Predictors and Consequences of Prescription Opioid Use in Women Living With and Without HIV: 20-Year Follow-Up

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Abstract

Objective: To examine predictors and consequences of prescription opioid use among a cohort of women living with HIV (WLWH) and women without HIV from 2000 to 2019.

Materials and Methods: The Women's Interagency HIV Study is a multisite, prospective cohort study. Cumulative proportion of visits with prescription opioid use was categorized as follows: minimal (0%–9%), intermediate (10%–39%), and chronic (>40%). Logistic regression examined independent predictors, and proportional hazards regression estimated unadjusted and adjusted hazards of all-cause mortality, comparing intermediate and chronic prescription opioid use with minimal use.

Results: Annual prevalence of prescription opioid use significantly increased from 12.6% to 19.3% from 2000 to 2019 ($p < 0.0001$). Prescription opioid use was minimal in 75%, intermediate in 16%, and chronic in 9% of women. WLWH had 56% higher odds of chronic prescription opioid use compared with women without HIV. Even after adjusting for quality-of-life scores including ratings of pain, women with intermediate and chronic prescription opioid use had greater odds of being sexual minorities (lesbian or bisexual), unemployed, and were more likely to report benzodiazepine and nonprescription substance use compared with those with minimal use. Intermediate and chronic prescription opioid use were each associated with an almost 1.5-fold increased risk of all-cause mortality.

Conclusions: Despite federally mandated opioid prescribing guidelines, prescription opioid use and related mortality significantly increased in women experiencing physical and psychosocial vulnerabilities. The higher mortality rate found among prescription opioid users may reflect the many underlying chronic medical and

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psychosocial conditions for which these opioids were prescribed, as well as complications of opioids themselves. Findings underscore the need for non-opioid and nonpharmacological interventions for chronic pain, particularly in sexual minorities and WLWH. Avoiding concurrent use of opioids with benzodiazepines and nonprescription drugs might reduce mortality.
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Introduction

The opioid epidemic is a major public health crisis in the United States. Opioid use, overdoses, and related deaths are increasing; of the 67,367 overdose deaths reported during 2018, 70% involved opioids.[1,2] Although more men than women are dying of drug overdoses, the crude rate of drug overdose deaths in women increased by 260% between 1999 and 2017, with deaths from any opioid use rising almost 500%.[3]

Opioids may be prescribed for pain or other symptoms, and nonprescription use is reported for self-medicating chronic pain, withdrawal symptoms, and euphoria. Women are more likely than men to receive outpatient opioid prescriptions and to initiate their opioid use through prescriptions.[4] Although estimates suggest that 48% of people in care for HIV have substance use disorders, the prevalence of opioid use disorder (OUD) is lower, at roughly 4%.[5] Sharma et al. found that 65% of women living with HIV (WLWH) and 67% of women without HIV in the Women's Interagency HIV Study (WIHS) used prescription opioids for pain management.[6] While most participants reported receiving prescriptions for opioids, 8% of WLWH and 14% of women without HIV reported nonprescribed opioid use.

Prescription opioid use is also found to be correlated with geography, race and age as well as lower income, education, unemployment, depressive symptoms, pain symptoms, decreased social, role, and physical functioning, sexual minority status (self-identification as lesbian or bisexual), a history of abuse, transactional sex, prescription benzodiazepine use, and nonprescription drug use including injection drug use.[7–10]

Longitudinal patterns of prescription opioid use among WLWH have not been well studied. One North Carolina study found opioid use decreased with longer time in HIV care during 2000–2014, and women were more likely to report episodic and chronic opioid use than men.[11] Analysis of the National Survey on Drug Use and Health data showed that trends in nonmedical use of prescription opioids and heroin use differ by sex, with women demonstrating slower decline in the rate of nonmedical use of prescription opioids and greater increases in the rate of heroin use compared with that of men.[12]

In the WIHS, all-cause mortality has decreased dramatically with increasing use of effective antiretroviral therapy.[13,14] However, patterns of prescription opioid use over time and their impact on mortality among WLWH, and at risk for HIV, have not been evaluated.

