolic syndrome (28% vs. 47%; $P < 0.001$), or to have chronic hepatitis C virus infection (5% vs. 9%; $P < 0.001$) and are more likely to have liver fibrosis

A)

B)
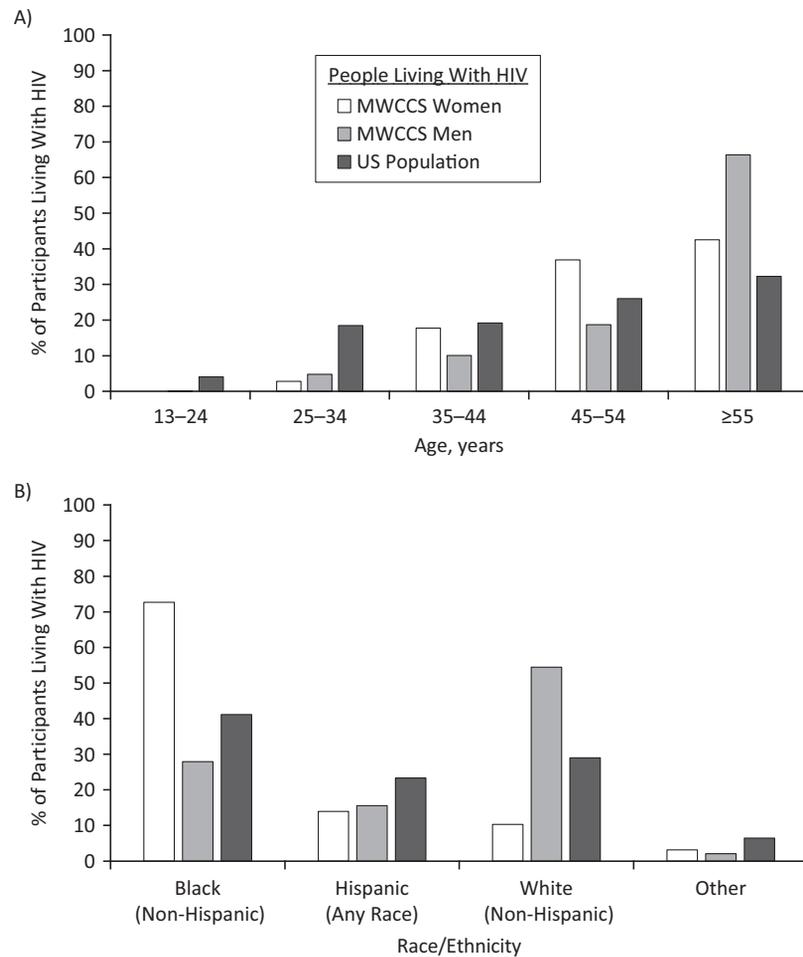
Figure 3. Distributions of current MACS/WIHS Combined Cohort Study (MWCCS) participants living with human immunodeficiency virus (HIV) according to age (A) and race/ethnicity (B), by sex and compared with all people living with HIV in the United States (8), October 2018–September 2019. AIDS, acquired immunodeficiency syndrome; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study. The "Other" category comprises Asian, Native Hawaiian/other Pacific Islander, Native American/Alaska Native, and other races/multiracial.

(4% vs. 3%; $P = 0.05$) and a history of cancer (10% vs. 6%; $P < 0.001$); see Web Table 1. These differences may be explained by sex-based differences in age, hepatitis C and other risk factors, and confounders.

Novel data on cardiac, pulmonary, and sleep-related health from 4 recent substudies funded by the National Heart, Lung, and Blood Institute are available for analysis. These include data from 1) electrocardiograms performed on 3,408 participants (MACS: 2016–2017 ($n = 1,473$); WIHS: 2017–2019 ($n = 1,935$)) (13–15) with Zio Patch rhythm monitoring (iRhythm Technologies, Inc., San Francisco, California; among men only); 2) echocardiograms performed on 2,412 participants (MACS: 2017–2018 ($n = 1,156$); WIHS: 2018–2019 ($n = 1,256$)); 3) pulmonary function testing on 2,850 participants (MACS: 2017–2018 ($n = 1,165$); WIHS: 2018–2019 ($n = 1,685$)), with pre- and postbronchodilator administration spirometry and diffusing capacity (16); and 4) overnight sleep studies performed on 842 participants (MACS only: 2018–2019).

