Title

Association between Use of Methadone, Other Central Nervous System Depressants, and QTc Interval–Prolonging Medications and Risk of Mortality in a Large Cohort of Women Living with or at Risk for Human Immunodeficiency Virus Infection

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Abstract

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Study Objective: To evaluate the association between use of methadone, other central nervous system (CNS) depressants, and QTc interval–prolonging medications and risk of mortality among human immunodeficiency virus (HIV)-infected and at-risk HIV-uninfected women.

Design: Multicenter, prospective, observational cohort study (Women's Interagency HIV Study [WIHS]).

Participants: A total of 4150 women enrolled in the WIHS study between 1994 and 2014 who were infected (3119 women) or not infected (1031 women) with HIV.

Measurements and Main Results: Data on medication utilization were collected from all study participants via interviewer-administered surveys at 6-month intervals (1994–2014). Mortality was confirmed by National Death Index data. With age defining the time scale for the analysis, Cox proportional hazards models were used to estimate hazard ratios (HRs) for all-cause mortality in HIV-infected and -uninfected women and non–acquired immunodeficiency syndrome (AIDS) deaths in HIV-infected women. A total of 1046 deaths were identified, of which 429 were considered non-AIDS deaths. Use of benzodiazepines, CNS depressants (excluding methadone), and number of medications with conditional QTc interval–prolonging effects were each associated with all-cause mortality in multivariate models of HIV-infected women: hazard ratio (HR) 1.28, 95% confidence interval (CI) 1.01–1.60, p=0.037; HR 1.61, 95% CI 1.35–1.92, p<0.0001; and HR 1.15 per drug, 95% CI 1.00–1.33, p=0.047, respectively. Other explanatory variables for all-cause mortality in this model included HIV viral load, CD4+ cell count, renal function, hemoglobin and albumin levels, HIV treatment era, employment status, existence of depressive symptoms, ever use of injection drugs, and tobacco smoking. Of interest, use of CNS depressants (excluding methadone) was also associated with non-AIDS deaths (HR 1.49, 95% CI 1.49–2.2, p<0.0001). Although use of benzodiazepines and conditional QT interval–prolonging medications were associated with increased risk of non-AIDS mortality (HR 1.32 and 1.25, respectively), the effect was not statistically significant (p>0.05).

Conclusion: In this cohort of HIV-infected and at-risk HIV-uninfected women, use of benzodiazepines, CNS depressants, and conditional QTc interval–prolonging medications were associated with a higher risk of mortality independent of methadone and other well-recognized mortality risk factors. Care must be taken to assess risk when prescribing these medications in this underserved and at-risk patient population.

Individuals with chronic health conditions frequently take multiple medications including common use of opioid pain medications, sedatives, and muscle relaxants.(1) The Women's Interagency HIV Study (WIHS) cohort, which is the largest longitudinal observational study of human immunodeficiency virus (HIV) in women that includes a risk set–matched HIV-seronegative comparison group, has observed mortality rates of 25.2% (1180 women) over a period of 20 years (1994–2014), with 31.3% for HIV-infected and 6.8% for HIV-uninfected women. Reviewing the data over this period, we made a notable observation that the death rate for women who had ever used methadone in the WIHS was 45.0% (468/1039), whereas

this rate was 20.0% (712/3567) for non–methadone users. This observation necessitated further investigation.

Methadone, a long-acting, synthetic opioid receptor agonist, is a widely used pharmacotherapy for the treatment of opiate addiction as well as chronic pain. Although an effective and useful drug, methadone use is associated with mortality.(2–5) Whereas deaths related to opioids are primarily a result of overdose leading to respiratory suppression, methadone has been independently associated with prolongation of the QTc interval in electrocardiograms, which increases the risk of developing life-threatening arrhythmias and sudden cardiac death.(6–9) Furthermore, HIV-infected patients receiving combination antiretroviral therapy (cART) are at higher risk of arrhythmia while receiving methadone.(7, 10) This increased risk has the potential to predispose recipients of cART to arrhythmias and sudden mortality. Methadone use may be of a particular concern in HIV-infected women due to the association of female sex with longer baseline QTc intervals (11).

Sedatives and respiratory depressants may also be a particular concern in the HIV-infected population. Respiratory function abnormalities were associated with an increased risk of death in HIV-infected WIHS participants, and impaired pulmonary diffusion capacity was highly prevalent in WIHS participants.(12, 13) In this setting, drugs that diminish respiratory drive may result in marked abnormalities in ventilation.