The objectives of this study were to (1) estimate the predictors of distinct patterns of prescription opioid use in a national cohort of WLWH or at risk for HIV during 2000–2019 and (2) estimate the unadjusted and adjusted associations of distinct patterns of prescription opioid use with all-cause mortality.

Materials and Methods

The WIHS is a multicenter study of HIV disease progression in WLWH and women at risk for HIV because of self-reported sexual or drug use risk behaviors ($n=4{,}982$).[15,16] Six sites (Bronx, Brooklyn, Washington DC, San Francisco, Los Angeles, and Chicago) enrolled participants during 1994–1995, 2000–2002, 2011–2012, and five southern sites (Atlanta, Birmingham, Jackson, Chapel Hill, and Miami) enrolled during 2013–2015.[17] The research protocol was approved by the institutional review board at each participating site.

Participants are surveyed on demographic and clinical information, have brief examinations, and provide biological specimens during semi-annual study visits. Each institution obtained written informed consent per human subjects' research committee guidelines. This study included 4,028 participants seen between January 2000 and December 2019. The baseline visit for this analysis was the participant's first study visit during this period.

We assessed current (in the past 6 months) opioid use by self-report at baseline and each subsequent study visit. Women were asked to report all prescribed medications, and those reporting drugs matching a list of opioids were categorized as taking prescribed opioids; those reporting matching medications for treating substance use disorder or responding affirmatively to participating in methadone or buprenorphine program were categorized as using medication for OUD (MOUD). Women who reported using heroin or methadone that was not prescribed, including both injected and noninjected use, were categorized as taking nonprescription opioids.

Annualized binary variables were created for each type of opioid use. If a given type of opioid use was reported at either visit in a given year, the binary variable was counted as yes for that year. To estimate the annual prevalence of opioid use, the annualized binary variables were combined and categorized into four mutually exclusive groups: (1) any prescription opioid use; (2) MOUD with or without nonprescription opioid use; (3) nonprescription opioid use only; and (4) no use.

We then defined three groups of prescription opioid use as the outcome for the first objective and the primary exposure for the second objective in the following way. At each visit, the number of visits of prescription opioid use, up to and including the current visit, was determined. The proportion of prescription opioid use visits was calculated as this sum divided by the total number of visits the participant attended, up to and including the current visit. This proportion was converted to a percentage and categorized into three groups based on distribution and clinical relevance: 0%–9% (minimal use), 10%–39% (intermediate use), 40% or more (chronic use). Because the only possible categories for the first two visits were minimal or chronic use, those visits were dropped and the remaining visits were annualized by keeping the last visit for a given calendar year.

Death certificates were obtained, and National Death Index Plus (NDI) searches were conducted annually for all known deaths and all participants lost to follow-up. Time to death from any cause was the outcome of interest for the second objective. We classified deaths with any of the following International Classification of Diseases, Tenth Revision codes as drug-related: T40.1–T40.6, T42.4, T43.0–T43.2, X40–X44, X60–X64, X85, and Y10–Y14.[3] Deaths without any of those codes were classified as non-drug-related, and deaths with missing causes were classified as unknown.

Potential confounders included both nonvarying factors (study site prevalence, race/ethnicity, sexual preference, and HIV status) and time-varying factors (categorized age, employment status, annual household income, housing status, type of health insurance, depressive symptoms measured by the Center for Epidemiological Studies Depression Scale [CES-D ≥ 16]), history and recent use of crack, cocaine, or heroin or intravenous drugs, smoking, risky alcohol use (>7 drinks/week), prescribed benzodiazepine use, transactional sex, and quality-of-life (QOL) scales from the Medical Outcomes Study.[18]

The QOL summary score that includes subscales of physical functioning (20% of summary score), pain (17% of summary score), and energy and fatigue (28% of summary score) was used as the surrogate measure of chronic pain. To resolve missing data on time-varying factors, we used list-wise carry-forward for up to 2 years. Variables without available data from the previous 2 years were left as missing and categorized as unknown.