Available specimens

The national repository for the MWCCS (Precision for Medicine, Frederick, Maryland) includes all of the historically collected biospecimens and has the capacity to store prospectively collected materials. The repository includes a wide range of types of samples collected at MACS and WIHS semiannual visits.

In Table 6, the number of person-visits for which samples are available in the repository is listed for each biospecimen type. These include the number of person-visits with samples for current participants (i.e., those active in the study in 2018–2019), and the number of person-visits for all participants who were ever included in the study. Many visits included multiple samples per participant per visit; the number of samples available in the repository is shown in Web Table 2.

Serum and plasma have been collected at every semiannual in-person visit since the beginning of each study.

Table 4.   Behavioral Characteristics of MACS Men and WIHS Women at Their 2018–2019 Study Visit, by Sex and HIV Status

Characteristic at Most Recent Study Visit	Total (n = 4,016)		Prevalence, %							
			Men				Women			
	No.	%	All Men (n = 1,901)	PLWH (n = 1,004)	HIV-SN (n = 897)	P Value	All Women (n = 2,115)	PLWH (n = 1,488)	HIV-SN (n = 627)	P Value
Drug use										
Ever injecting drugs	571	14	12	16	7	<0.001	16	16	17	0.67
Ever using marijuana	3,024	75	80	80	81	0.65	71	68	78	<0.001
Ever using cocaine or heroin	2,205	55	55	61	48	<0.001	55	53	59	0.01
Recent drug use (past 6 months)										
Marijuana	1,149	29	36	39	32	0.002	23	21	28	0.001
Medical marijuana	327	8	14	17	10	<0.001	3	4	2	0.03
"Poppers"[a]	397	N/A	21	25	18	<0.001	N/A	N/A	N/A	N/A
Prescription barbiturates	552	14	19	19	18	0.81	9	10	7	0.04
Opioids (nonprescription or prescription)	441	11	7	7	7	0.95	15	15	14	0.30
Cocaine or heroin	300	8	8	10	6	0.003	7	6	9	0.01
PrEP use										
Ever use of PrEP	130	9	N/A	N/A	13	N/A	N/A	N/A	2	N/A
Recent use of PrEP	111	7	N/A	N/A	12	N/A	N/A	N/A	1	N/A
Cigarette smoking										
Ever having smoked	2,740	68	69	70	67	0.19	68	66	73	0.002
Current smoker	1,111	28	18	22	14	<0.001	36	34	41	0.004
Pack-years of smoking (among ever smokers)[b]	10 (3–23)		11 (1–30)	12 (2–29)	10 (0.3–32)	0.05	10 (4–19)	9 (4–18)	10 (3–20)	0.80
Alcohol use[c]										
Abstainer (no drinks)	1,508	38	22	23	21	0.11	53	56	45	<0.001
Light drinking	1,953	50	69	69	69		32	31	36	
Moderate, heavy, or binge drinking	484	12	9	8	11		15	13	20	
Sexual behaviors										
Ever having a male sexual partner	3,950	98	97	97	96	0.22	100	100	100	0.30
Ever having a female sexual partner	1,923	48	67	70	63	0.005	32	29	39	<0.001
Recent sex (past 6 months)										
Any recent male partners	2,240	56	61	62	60	0.56	53	49	61	<0.001
Any recent female partners	181	5	7	6	8	0.11	3	2	5	<0.001