Given the univariate finding of high incidence of mortality in women in the WIHS who used methadone, we sought to determine in a multivariate analysis whether methadone use may influence mortality among both HIV-infected and HIV-uninfected women in the WIHS. Since methadone has pharmacologic action on the QTc interval, respiratory system, and central nervous system (CNS) system, which each could contribute to mortality, and given the complex patients in our samples, care was taken to adjust the analysis for known nonmedication explanatory variables for mortality as well as other medications that shared the above described undesirable pharmacologic actions of methadone. These medications included benzodiazepines, QTc interval–prolonging medications, and other CNS depressants, as well as drug-drug interactions that could lead to CNS depression, which could influence mortality among women in the WIHS living with and without HIV. In this study, we report the impact of all of these explanatory variables on mortality.

Methods

Study Population

The WIHS is a multicenter, prospective, observational cohort study of women with and at risk for HIV infection; follow-up visits occur every 6 months. HIV-negative women reporting one or more of the following behaviors were considered at risk for HIV: injection drug use; having a sexually transmitted disease; having unprotected sex with three or more men or protected sex with more than five men; or having exchanged sex for drugs, money, or shelter.(14) At each visit, scripted interviews to collect self-reported data, clinical examinations, and various laboratory testing are conducted. The cohort is highly representative of women in the United States who are living with HIV infection.(14) Cohort methods have been described previously.(14, 15) For this analysis, use of methadone, other

CNS depressants, QTC interval-prolonging medications and interacting drugs were determined for 4150 WIHS participants over a 20-year period (1994–2014). WIHS participants consented to each visit according to human subject's protection protocols in place at each of the collaborating institutions.

Mortality Outcome

Cause of death was ascertained from various sources including death certificates (National Death Index), medical records, providers, and family/friends. This information was used to construct a final variable of causes of death based on the following four categories: acquired immunodeficiency syndrome (AIDS), non-AIDS, indeterminate, or unknown.(16) Importantly, medications such as methadone or other CNS depressants could contribute to all of these reported causes of death. Therefore, this analysis focused not only on non–AIDS-related deaths but also on all-cause mortality for all HIV-infected WIHS participants, with methadone use being a key predictor. All deaths in HIV-uninfected women were considered to be non-AIDS deaths. Because of a lag in the availability of comprehensive data from the National Death Index, mortality ascertainment for this study was complete for dates of death up to December 31, 2013; no deaths or observation time after that date were included in the analyses. All time following study disenrollment occurrence was also excluded.

Methadone Use

Various survey items were used to ascertain methadone treatment. Six forms of self-reported use (recent, recent prescribed, recent unprescribed, ever, ever prescribed, and ever unprescribed) were created from the available data. Prescribed methadone use was not specifically queried as part of the cohort data collection protocol from visits 17 (2002) to 38 (2013), so variables depending on that information were set to missing after 2 years of carry forward from visit 16.

Other Medication Explanatory Variables

Variables capturing use of QTc interval–prolonging medications, medications that could alter methadone plasma exposure, and use of other combinations of medications that could contribute to CNS depression were defined. Self-reported data from drug-specific multiple-choice and text fields were used to populate these variables. The medications contributing to QTc interval prolongation were divided into three categories: known, possible, or conditional (Supplementary Table S1).(17) By CredibleMeds'(18) (www.Crediblemeds.org); the conditional risk category includes medications that are associated with QTc interval prolongation only under certain conditions of their use that result in QTc interval prolongation. Tables of cytochrome P450 (CYP) 3A4, 2B6, and 2C19 inhibitors, and P-glycoprotein inhibitors were assembled (Supplementary Table S2).(19) Drug-drug interactions that could lead to CNS depression with (Supplementary Table S3) or without (Supplementary Table S4) methadone were identified and categorized as major, moderate, or mild using the Micromedex online drug reference database (20) (Figure 1). These included alcohol, opioids (methadone excluded), H_1-antihistamines, first-generation typical antipsychotics, barbiturates, hypnotics, benzodiazepines, and skeletal muscle relaxants.

Other Explanatory Variables

Care was taken to adjust for factors that might plausibly influence mortality risk, including those previously reported in the WIHS.(16, 21–28) In all, there were 53 candidate explanatory variables (Table 1 and Supplementary Table S5). To account for calendar time as a potential predictor of mortality reflecting changes in HIV care over this project period (1994–2014), a variable dividing this period into three separate treatment eras was created: prior to 1998, 1998–2004, and after 2004.