To identify longitudinal correlates of prescription opioid use categories (intermediate and chronic use vs. minimal use), we used multinomial logistic regression models with generalized estimating equations to account for within-person correlation.[19] These models included age at the time of data collection to adjust for trends over time. For our examination of opioid use with mortality, we used Cox proportional hazards models with staggered entries, treating opioid use as time-varying.[14] Univariate models were run for each potential confounder.

All potential confounders with 95% confidence intervals (CIs) for the odds ratio (OR, logistic regression) or hazard ratio (HR, Cox regression) excluding 1.00 were considered statistically significant and were then included in a single model. Any potential confounders with a 95% CI including 1.00 were not included in the full model. To address residual confounding, factors dropped after univariate analysis were added back one at time and retained if the adjusted 95% CI excluded 1.00. All analyses were conducted using SAS (version 9.4).

Results

Although the majority of the 4,028 women reported no prescription opioid use, 469 (13%) reported taking prescription opioids at their baseline visit (Table 1). Baseline prevalence was 10% or more in San Francisco, Chicago, Atlanta, Birmingham, Chapel Hill, and Jackson. Prescription opioid users were older. White women had higher rates of prescription opioid use, along with participants who reported unemployment, very low annual income, and having public medical insurance.

Prescription opioid users had more depressive symptoms (higher CES-D scores) and lower QOL scores (reflecting higher pain, poorer physical functioning, and more fatigue). A history of transactional sex, use of prescription benzodiazepine, heroin, cocaine, or crack, and smoking were all more prevalent among women with prescription opioid use. Latinas had lower rates of prescription opioid use compared with Black and White women.

Figure 1 shows a substantial increase in percentage of women reporting any prescription opioid use over 20 years, increasing from 12.6% in 2000 to a peak of 23.4% in 2017 and modest decline to 19.3% in 2019. This upward trend was also present in the first three enrollment waves when assessed individually by enrollment wave (data not shown); it ranged from 12.6% in 2000 to 25.4% in 2019 for 1994–1995 recruits, from 5.2% in 2002 to 17.7% in 2019 for 2001–2002 recruits, from 20.6% in 2011 to 25.3% in 2019 for 2011–2012 recruits, and from 15.1% in 2014 to 13.2% for 2013–2015 recruits. This upward trend was also present in most sites when assessed individually by site (data not shown). The rate of nonprescription opioid use decreased from 3.5% in 2000 to 0.5% in 2019 and reported use of MOUD also decreased from 11.6% in 2000 to 4.0% in 2019.

Table 2 shows the model of unadjusted and adjusted predictors of intermediate (16% of cohort) and chronic (9% of cohort) prescription opioid use compared with minimal use (75% of cohort). The model used 40,058 observations contributed by 3,922 individual women. The average (standard deviation) number of observations per woman was 10 (6). Participants with a history of using crack, cocaine, or heroin or intravenous drugs (adjusted odds ratio [aOR], 1.85, 95% CI 1.46–2.35), reporting prescription benzodiazepine use (aOR, 1.83, 95% CI 1.44–2.32), and enrollment at a study site with ≥10% baseline prescription opioid use (aOR, 1.93, 95% CI 1.59–2.33) had almost twofold greater odds of being classified as engaging in intermediate prescription opioid use compared with minimal use.

The likelihood was even higher for chronic opioid use; those with a history of crack, cocaine, or heroin or intravenous drug use or participating at a site with higher baseline prescription opioid use had an almost fourfold greater odds of engaging in chronic prescription opioid use compared with minimal use. Recent crack–cocaine, cocaine, or heroin use (aOR 2.12, 95% CI 1.25–3.58), HIV infection (aOR 1.56, 95% CI 1.06–2.29), and older age (aOR 1.45, 95% CI 1.25–1.68) were statistically significantly associated with chronic opioid use compared with minimal opioid use.