Table continues

Table 4. Continued

Characteristic at Most Recent Study Visit	Total (n = 4,016)		Prevalence, %							
			Men				Women			
	No.	%	All Men (n = 1,901)	PLWH (n = 1,004)	HIV-SN (n = 897)	P Value	All Women (n = 2,115)	PLWH (n = 1,488)	HIV-SN (n = 627)	P Value
No. of recent sexual partners[d]										
0	1,580	40	34	34	34	0.34	45	49	35	<0.001
1	1,495	38	26	25	28		48	46	53	
≥2	871	22	40	41	38		7	4	11	
Sexually transmitted infection (other than HIV)										
Ever	2,704	67	91	93	88	<0.001	47	49	41	<0.001
Past 6 months	295	7	14	14	14	0.99	2	2	1	0.38

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; MACS, Multicenter AIDS Cohort Study; N/A, not applicable; PLWH, people living with HIV; PrEP, preexposure prophylaxis; SN, seronegative; WIHS, Women's Interagency HIV Study.
[a] Sexual enhancement drugs containing alkyl nitrites.
[b] Values are expressed as median (interquartile range).
[c] Alcohol use was categorized differently for men and women, using number of drinks per week. Light alcohol use was defined as 1–7 drinks/week in the WIHS and 1–13 drinks/week in the MACS. Any alcohol use above this level was included in the "moderate, heavy, or binge drinking" group. Binge drinking is reported separately in the text and was defined as consuming ≥4 (women) or ≥5 (men) alcoholic drinks at one sitting at least once per month.
[d] Among participants with a known number of recent sexual partners (n = 3,945).

There are 224,856 person-visits with archived serum and 225,277 person-visits with archived plasma remaining in the biorepository (Table 6), including 1,165,535 and 1,368,395 vials, respectively (Web Table 2). Beginning in 1994, peripheral blood mononuclear cells were collected in both studies from blood samples taken at every visit, and cell pellets were generated when the quantity of material was sufficient. There are 217,167 person-visits with viable cryopreserved peripheral blood mononuclear cells and 88,355 person-visits with cell pellets remaining in the biorepository (Table 6). Urine was collected at every visit during selected periods (men: 1984–1991 and 2009–2014; women: 1994–1998 and annually from 2009 to 2019). Among women, cervicovaginal lavage samples have been collected since 1994. Plasma ethylenediaminetetraacetic acid collection was added for men in 2006 and in 2014 for women. Stool and semen were collected from men and then stopped, as were saliva samples from both men and women (see Table 6 for dates).

DISCUSSION

Participants from the MACS and WIHS provide a rich resource, with detailed, prospectively collected longitudinal data and an array of biospecimens with which to retrospectively examine a wide range of epidemiologic, mechanistic, and clinical research questions related to the progression of HIV. There is an average of 17 years of semiannual collection of comprehensive risk factor information for these participants and similarly collected data (using the same protocol) for HIV-seronegative participants, providing a critical control group for analyses of associations with HIV within each cohort.

We have shown that the study populations of both cohorts are ideal for integration into a single cohort to examine comorbidity among persons living with treated HIV, since most participants report being on ART (with a median of 17 years since ART initiation) and have well-controlled disease (a median current CD4 count of 669 cells/mm³). However, the study also includes participants who started therapy late, participants who are not adherent, and participants with a history of clinical AIDS, allowing analyses of associations with these differences as well. This paper harmonizes these data and presents key characteristics of active participants in the MACS and WIHS, demonstrating the types of comparable data that are available historically in both cohorts and can now be used in joint analyses. Participants largely represent adult PLWH in the United States by age and race/ethnicity (Web Figure 2) and geography (recruitment of Southern men will be a focus of the new recruitment). Because most participants have been treated for many years, they may not represent persons newly initiating therapy; however, 13% of the cohort was recruited in the past 5 years, with additional

Table 5. Prevalence of Comorbidity Among MACS and WIHS Participants Living With HIV and HIV Seronegative Participants at Their 2018–2019 Study Visit, by HIV Status[a]