Statistical Analysis

All analyses were conducted by using R (R Foundation for Statistical Computing, Vienna, Austria) and SAS (SAS Institute Inc., Cary, NC) software. The mortality analysis did not combine HIV-infected and HIV-uninfected women since we suspect patterns and causes of mortality may differ in these two groups. Separate Cox proportional hazards models were constructed for HIV-infected and HIV-uninfected women. In HIV-infected participants, Cox proportional hazards models estimated hazard ratios (HRs) for all-cause and non-AIDS deaths using data from study enrollment to the end of 2013. Because of the importance of age in the risk of death, we used it to define the time scale for analysis instead of modeling its effect as a covariate. This fully controls for the effect of age while avoiding parametric assumptions about its effects. This same approach was taken to estimate HR in HIV-uninfected participants with the exception that in this group, all-cause and non-AIDS mortality are the same. Analyses were adjusted for various factors including previously described WIHS mortality risks and use of other opioids, CNS depressants, and drugs affecting QTc interval. All variables that were not fixed characteristics were handled as time-varying covariates: at a given time, each woman's predictor variables were equal to their reported, measured, or derived value at her most recent prior visit, as long as it was within 2 years. After 2 years with no data collection, variables were considered as missing, and those times were not included in the analyses. CD4+ cell counts >1000 were set to =1000. The "ever" variables were defined using data only up to the most recent previous visit, never any later visits. For all-cause mortality, the effect of $\log_{10}$ HIV viral load was nonlinear, so we modeled it as a linear spline, with knots (points where the line can change slope) at 3, 4, and 5. We selected primary multivariate models for presentation using forward stepwise selection with p<0.05 required for entry, with forced inclusion of HIV status, CD4+ cell count, and HIV viral load variables. We then evaluated each remaining unselected candidate predictor as a single addition to the chosen multivariate model. The analysis included all women who had at least one follow-up visit or who were known to have died after their baseline visit. Observation time for these analyses ended at the earliest of the following: time of death, 2 years after the last collection of predictor variables, disenrollment, or December 31, 2013.

Results

Characteristics of the Study Population

Age at study entry ranged from 18–69 years with a median age of 36 years for HIV-infected women, and 18–62 years with median age of 36 years for HIV-uninfected women. The duration of follow-up among those who did not die during the study period ranged from 0.4–

20 years, with median of 12 years for HIV-infected and -uninfected groups. Table 1 summarizes the characteristics of the 4150 women who contributed to this study, stratified by their HIV infection status as of their last observation. HIV-infected individuals were more likely (p<0.05) to have died, used prescribed methadone, had symptoms of depression, been infected with hepatitis B virus, ever used injection drugs, smoked, consumed alcohol, been unemployed, and had diminished estimated glomerular filtration rate (eGFR) and abnormal (values above or below normal range) hemoglobin and albumin levels relative to HIV-uninfected participants. There was no statistically significant difference between HIV-infected and -uninfected women at their last visit with respect to hypertension, self-reported race-ethnicity, hepatitis C virus (HCV) infection, recent use of injection drugs, or nonprescribed use of methadone.

The HIV-infected participants were more likely to have been taking medications that inhibit CYP3A4 and CYP2C19 metabolizing enzymes and P-glycoprotein efflux transporters (Supplementary Table S5). Additionally, the use of medications that could have contributed to CNS depression when combined with methadone was common among HIV-infected women. They were also more likely to use medications and opioids other than methadone that are known to increase the risk of CNS depression, benzodiazepines, and QTc interval–prolonging medications (all p<0.05). (Table 1 and Supplementary Table S5).

Explanatory Variables for All-Cause Death

Table 2 summarizes the results of Cox proportional hazards analyses, modeling explanatory variables' associations with all-cause death in HIV-infected and -uninfected participants. Except for methadone use variables, for brevity, only explanatory variables with p values less than 0.05 are shown in this table. Supplementary Table S6 reports the HRs for all explanatory variables in the models. Factors that contributed independently to increased risk of mortality in the multivariate model, in both HIV-infected and -uninfected participants, can be divided into two groups: nonmedication and medication factors.

HIV-Infected Participants—In the final multivariate model (Table 2), nonmedication factors associated with increased mortality (P<0.05) included decreased albumin levels, decreased eGFR, unemployment, depressive symptoms, ever use of injectable illicit drugs, decreased hemoglobin level, and current and past smoking. Medication factors associated with increased risk of included use of medications (other than methadone) that increase risk of CNS depression (HR 1.61, 95% CI 1.35–1.92, p <0.0001), benzodiazepine use (HR 1.28, 95% CI 1.01–1.60, p = 0.037) and number of medications with known conditional QTc interval–prolonging effects (HR 1.15 per drug used, 95% CI 1.00–1.33, p = 0.047). Factors associated with decreased risk of mortality included increasing CD4+ cell count, undetectable HIV viral load, and visit during the more recent HIV treatment era. Although methadone use, prescribed or otherwise, was strongly associated with mortality in the univariate analysis (HR range 1.38–2.9, P 0.0002), these relationships were greatly attenuated and not statistically significant following adjustment for other explanatory variables in the multivariate analysis (HR range 0.88–1.08, all p 0.29).