Using benzodiazepines correlated with threefold greater odds of chronic prescription opioid use compared with minimal use. In addition, sexual minority status (*i.e.*, lesbian or bisexual) and being unemployed were each significantly associated with a greater than 1.5-fold greater odds of intermediate prescription opioid use compared with minimal use. Higher QOL scores (less pain and fatigue, better physical functioning) are associated with lower odds of intermediate (half the odds vs. minimal use) and chronic (1/3 the odds vs. minimal use) prescription opioid use.

Table 3 examines predictors of mortality during the study period. Intermediate (adjusted hazard ratio[aHR] 1.45, 95% CI 1.20–1.76) and chronic (aHR 1.39, 95% CI 1.11–1.74) prescription opioid use were significantly associated with almost 50% faster rates of all-cause mortality. HIV infection (aHR 2.74, 95% CI 2.12–3.54), history of current crack, cocaine, heroin, or injection drug use, smoking, older age, unemployment, extremely low income, public medical

Table 1. Characteristics and Prescription Opioid Use Reported in the First Year 2000–2019 (Study Baseline)

Characteristic	*Overall (n = 4,028)* Col %	*No RX use (n = 3,559)* Col %	*RX used (n = 469)* Col %
HIV status			
Seronegative	27	28	22
Seropositive	73	72	78
Site prevalence			
<10% (Bronx, Brooklyn, District of Columbia, Los Angeles, and Miami)	58	62	31
>10% (San Francisco, Chicago, Chapel Hill, Atlanta, Birmingham, and Jackson)	42	38	69
Age (years), mean (SD)	39 (9)	38 (9)	43 (9)
Self-identified race/ethnicity			
African American, non-Hispanic	64	63	66
Hispanic/Latina	21	22	13
White, non-Hispanic	12	11	19
All other races/ethnicities	3	3	3
Self-identified sexual preference			
Heterosexual	87	88	84
Lesbian/bisexual/other	13	12	16
Employment status			
Employed	30	31	20
Unemployed	70	69	80
Annual income			
≤$12,000	53	52	58
$12,001–$24,000	23	23	20
>$24,000	21	22	18
Not reported (missing)	3	3	3
Housing status			
Stable	67	67	68
Unstable	33	33	32
Insurance			
Public only	46	45	55
Private only	17	18	14
Combination of public and private	7	7	13
No insurance	30	31	19
Depressive symptoms (CES-D score ≥16)			
No	48	50	34
Yes	52	50	66
Quality-of-life summary score,[a] mean (SD)	68 (19)	70 (18)	55 (20)
Quality-of-life component scores (% of summary score)			
Emotional functioning score[a] (20), mean (SD)	65 (23)	66 (23)	59 (23)
Energy and fatigue score[a] (28), mean (SD)	59 (24)	60 (24)	48 (23)
Social functioning score[a] (5), mean (SD)	78 (24)	79 (24)	66 (25)
Role functioning score[a] (10), mean (SD)	81 (24)	83 (23)	64 (28)
Physical functioning score[a] (20), mean (SD)	73 (26)	75 (25)	56 (28)
Pain score[a] (17), mean (SD)	73 (24)	76 (23)	53 (26)
History of transactional sex			
Ever			
No	64	65	56
Yes	36	35	44
Recent			
No	94	94	93
Yes	6	6	7
Prescription benzodiazepine use			
No	94	96	80
Yes	6	4	20

(*continued*)

Table 1. (Continued)

Characteristic	*Overall* (n = *4,028*) Col %	*No RX use* (n = *3,559*) Col %	*RX used* (n = *469*) Col %
Crack/Cocaine/Heroin/IDU			
Ever			
No	44	46	29
Yes	56	54	71
Recent			
No	82	83	77
Yes	18	17	23
Recent tobacco use			
Nonsmoker	48	49	41
Smoker	52	51	59

[a]Medical Outcomes Study scales (Bozzette et al.[18]).