Characteristic at Most Recent Study Visit[b]	No. of Participants	Prevalence, %			P Value[c]
		Total (*n* = 4,016)	PLWH (*n* = 2,492)	HIV-Seronegative (*n* = 1,524)	
Metabolic characteristics					
Body mass index category[d]					0.70
Underweight ($<$18.0)	62	2	2	2	
Normal-weight (18.0–24.9)	994	25	25	26	
Overweight (25.0–29.9)	1,149	31	31	31	
Obese ($\geq$30.0)	1,588	42	43	41	
Hypertension	2,164	56	55	56	0.83
Diabetes mellitus	828	22	23	20	0.04
Metabolic syndrome	1,300	37	40	33	<0.001
Cardiovascular disease					
Dyslipidemia	2,435	64	65	63	0.33
Use of cholesterol-lowering medication	1,316	33	33	33	0.54
ACC/AHA Pooled Cohort Equations score (risk of coronary death or MI)					<0.001
Low ($<$5.0%)	1,470	41	45	33	
Moderate (5.0%–7.4%)	451	12	13	11	
High ($\geq$7.5%)	1,704	47	42	56	
Framingham Risk Score (risk of coronary death or MI)					<0.001
Low ($<$10%)	2,496	67	70	62	
Moderate (10–20%)	496	13	10	18	
High ($>$20%)	728	20	20	20	
History of cancer	290	7	8	6	0.10
Kidney function					<0.001
Normal (eGFR $\geq$60.00 mL/minute/1.73 m^2)	3,339	88	85	92	
Kidney disease (eGFR 15.00–59.99 mL/minute/1.73 m^2)	429	11	14	7	
Kidney failure (eGFR $<$15.00 mL/minute/1.73 m^2)	27	0.7	0.8	0.5	
Instrumental activities of daily living					<0.001
Not impaired (within normal limits)	2,286	70	67	75	
Mild impairment	325	10	11	8	
Severe impairment	676	21	22	18	
Aging					
"Slow walker" phenotype	391	12	11	12	0.39
"Weak" (grip-strength) phenotype	768	24	22	26	0.005
Fried frailty phenotype (men only)					0.46
Nonfrail	909	57	59	56	
Prefrail	568	36	35	37	
Frail	111	7	6	8	

Table continues

Table 5.   Continued

Characteristic at Most Recent Study Visit[b]	No. of Participants	Prevalence, %			P Value[c]
		Total (n = 4,016)	PLWH (n = 2,492)	HIV-Seronegative (n = 1,524)	
CES-D score ≥16 (at risk for depression)	1,108	28	30	25	0.002
Liver function					
Abnormal AST level (>40 IU/L)	192	5	6	3	<0.001
Abnormal ALT level (>40 IU/L)	241	7	7	6	0.07
Significant fibrosis					
FIB-4 score >3.25	103	3	3	2	0.005
APRI score >1.50	30	0.8	1.1	0.4	0.02
HBV status[e]					<0.001
Never infected	2,371	59	55	66	
Resolved	1,290	32	34	30	
Chronic	112	3	3	2	
Unknown/inconclusive	243	6	8	3	
HCV status[e]					<0.001
Never infected	3,506	88	86	91	
Resolved infection (antibody-positive, RNA-negative)	90	2	3	2	
Chronic infection (active infection, RNA-positive)	260	7	8	5	
Unknown (antibody-positive, RNA unknown)	139	4	4	2	

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; APRI, AST:platelet ratio index; AST, aspartate aminotransferase; CES-D, Center for Epidemiologic Studies Depression Scale; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis 4; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MACS, Multicenter AIDS Cohort Study; MI, myocardial infarction; PLWH, people living with HIV; WIHS, Women's Interagency HIV Study.

[a] See Web Table 2 for definitions of these comorbid conditions.

[b] For some of the measures in this table, no data from the past 2 years were available. The prevalences reported in the table exclude missing data on the following variables: BMI (n = 273; 7%), hypertension (n = 119; 3%), diabetes mellitus (n = 172; 4%), metabolic syndrome (n = 509; 13%, including 3% never measured), dyslipidemia (n = 234; 6%), ACC/AHA Pooled Cohort Equations score (n = 391; 10%), Framingham Risk Score (n = 296; 7%), kidney function (eGFR) (n = 221; 6%), ALT (n = 324; 8%), AST (n = 221;6%), FIB-4 or APRI score (n = 223; 6%), instrumental activities of daily living (n = 729; 5% not measured in the past 5 years, and 13% never measured), "slow walker" phenotype (n = 640; 16%, including 8% never measured), "weak" phenotype (n = 770; 19%, including 8% never measured), and Fried frailty phenotype (n = 313; 16% (men only)). See Web Table 1 for definitions of these conditions.