HIV-Uninfected Participants—In the final multivariate model, nonmedication factors associated significantly with increased mortality were depressive symptoms, hepatitis B virus infection, ever use of injectable drugs, decreasing albumin level, decreasing eGFR, and unemployment (Table 2). The only medication factor associated significantly with increased risk of mortality was use of medication combinations associated with increased risk of CNS depression (HR 2.4 per drug used, 95% CI 1.49–3.9, p <0.0003). Methadone association with mortality was not statistically significant when adjusted for other explanatory variables in the final multivariate model (HR range 0.57–1.50, P 0.089).

Explanatory Variables for Non-AIDS Death

Supplementary Table S7 summarizes the results of multivariate Cox proportional hazards models of explanatory variables for non-AIDS death in HIV-infected participants. Note that this table tabulates the same results that are listed in Supplementary Table S6 and Table 2 for HIV-negative participants since for these participants all deaths are non-AIDS deaths. As in the all-cause mortality analysis, all types of methadone use among HIV-infected participants were associated with non-AIDS death by univariate comparison (HR range 1.88–2.6, all p 0.029). However, this association was attenuated to the null once other factors were considered via multivariate modeling (HR range 0.95–1.09, all p 0.65). The explanatory variables that were associated with non-AIDS death can also be considered as nonmedication and medication related. There is considerable overlap in effect size for nonmedication explanatory variables of association with all-cause and non-AIDS mortalities (Table 2 and Supplementary Tables S6 and S7) in HIV-infected participants. For medication-related explanatory variables, use of medications other than methadone that increase risk of CNS depression was the only predictor associated with non-AIDS deaths (HR 1.49, 95% CI 1.49–2.2, p < 0.0001). Although the use of benzodiazepine (HR 1.32, 95% CI 0.83–2.1, p = 0.24) and conditional QT interval–prolonging medications (HR 1.25 per drug, 95% CI 0.97–1.62, p = 0.089) demonstrated some association with increased risk of mortality, the associations failed to meet the a priori significance threshold (p>0.05).

Exploratory Analysis of Methadone Interactions

A secondary analysis of plausible high-risk drug interactions (i.e., use of or number of medications with major additive CNS depression risk with methadone, use of or number of known and possible QTc interval–prolonging medications, or use of CYP3A4 inhibitors) with methadone did not result in statistically significant (p<0.05) associations with all-cause or non-AIDS mortality (results not shown).

Discussion

Although CNS depressants are considered to be high-risk medications, our study is novel in that it identifies important medication and nonmedication risk factors for mortality in a representative population of women living with or at risk for HIV. The knowledge of these risk factors can help clinicians to better manage the pharmacologic needs of their patients who present with combinations of risk factors for mortality identified in this study.

This study was driven by a univariate comparison demonstrating that higher mortality existed among women who had ever used methadone in the WIHS. Although prescribed and unprescribed use of methadone were strongly associated with all-cause and non-AIDS death in univariate analyses, this association was due to confounding with other factors. However, the confidence intervals in the multivariate analysis for methadone explanatory variables were too wide to exclude the possibility of an effect. Use of methadone could also function as a noncausative factor that frequently coexists with other factors that do contribute to mortality; thus, methadone use may be seen as a noncausative indicator of risk.

The findings of this study are consistent with previous WIHS reports that used a smaller sample and fewer explanatory variables that identified low CD4+ cell count(21–24, 26, 28), higher quantitative HIV viral RNA load(23, 24, 26, 28), low serum albumin level(23, 24, 26), reduced kidney function(22), and low hemoglobin level(26, 28) as factors associated with increased risk of all-cause mortality in HIV-infected women. Explanatory variables associated with increased risk of non-AIDS mortality in HIV-infected women in our study—decreasing CD4+ cell count, unemployment, depression, smoking, ever use of injectable illicit drugs, and hypertension—also are consistent with the findings of previously published studies of non-AIDS mortality in the WIHS(16, 27). Factors previously identified to be associated with all-cause mortality that were not statistically significantly associated in our study included HCV infection (22) and self-reported black race (22). The lack of a strong association between HCV infection and mortality in our models is similar to some but not all prior WIHS analyses.(16, 22, 27)