CES-D, Center for Epidemiological Studies Depression Scale; Col %, column percent; IDU, injection drug use; RX, prescription opioid; SD, standard deviation.

insurance, housing instability, and depressive symptoms were also independently associated with faster all-cause mortality rates in the model.

There were 601 deaths (68 HIV–, 533 HIV+) during the study period, with 62 drug-related (13 HIV–, 49 HIV+) and 114 HIV/AIDS deaths. The rate of drug-related deaths did not increase over the course of the study period.

Discussion

The prevalence of prescription opioid use among women in the WIHS doubled during the 20-year study period, even in the midst of federal and state efforts to curb prescriptions of opioid medications in response to the opioid epidemic.[20] Although the use of prescription opioids increased through 2017 and remained elevated through 2019 in the WIHS, national trends showed decreases from 2000 to 2011 in the general U.S. population.[21] In the WIHS, WLWH and sexual minority women had higher odds of engaging in chronic prescription opioid use. Findings underscore the urgent need for the implementation of non-opioid and nonpharmacological approaches to pain management, particularly among WLWH and sexual minority women.

While a history of injection drug use was reported by 36% of women using prescription opioids at baseline, the use of nonprescription opioids decreased in the years after enrollment, contrary to national trends of significant increases in heroin use and overdoses in women during the same period.[3] Having continued access to prescription opioids from their providers during this period might have reduced women's need to resort to nonprescription drugs such as heroin and fentanyl, as have been reported during this time period.[22] Of course the responsibility of clinicians and pharmaceutical companies in the aggressive marketing and distribution of opioid medications, which has led to this public health crisis cannot be underestimated.[23]

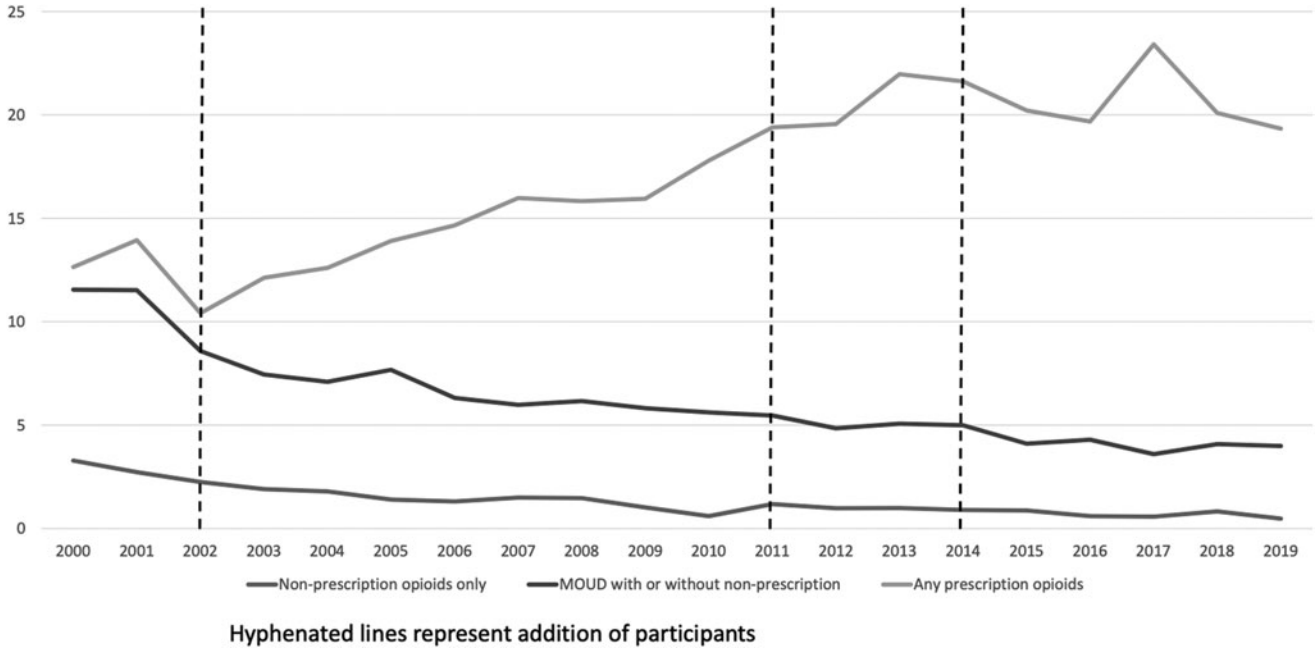

FIG. 1. Annual prevalence of opioid use in the Women's Interagency HIV Study 2000–2019.