[c] P values reported among participants with known values for each variable (i.e., excluding those with missing values).

[d] Weight (kg)/height (m)².

[e] HBV and HCV status were determined for all participants at their baseline (for each wave of participant enrollment). Some additional HCV measurements were made during follow-up among select participants (see Web Table 1). For HBV, additional measurements were done during follow-up in the MACS but not in the WIHS. Therefore, participant status may not reflect current status, since some participants classified as having active infection at baseline have probably since cleared their infections and some persons who were not infected at baseline could have since become infected.

enrollment of early-stage PLWH newly initiating therapy being planned.

Combining the MACS and WIHS cohorts into the MWCCS was a challenging process and led to several lessons learned (Figure 4). Merging of the scientific operations, cultures, and scientific priorities of 2 large decades-long cohort studies took time, but it was successfully accomplished. This created a study population with several notable strengths, as well as some limitations. First, the data centers for the 2 cohorts have merged and have harmonized core historical exposure and outcome data. Second, there are significant demographic differences in age, race/ethnicity,

Table 6. Numbers of Participant Visits With Samples in the MACS/WIHS Combined Cohort Study Biorepository as of May 1, 2020, and the Time Period During Which Each Type of Sample Was Collected in the MACS and WIHS

Specimen Type	No. of Participant Visits										Date Range of Data Collected	
	All Participants (Active, Censored, and Deceased)					Current Participants (n = 4,016)					Men (MACS)	Women (WIHS)
	Total	Men		Women		Total	Men		Women			
		PLWH	HIV-SN	PLWH	HIV-SN		PLWH	HIV-SN	PLWH	HIV-SN		
Serum	224,856	68,500	63,908	68,968	23,480	120,521	33,240	33,285	39,105	14,891	1984–2019	1994–2019
Plasma[a]	225,277	68,665	63,769	69,379	23,464	107,922	39,122	14,839	39,122	14,839	1984–2019	1994–2019
Plasma EDTA	45,764	21,215	20,562	2,824	1,163	58,010	38,043	16,021	2,798	1,148	2006–2019	2014–2019
Peripheral blood mononuclear cells	217,167	63,825	62,509	67,741	23,092	105,938	38,352	14,617	38,352	14,617	1994–2019	1994–2019
Cell pellets	88,355	1,499	1,309	63,440	22,107	53,974	946	856	37,691	14,481	1994–2019	1994–2019
Urine (clean void)[b]	43,453	12,558	12,481	14,109	4,305	60,924	39,105	14,891	4,955	1,973	1984–2014	1994–2019
Urine (supernatant)[b]	35,039	N/A	N/A	25,919	9,120	21,546	N/A	N/A	15,253	6,293	NC	1994–2019
Cervicovaginal lavage	91,853	N/A	N/A	67,390	24,463	54,064	N/A	N/A	38,043	16,021	NC	1994–2019
Oral sample[c]	7,512	669	1,000	4,773	1,070	2,165	121	235	1,437	372	1984–1993	1995–2004
B-cell lines	3,354	2,655	699	N/A	N/A	704	509	195	N/A	N/A	N/A	NC
Stool	6,851	3,252	3,599	N/A	N/A	3,946	2,798	1,148	N/A	N/A	1984–1985	NC
Semen	21,557	10,290	11,267	N/A	N/A	1,809	1,437	372	N/A	N/A	1984–1993	NC

Abbreviations: AIDS, acquired immunodeficiency syndrome; EDTA, ethylenediaminetetraacetic acid; HIV, human immunodeficiency virus; MACS, Multicenter AIDS Cohort Study; N/A, not applicable; NC, not collected; PLWH, people living with HIV; SN, seronegative; WIHS, Women's Interagency HIV Study.