Although confirming the findings of previously reported mortality studies of the WIHS, our models also identified novel medication-related risk factors in this population. In the all-cause mortality analysis, benzodiazepine use was associated with a statistically significant increased risk of mortality. The data linking use of these drugs to mortality in various populations are mixed. (29–33) Our study is the first to report the association of benzodiazepines with all-cause mortality among HIV-infected women. Although benzodiazepine use was associated with increased risk of non-AIDS death, the finding did not reach statistical significance. Benzodiazepines as a class have a ceiling effect that limits their lethal toxicities (i.e., CNS and respiratory depression) at higher doses, but lethal effects can occur when they are combined with other drugs such as alcohol, antihistamines, antipsychotics or barbiturates. Thus, the observed association with mortality for benzodiazepines may not be causal but an indicator of other underlying factors, disease and non-disease, that were not studied. Despite inclusion of the aforementioned risk factors of mortality in our analysis, it appears that there exists a complex relationship between benzodiazepine use and mortality. Nevertheless, the association with mortality should prompt careful use of this class of drugs, particularly among patients with other risk factors, including concurrent medications.

Any use of CNS depressant medications was associated with increased risk of all-cause mortality and non-AIDS mortality in HIV-infected women. CNS depressants are widely used in the United States and yet the dangers associated with these medications are often not well appreciated by patients and clinicians. Hypnotics(31), H_1-antihistamines(34),

opioids(35), and benzodiazepines used in combination with alcohol(36) have been associated with mortality in various populations in the United States.

We also examined combinations of medications that increase the risk of QTc interval prolongation. Use of medications that may prolong the QTc interval in a conditional manner was associated with increased all-cause mortality in HIV-infected women. Although conditional circumstances associated with increased QTc prolongation (e.g., hypokalemia, hypomagnesemia) for these medications has not previously included HIV infection, HIV-infected women are at high risk of having long QTc intervals due to their sex and potentially due to antiretroviral treatments. Many antiretroviral drugs inhibit the CYP system and drug transporters, resulting in decreased metabolism of these QTc interval–prolonging medications. Known, conditional, and possible QTc interval–prolonging medications were all associated with increased risk of non-AIDs death in HIV-infected women, but the confidence intervals were wide and the findings were not statistically significant. Thus, an effect is possible but not well defined. Nevertheless, routine electrocardiographic monitoring should be considered in the care of HIV-infected patients receiving any QTc interval–prolonging medication when combined with cART.

Limitations to the study warrant consideration. First, the data in the WIHS were collected twice a year, so if a patient died months after their last WIHS visit, the available data may not represent the actual values at the time of death. Second, given that methadone response is greatly influenced by the tolerance of the individual to the medication, the absence of antemortem and postmortem methadone blood concentrations verifying a therapeutic or toxic level of methadone, as well as lack of data on dose, limits our understanding of the role of methadone in studying our outcome. Third, there was a considerable amount of missing methadone usage data specifically related to prescribed use of methadone, and this may have significantly limited our ability to capture the methadone effect in our analysis. The period of observation for this study ended in 2014; thus, these results may not reflect changes in the management of patients with opioid use disorders since then. Although patients who have newly identified opioid use disorders may be prescribed suboxone, there still remains a substantial cohort of patients who have longstanding previously diagnosed opioid use disorders and remain on methadone as well as patients who use methadone for chronic pain; therefore, we believe our study findings can still be relevant and useful. Lastly, the source of data for use of medications, including methadone, CNS depressants, and benzodiazepines, are self-reports that are limited to a recall time frame of the participants. Based on this, we anticipate that the point estimates are an underestimation for medication if medication use is underreported.

Conclusion

Assessment of the contribution of methadone, CNS depressants, benzodiazepines, and QTc interval–prolonging medications to mortality is complex. Although our investigation accounted for many factors, this analysis would benefit from a better understanding of the circumstances of death, toxicologic analysis, and more complete data on prescribed use of medications in the WIHS. Nevertheless, our study identified important risk factors—benzodiazepine, CNS depressant, and conditional QTc interval–prolonging medication use

—that were associated with mortality in the WIHS. Since the WIHS represents a vulnerable population of women living with HIV in the United States, care must be taken when prescribing these medications in this underserved and at-risk patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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Figure 1.
Medication combinations that can increase the risk of central nervous system depression and levels of each drug interaction. The levels of interaction are defined as follows: major (red) = the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects); moderate (orange) = the interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy; minor (blue) = the interaction would have limited clinical effects, and manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy; and no interaction found (green) according to the Micromedex online drug reference database [20].

Table 1.