Table 2. Predictors of Intermediate and Chronic Opioid Use in the Women's Interagency HIV Study 2000–2019 ($N = 3,922$)

	Intermediate versus minimal[a]				*Chronic versus minimal*[a]			
	OR	*95% CI*	*AOR*	*95% CI*	*OR*	*95% CI*	*AOR*	*95% CI*
History of use crack, cocaine, heroin, or injection drug use versus none	**2.72**	**2.25–3.30**	**1.85**	**1.46–2.35**	**6.53**	**4.58–9.32**	**3.91**	**2.56–5.95**
Recent crack, cocaine, heroin, or injection drug use versus none	**2.74**	**2.11–3.57**	1.23	0.90–1.67	**6.57**	**4.22–10.22**	**2.12**	**1.25–3.58**
Prescription benzodiazepine use	**3.28**	**2.64–4.08**	**1.83**	**1.44–2.32**	**8.97**	**6.86–11.73**	**3.08**	**2.26–4.19**
HIV seropositive	0.93	0.77–1.12	0.83	0.68–1.01	**1.87**	**1.34–2.62**	**1.56**	**1.06–2.29**
Site baseline prevalence ≥10% (versus Bronx, Brooklyn, District of Columbia, Los Angeles, and Miami)	**2.30**	**1.92–2.75**	**1.93**	**1.59–2.33**	**5.73**	**4.29–7.66**	**4.12**	**2.95–5.77**
Age (per 10 years)	**1.37**	**1.34–1.41**	**1.12**	**1.02–1.22**	**1.93**	**1.85–2.00**	**1.45**	**1.25–1.68**
Hispanic/Latina versus Black, non-Hispanic	**0.65**	**0.53–0.81**	**0.72**	**0.57–0.91**	0.73	0.50–1.07	0.89	0.59–1.34
White, non-Hispanic versus Black, non-Hispanic	1.11	0.84–1.47	0.82	0.61–1.11	**2.28**	**1.56–3.33**	1.17	0.73–1.89
All other races/ethnicities versus Black, non-Hispanic	0.97	0.62–1.50	0.87	0.56–1.35	1.48	0.72–3.04	1.36	0.62–2.99
Lesbian/bisexual/other	**2.17**	**1.72–2.73**	**1.52**	**1.18–1.96**	**2.53**	**1.77–3.62**	**1.61**	**1.06–2.44**
Not employed	**2.28**	**1.93–2.69**	**1.34**	**1.12–1.59**	**4.96**	**3.53–6.97**	**1.74**	**1.18–2.55**
Unstable housing	1.15	0.98–1.33	**0.82**	**0.70–0.97**	1.24	0.98–1.56	0.83	0.64–1.08
Quality-of-life index score[b]	**0.45**	**0.41–0.49**	**0.53**	**0.48–0.57**	**0.25**	**0.22–0.28**	**0.32**	**0.27–0.37**
History of transactional sex versus never	**1.92**	**1.61–2.30**	0.99	0.79–1.23	**2.24**	**1.68–2.99**	0.83	0.57–1.19
Recent transactional sex versus never	**1.94**	**1.24–3.06**	0.94	0.58–1.53	1.13	0.61–2.10	**0.45**	**0.23–0.89**

Bold indicates statistical significance based on 95% CI excluding 1.00.
[a]Prescription opioid use reported at 0%–9% (minimal), 10%–39% (intermediate), or 40%–100% (chronic) of visits.
[b]Medical Outcomes Study scales (Bozzette et al.[18]); one unit difference in *Z*-score.
AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