[a] Plasma samples were stored in cell preparation tubes containing the anticoagulants heparin and sodium citrate for the MACS and WIHS, respectively.

[b] Oral samples were throat washes in the MACS and saliva samples in the WIHS.

[c] Urine was collected at every visit during selected periods (men: 1984–1991 and 2009–2014; women: 1994–1998 and annually from 2009 to 2019).

Figure 4. Lessons learned from merging the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) cohorts into the MACS/WIHS Combined Cohort Study. AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; sIRB, single institutional review board.

socioeconomic status, and geography between women from the WIHS and men from the MACS, which can confound analyses by sex. These differences in part represent racial/ethnic (Web Figure 2B) and socioeconomic differences in MSM living with HIV and women living with HIV in the United States. However, they pose a notable limitation of the merger and will need to be accounted for in analyses. Third, integrating operations required agreeing on shared language for data-sharing (Data Use Agreement) and specimen-sharing (Material Transfer Agreement) agreements across the many legal entities involved, which was time-consuming but resulted in a large merged study repository with similar sample types and study intervals in the 2 cohorts. Fourth, going forward, men and women living with HIV and similar seronegative individuals will be followed using identical protocols, facilitating sex-based comparisons.

MACS and WIHS study investigators have published over 2,900 research articles to date. In 2019, 194 research proposals (called concept sheets) were submitted to the MWCCS for new studies, including 99 from investigators not affiliated with the MWCCS. The MWCCS has 13 scientific working groups in which study investigators collaborate within specific research areas, including aging, clinical outcomes, cardiovascular disease, genomics, human papillomavirus infection, liver disease, malignancy, metabolism, neuropsychology, psychosocial factors, pulmonary function,

sleep, and viral immune pathogenesis. Examples of high-impact MACS and WIHS research include: identification of causes of and disparities in mortality among PLWH (10, 17); exploration of the associations of HIV infection with diabetes (18, 19) and cardiovascular disease (20–22); examination of cervical human papillomavirus infection among PLWH (23–26); evaluation of hepatitis C virus–related liver disease as a major cause of morbidity and mortality in PLWH (27, 28); characterization of the impact of HIV on neurocognitive function (29–31) and frailty (32, 33); and increasing understanding of the roles of psychosocial and geographic factors in health-care access, utilization, and outcomes among PLWH (34–36). Examples of impactful findings include research utilizing biospecimens to evaluate prognostic markers for HIV and AIDS and to understand the HIV reservoir (37–40), studies on the associations of HIV infection and HIV therapies with comorbidity (18, 41–43), and studies comparing PLWH and HIV-seronegative persons in the cohorts to understand the associations of HIV infection with comorbidity and mortality (28, 44). In addition, the MACS and WIHS have contributed to many impactful multicohort analyses, such as the examples in references 45–48, each of which has been cited over 950 times (45–48).

With the shift in research focus in recent years from ascertaining the natural history of HIV and responses to ART, to evaluating HIV serostatus-based differences in aging, the merged MWCCS serves as a robust and well-characterized cohort in which to study the myriad factors and circumstances that surround these processes. We encourage interested investigators, especially those at an early career stage, to submit proposals for research. Proposals to use biospecimens or study data are submitted using our online system (see website for details) (6) and reviewed by relevant working groups. External investigators are assigned an MWCCS liaison to facilitate communication and feasibility during concept sheet preparation. Some samples from high-priority visits (for example, visits around HIV seroconversion or comorbidity diagnosis) are considered restricted and require additional committee review and approval before release.

In summary, the MWCCS is a trans-NIH–supported observational cohort study that aims to advance understanding of the effects of HIV on aging, chronic comorbid illnesses, and psychosocial outcomes. It provides access to the rich retrospective data and biospecimens already collected in both the MACS and the WIHS and serves as a unique and valuable resource for investigators not only to study HIV-related research questions but also to increase knowledge of these diseases in HIV-seronegative individuals.

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