Demographic and Disease Characteristics of the 4150 Participants using the Observation from the Most Recent Completed Visit for Each Participant

Characteristic	HIV (−) women (n=1031)	HIV (+) women (n=3119)
Viral load undetectable	1031 (100%)	1206 (40.9%)
CD4+ cell counts (cells/µl) (mean ± SD)	NA	421 ± 302
All-cause death	70 (6.8%)	976 (31.3%)
Non-AIDS death	70 (6.8%)	359/2996 (12%)
Methadone		
Recent[£] (n=1185) [*]	24/204 (11.8%)	166/981 (16.9%)
Prescribed (n=1185) [*]	19/204 (9.3%)	155/981 (15.8%)
Not prescribed (n=3798) [*]	11/905 (1.2%)	25/2893 (0.9%)
Ever (n=1203) [*]	44/211 (20.9%)	311/992 (31.4%)
Prescribed (n=1203) [*]	36/211 (17.1%)	262/992 (26.4%)
Not prescribed (n=4140) [*]	142/1029 (13.8%)	426/3111 (13.7%)
CES-D score > 16 (n=3869) [*]	287/926 (31%)	1214/2943 (41.3%)
Hepatitis C infection	664 (64.4%)	1918 (61.5%)
Hepatitis B infection	5 (0.5%)	81 (2.6%)
Injectable illicit drug use		
Recent[£] (n=3937) [*]	55/945 (5.8%)	199/2992 (6.3%)
Ever	261 (25.3%)	982 (31.5%)
Smoking status		
Never	238 (23.1%)	896 (28.7%)
Current	509 (49.4%)	1347 (43.2%)
Past	284 (27.5%)	876 (28.1%)
Alcohol use		
Abstain	423/944 (44.8%)	1792/2983 (60.1%)
1–7 drinks/week	367/944 (38.9%)	912/2983 (30.6%)
8–12 drinks/week	50/944 (5.3%)	94/2983 (3.2%)
>12 drinks/week	104/944 (11%)	185/2983 (6.2%)

Characteristic	HIV (−) women (n=1031)	HIV (+) women (n=3119)
Race-ethnicity categories		
White	140 (13.6%)	450 (14.4%)
African-American	584 (56.6%)	1812 (58.1%)
Hispanic	266 (25.8%)	754 (24.2%)
Other	41 (4.0%)	103 (3.3%)
Hemoglobin level (g/dL)		
Critical low: <7	0/872 (0%)	10/2958 (0.3%)
Low: 7–11.9	227/872 (26%)	1332/2958 (45%)
Normal: >11.9–15.6	634/872 (72.7%)	1589/2958 (53.7%)
High: >15.6	11/872 (1.3%)	27/2958 (0.9%)
Albumin level (g/dL)		
Very low: 1.2– 2.1	1/889 (0.1%)	29/2894 (1.0%)
Low: >2.1–3.4	32/889 (3.6%)	398/2894 (13.8%)
Low normal: >3.4–3.9	127/889 (14.3%)	727/2894 (25.1%)
Normal: >3.9–4.2	283/889 (31.8%)	768/2894 (26.5%)
High Normal: >4.2–4.8	420/889 (47.2%)	905/2894 (31.3%)
High: >4.8	26/889 (2.9%)	67/2894 (2.3%)
Estimated glomerular filtration rate (ml/min/1.73 m^2)		
Normal: 90	659/1028 (64.1%)	1758/3109 (56.5%)
Mild kidney disease: 60–89	306/1028 (29.8%)	945/3109 (30.4%)
Moderate kidney disease: 30–59	45/1028 (4.4%)	284/3109 (9.1%)
Severe kidney disease: 15–29	9/1028 (0.9%)	44/3109 (1.4%)
Kidney failure: <15	9/1028 (0.9%)	78/3109 (2.5%)
Unemployed	565/945 (59.8%)	2205/2998 (73.5%)
Hypertension	629 (61.0%)	2001 (64.2%)
HIV treatment era		
<1998	78 (7.6%)	425 (13.6%)
1998–2004	126 (12.2%)	552 (17.7%)
>2004	827 (80.2%)	2142 (68.7%)
Medications with major additive CNS depression risk with concurrent methadone use	192 (18.6%)	753 (24.1%)

Characteristic	HIV (−) women (n=1031)	HIV (+) women (n=3119)
Benzodiazepine	67 (6.5%)	264 (8.5%)
Opioids [¥]	115 (11.2%)	448 (14.4%)
Medications that can increase risk for CNS depression [¥]	124 (12.0%)	474 (15.2%)
No. of medications with conditional QT interval–prolonging effects [¥]		
0	901/1030 (87.5%)	2578/3114 (82.8%)
1	103/1030 (10%)	465/3114 (14.9%)
2	25/1030 (2.4%)	62/3114 (2%)
3	1/1030 (0.1%)	8/3114 (0.3%)
4	0	1/3114 (0.0%)

Data are no. (%) of women unless otherwise specified.