The rate of MOUD was stable from 2000 to 2013 and then decreased slightly thereafter. The decrease could be explained in part by differing rates of prescription opioid use by enrollment waves (higher rates in earlier cohorts and lower reported use of opioids by women in the southern cohort). In addition, there was a general decrease over time of nonprescription opioids once enrolled in the study. Evidence-based MOUD, including methadone and buprenorphine treatment, is standard of care for those with OUD, due to its proven effectiveness to reduce opioid use and health consequences, including overdose and deaths.[24,25] However, too few programs, insufficient numbers of trained providers, patient co-existing mental illness, and stigmatized treatment limit access to MOUD among many persons with OUD, including people living with HIV.[26,27]

This longitudinal study characterized patterns of prescription opioid use over 20 years to identify predictors of intermediate and chronic prescription opioid use. In the adjusted

Table 3. Predictors of All-Cause Mortality

	HR	*95% CI*	*AHR*	*95% CI*
HIV seropositive	**3.23**	**2.51–4.16**	**2.74**	**2.12–3.54**
Intermediate opioid use versus minimal opioids only	**2.16**	**1.80–2.61**	**1.45**	**1.20–1.76**
Chronic opioid use versus minimal opioids only	**3.12**	**2.51–3.88**	**1.39**	**1.11–1.74**
History of use crack, cocaine, heroin, or injection drug use versus none	**3.18**	**2.58–3.93**	**1.58**	**1.261.98**
Recent crack, cocaine, heroin, or injection drug use versus none	**4.33**	**3.29–5.69**	**1.56**	**1.15–2.11**
Current smoker versus current nonsmoker	**2.16**	**1.83–2.55**	**1.27**	**1.06–1.53**
Age (per 10 years)	**1.73**	**1.59–1.89**	**1.39**	**1.26–1.54**
Not employed	**6.61**	**4.99–8.76**	**2.36**	**1.72–3.25**
Annual household income ≤$12,000 versus >$24,000	**5.40**	**3.99–7.29**	**1.73**	**1.24–2.41**
Annual household income $12,001–$24,000 versus >$24,000	**2.44**	**1.72–3.46**	1.24	0.86–1.79
No medical insurance versus private medical insurance	**2.03**	**1.25–3.30**	1.11	0.67–1.85
Public medical insurance versus private medical insurance	**6.94**	**4.74–10.15**	**1.91**	**1.25–2.91**
Unstable housing	**1.60**	**1.32–1.94**	**1.25**	**1.02–1.52**
Depressive symptoms (CES-D score ≥16)	**2.66**	**2.25–3.13**	**1.70**	**1.43–2.01**

Bold indicates statistical significance based on 95% CI excluding 1.00.
AHR, adjusted hazard ratio; HR, hazard ratio.

longitudinal model, we examined what factors in addition to pain, poor physical functioning, and decreased energy and fatigue (measured by the QOL summary score) predicted intermediate and chronic prescription opioid use. Previous crack, cocaine, or heroin including injection use as well as prescribed benzodiazepines were associated with higher odds of intermediate and chronic prescription opioid use. This is consistent with previous studies which showed polysubstance use, including nonprescription substances and benzodiazepines, is associated with prescription opioid use and misuse.[28,29]

Participants from sites with high rates of prescription opioids continued to have higher rates of use throughout the study. Most women in the WIHS, especially WLWH, had access to health care providers during the study period, which might account for the increased rate of prescription opioid use as the study continued, especially among women with HIV. Also, while the cohort's HIV outcomes improved significantly and mortality decreased, participants might have been prescribed opioids because of their ongoing or new physical and psychological pain, as suggested by the association of lower physical, social, and role functioning and higher pain burden (lower QOL scores) with intermediate and chronic opioid use.

The higher rate of opioid use among sexual minority women has been reported previously in national data sets, with highest rates found among bisexual females.[8,30] Minority stress from sigma and discrimination coupled with lack of strong community support might be responsible for bisexual females turning to substance use and misuse to address these challenges. Providing support and culturally tailored substance use treatment may produce better health outcomes.

Unemployment was also a predictor of both intermediate and chronic prescription opioid use. Opioid use has been shown to be associated with significant greater likelihood of unemployment due to disability[31] and to be more prevalent in economically disadvantaged areas. For women in our study, it might also be a marker for lack of general opportunities for gainful employment.

Addressing these structural and cultural challenges by meeting the clinical and social needs of WLWH and women without HIV may contribute to improved comprehensive care opportunities and retention in evidence-based treatment including MOUD, leading to better health and QOL for women at risk for OUD.[32]

A previous study also found an elevated risk of mortality due to prescription opioid use in a cohort of people with and without HIV, especially when accompanied by co-prescribing of benzodiazepines for those individuals with HIV.[33] Although mortality was higher among prescription opioid users in this study, we did not find an increase in drug-related deaths over the course of the study. This differs from overall national U.S. trends reporting increased drug-related and opioid deaths between 1999 and 2017 in women, especially those 55–64 years.[3]

While prescription opioid use increased in the WIHS cohort, nonprescription drug use did not, in contrast to the national trend.[21] Perhaps the stable rate of drug-related deaths was due to providers prescribing opioids, and the concurrent reduction in nonprescription drug use (Fig. 1). Thus, the national increase in drug overdoses and deaths from heroin and fentanyl associated with misuse was not observed in our cohort as prescription opioid rates remained high.[3]

The higher mortality rate found among prescription opioid users may reflect the many underlying chronic medical and psychosocial conditions for which these opioids were prescribed, as well as complications of opioids themselves. The study found that mortality was higher for both chronic and intermediate prescription opioid use compared with minimal use, as others have found. Previous study of long-acting opioids prescribed for chronic noncancer pain also found a 1.6 increased risk of all-cause mortality possibly due to opioid-related cardiac or respiratory effects when compared with those treated with anticonvulsants or cyclic antidepressants.[34] Other studies have investigated the immunosuppressive properties of prescribed opioids, which may increase susceptibility to infections.[35–37]

Limitations of the study include self-reporting and lack of specificity of the prescription opioid data. Details on why, how much, and how often the participants took prescription opioids are not available. The increase in prescription opioid use and decrease in nonprescription opioids use might be due in part to study participation and resultant behavior change, as well as the lower opioid prevalence reported among women enrolled into WIHS after the initial study enrollment in 1994–1995. However, opioid use may be underreported due to social desirability bias and if so, the associated risk of opioid use with all-cause death might be higher than estimated. Tolerance, overdose episodes, or drug–drug interactions are also not assessed.

We are not able to precisely determine OUD among those reporting prescription opioid use. From our analysis, we cannot determine if women initially reporting nonprescription opioid use switched during the study to prescription opioid use. Also, the WIHS was not a closed cohort during this 20-year study period, so the longitudinal trends do not reflect a stable population, but one in which new participants joined the study at several enrollment times.

Conclusions

Even with federal and state mandates to decrease prescription opioid use, WLWH and women without HIV in the WIHS experienced multiple structural, economic, psychosocial assaults during this 20-year study, which predicted more severe patterns of prescription opioid use. Lending support to the clinical relevance of these findings, intermediate and chronic prescription opioid use predicted faster all-cause mortality rates. These findings underscore the need to provide effective and evidence-based interventions to address pain, economic despair and depression, and substance use disorders, particularly in WLWH and sexual minority women to reduce the use of prescription opioids and mitigate the increased risk for mortality.

Authors' Contributions

M.H.C., L.B., and A.W.C. contributed to the design, analyzed and interpreted the data for the study. M.H.C., K.M.W., A.S., M.P., M.-C.K., T.E.W., B.A., J.M., A.A.A., and G.W. contributed to the acquisition of the data. M.H.C. drafted the article, and all authors contributed to revising it critically for intellectual content. All authors provided final approvable and are accountable for all aspects of the study.

Disclaimer

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