CES-D = Center for Epidemiological Studies–Depression; NA = not applicable.

[*]
Because of missing values for participants, the subgroup sample sizes may not sum up to 1031 and 3119 for HIV (−) and HIV (+) women, respectively

[£]Recent was defined as in the past 6 months.

[¥]Methadone was excluded.

Table 2.

Univariate and Multivariate Cox Proportional Hazards Models of All-Cause Death[£]

Predictor	Univariate Model				Multivariate Model			
	HIV (−) women		HIV (+) women		HIV (−) women		HIV (+) women	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Methadone								
Recent	2.4 (1.07–5.2)	0.033	1.72 (1.42–2.1)	<0.0001	1.18 (0.48–2.9)	0.71	0.92 (0.73–1.17)	0.52
Prescribed	2.2 (0.98–5.0)	0.054	1.64 (1.34–2.0)	<0.0001	1.20 (0.49–2.9)	0.69	0.92 (0.73–1.17)	0.51
Not prescribed	3.5 (1.09–11.2)	0.036	2.9 (1.81–4.6)	<0.0001	1.50 (0.44–5.1)	0.52	1.08 (0.64–1.82)	0.78
Ever	2.4 (1.15–5.0)	0.020	1.38 (1.67–1.64)	0.0002	0.74 (0.29–1.9)	0.54	0.88 (0.70–1.11)	0.29
Prescribed	2.0 (0.97–4.2)	0.062	1.50 (1.26–1.79)	<0.0001	0.78 (0.32–1.87)	0.57	0.90 (0.71–1.13)	0.36
Not prescribed	1.45 (0.84–2.5)	0.18	1.52 (1.30–1.78)	<0.0001	0.57 (0.30–1.09)	0.089	0.95 (0.79–1.14)	0.56
Log_{10} viral load (copies/ml)								
Effect per 1 log_{10}-increase within ranges								
<3	NA		3.7 (3.2–4.3)	<0.0001	NA		**0.96 (0.66–1.39)**	**0.83**
3–4			6.1 (5.2–7.1)	<0.0001			**0.69 (0.47–0.99)**	**0.049**
>4 – 5			10.9 (9.4–12.6)	<0.0001			**1.61 (1.17–2.2)**	**0.0034**
>5			23 (19.4–27)	<0.0001			**1.94 (1.49–2.5)**	**<0.0001**
Viral load undetectable	NA		0.25 (0.21–0.30)	<0.0001	NA		**0.82 (0.57–1.19)**	**0.31**
Log base 2 of CD4+ cell count	NA		0.48 (0.47–0.50)	<0.0001	NA		**0.59 (0.56–0.62)**	**<0.0001**
Depressive symptoms	2.9 (1.77–4.8)	<0.0001	2.6 (2.2–2.9)	<0.0001	**2.1 (1.24–3.6)**	**0.0062**	**1.39 (1.21–1.60)**	**<0.0001**
Hepatitis B infection	12.9 (1.69–99)	0.014	1.89 (1.37–2.6)	0.0001	**26 (3–229)**	**0.0032**	1.29 (0.92–1.8)	0.13
Injectable illicit drug use								
Recent	4.6 (2.4–8.7)	<0.0001	2.4 (1.98–3.0)	<0.0001	1.91 (0.92–4)	0.084	1.05 (0.83–1.32)	0.71
Ever	5.7 (3.4–9.8)	<0.0001	2.3 (1.97–2.6)	<0.0001	**3.6 (2–6.4)**	**<0.0001**	**1.34 (1.15–1.57)**	**0.0001**
Smoking status								
Never	1.0		1.0		1.0		**1.0**	
Current	7.9 (1.91–33)	0.0043	2.2 (1.87–2.7)	<0.0001	3.6 (0.82–15.8)	0.09	**1.24 (1.01–1.52)**	**0.039**
Past	4.7 (1.07–21)	0.04	1.59 (1.30–1.95)	<0.0001	2.4 (0.51–11.4)	0.27	**1.36 (1.1–1.7)**	**0.005**
Hemoglobin level (g/dL)								

	Univariate Model				Multivariate Model			
	HIV (−) women		HIV (+) women		HIV (−) women		HIV (+) women	
Normal: >11.9–15.6	1.0		1.0		1.0		1.0	
Critical low: <7	NA		63 (33–120)	<0.0001	NA		3.2 (1.52–6.8)	0.0022
Low: 7–11.9	1.52 (0.89–2.6)	0.12	4.5 (3.9–5.2)	<0.0001	1.49 (0.83–2.7)	0.18	1.56 (1.33–1.83)	<0.0001
High: >15.6	1.10 (0.15–8.1)	0.92	1.62 (0.83–3.1)	0.15	0.56 (0.071–4.4)	0.58	1.61 (0.83–3.2)	0.16
Albumin level (g/dL)								
Normal:>3.9–4.2	1.0		1.0		1.0		1	
Very low: 1.2– 2.1	12.4 (1.59–97)	0.016	19.7 (13.2–30)	<0.0001	31 (3.7–254)	0.0015	7.3 (4.7–11.3)	<0.0001
Low: >2.1–3.4	7 (3.5–14.1)	<0.0001	7.3 (6.1–8.9)	<0.0001	4.8 (2.2–10.1)	<0.0001	3.1 (2.50–3.8)	<0.0001
Low normal:>3.4–3.9	1.34 (0.69–2.6)	0.38	1.92 (1.58–2.3)	<0.0001	1.04 (0.53–2)	0.91	1.39 (1.14–1.69)	0.0013
High Normal:>4.2–4.8	0.78 (0.39–1.54)	0.48	0.74 (0.58–0.93)	0.011	0.78 (0.38–1.6)	0.50	0.86 (0.68–1.1)	0.24
High:>4.8	0.99 (0.13–7.5)	0.99	1.04 (0.55–1.97)	0.91	0.83 (0.11–6.4)	0.85	1.37 (0.72–2.6)	0.34
Estimated glomerular filtration rate (ml/min/1.73 m²)								
Normal: 90	1.0		1.0		1.0		1.0	
Mild kidney disease: 60–89	0.59 (0.33–1.07)	0.085	1.21 (1.34–1.41)	0.016	0.7 (0.37–1.3)	0.25	1.02 (0.87–1.2)	0.81
Moderate kidney disease: 30–59	2.2 (0.99–4.9)	0.053	3.4 (2.8–4.2)	<0.0001	2.3 (0.99–5.3)	0.05	1.86 (1.51–2.3)	<0.0001
Severe kidney disease: 15–29	3.6 (0.80–16.6)	0.093	8.8 (6.2–12.6)	<0.0001	1.33 (0.25–7.2)	0.74	3.5 (2.4–5.1)	<0.0001
Kidney failure: <15	9 (3–27)	<0.0001	6.1 (4.5–8.1)	<0.0001	8 (2.5–26)	0.0005	3.8 (2.8–5.1)	<0.0001
Unemployed	5.5 (2.5–12.1)	<0.0001	6.5 (5.0–8.3)	<0.0001	2.9 (1.3–6.6)	0.0094	2.4 (1.82–3.1)	<0.0001
HIV treatment era								
<1998	1.0		1.0		1.0		1.0	
1998–2004	0.73 (0.34–1.59)	0.44	0.45 (0.39–0.53)	<0.0001	0.74 (0.31–1.74)	0.49	0.68 (0.57–0.8)	<0.0001
>2004	0.40 (0.19–0.86)	0.018	0.24 (0.20–0.28)	<0.0001	0.46 (0.19–1.09)	0.077	0.55 (0.45–0.68)	<0.0001
Benzodiazepine use	2.1 (0.99–4.4)	0.055	1.60 (1.30–1.97)	<0.0001	0.7 (0.28–1.74)	0.44	1.28 (1.01–1.6)	0.037
No. of medications with conditional QT interval–prolonging effects ¥	0.86 (0.47–1.55)	0.61	1.16 (1.02–1.32)	0.026	0.67 (0.36–1.25)	0.21	1.15 (1.00–1.33)	0.047
No. of medications that can increase risk for CNS depression ¥	2.9 (1.86–4.6)	<0.0001	1.90 (1.66–2.2)	<0.0001	2.4 (1.49–3.9)	<0.0003	1.09 (0.6–1.97)	0.77
Medications that can increase risk for CNS depression ¥	3.3 (1.91–5.6)	<0.0001	2.1 (1.79–2.5)	<0.0001	1.51 (0.26–8.9)	0.65	1.61 (1.35–1.92)	<0.0001

Boldface hazard ratios and p values in the multivariate column are variables present in the final multivariate proportional hazards model. The rest of the values are results for each variable as a single addition to the final multivariate model.

CI = confidence interval; CNS = central nervous system; NA = not applicable.

£For brevity, only predictors (methadone excluded) with p values <0.05 are reported in this table. Supplemental Table 2 is a comprehensive version of this table.

¥Methadone was not included.