Journal of AIDS and HIV Research Vol. 4(8), pp. 213-218, August 2012
Available online http://www.academicjournals.org/JAHR
DOI: 10.5897/JAHR12.026
ISSN 2141-2359 ©2012 Academic Journals

*Full Length Research Paper*

# Is serious mental illness associated with earlier death among persons with human immunodeficiency virus (HIV)? A ten year follow up in Maryland Medicaid recipients

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Accepted 1 August, 2012

**Serious mental illness (SMI) is associated with earlier mortality. The objective of this study was to determine if SMI was associated with an increased risk of death among Maryland Medicaid beneficiaries with human immunodeficiency virus (HIV). This was a retrospective cohort study of adult Maryland Medicaid recipients with HIV receiving antiretroviral therapy (ART) after January 1, 1997. SMI was defined as a specialty mental health visit and an ICD-9 diagnosis of (1) schizophrenia or related psychoses, (2) bipolar disorder or (3) major depressive disorder. Cox proportional hazards regression models were used to estimate the hazard ratios for total mortality. Analyses were adjusted for demographic characteristics, percentage of days on ART, outpatient visits, and comorbid medical conditions. Overall, 623 individuals received ART after treatment inception. The total number of deaths was 271, out of which 60 deaths were in the SMI group (38.5%) and 211 in the non-SMI group (45%) (p = 0.05). In multivariable analysis, SMI was not associated with mortality. Increasing age, acquired immunodeficiency syndrome (AIDS) defining illness, renal failure, cerebrovascular disease, congestive heart failure, chronic liver disease, and substance abuse were independently associated with mortality, while increased percent days of HIV medication use and number of outpatient medical visits were associated with improved survival. In this sample, SMI is not associated with earlier death in patients with HIV infection. ART use and primary care engagement among HIV infected individuals are associated with improved survival, irrespective of an SMI diagnosis.**

**Key words:** Human immunodeficiency virus (HIV), serious mental illness (SMI), survival.

## INTRODUCTION

The prevalence of serious mental illness (SMI), among persons with human immunodeficiency virus (HIV) exceeds that of the general population with estimates varying widely depending on the sample and geographic location (Himelhoch et al., 2007a, b; Nurutdinova et al., 2012; Walkup et al., 2010). This increased prevalence of SMI among individuals with HIV is thought to be secondary to the higher prevalence of substance abuse and HIV transmission risk behaviors, including unprotected sex and exchange sex among persons with SMI (Dyer and McGuinness, 2008; Leucht et al., 2007; Meade and Sikkema, 2005).

Since its inception, highly active antiretroviral therapy (HAART) has reduced HIV related morbidity and mortality. While it might be expected that persons with SMI have lower uptake of HAART because of untreated symptoms or cognitive issues, among those with SMI engaged in HIV care, uptake of HAART and persistence of use has been comparable to individuals without SMI

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(Bogart et al., 2006; Himelhoch et al., 2009). A study among a large multi-site sample of HIV infected persons in care found that those with SMI were significantly less likely to discontinue HAART in their first and second years on treatment as compared to those without a psychiatric disorder (Himelhoch et al., 2009). These results are supported by another study among individuals with SMI, where persons with schizophrenia were at least as likely to initiate HAART and were as persistent in their use of protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI) as those without SMI; however, in this sample, persons with a severe affective disorder were less persistent in their HAART use as compared to those without SMI (Walkup et al., 2004).

With multiple co-morbid conditions, including heart disease, diabetes, substance abuse, and HIV, individuals with SMI have consistently been found to have a reduced life expectancy (Daumit et al., 2010; DeHert et al., 2011). In a cohort of Maryland Medicaid recipients, the standardized mortality ratio for persons with SMI was three times higher than the overall population (Daumit et al., 2010). HIV was the third most common cause of death. While SMI is positively associated with reduced life expectancy in the general population, it is not clear if the presence of SMI among persons with HIV is associated with increased mortality, especially with data suggesting that HAART persistence among individuals in care (a significant predictor of survival among persons with HIV) is comparable between HIV infected individuals with and without SMI. The objective of this study is to determine if SMI among persons with HIV receiving HAART is independently associated with decreased survival.

## METHODOLOGY

This was a retrospective cohort study of adult, Maryland Medicaid recipients living in the Baltimore metropolitan area or in the Maryland Eastern Shore. The original cohort included 26190 Medicaid recipients, 21 to 62 years of age, who had been continuously enrolled in Medicaid between July 1, 1992 and June 30, 1994. Recipients were followed through June 30, 2004. For this analysis, we included cohort members who met the criteria for a diagnosis of HIV/ acquired immunodeficiency syndromes (AIDS) (identified by ICD-9 Codes: 042, 043, 044, or V08) between July 1, 1994 and June 30, 2004 (N = 1,228) and whoever used any antiretroviral therapy (n = 623 out of 1,228) after July 1, 1997 to correspond with the availability of HAART.

Age, gender, race, type of residence (urban, suburban, rural), and diagnosis of SMI were obtained from Medicaid administrative claims data files. SMI was defined as a diagnosis of schizophrenia, bipolar disorder, major depression, or other mental disorder diagnoses and specialty mental health care use. Other mental disorder diagnoses included psychoses other than schizophrenia and affective psychoses, organic psychoses, obsessive-compulsive disorder and other anxiety disorders, but not substance-induced psychoses or dementias.

Medicaid hospitalization data was used to identify medical comorbidities from 1994 to 2004. Baseline medical comorbidities were based on data up to the study origin, and time-varying medical comorbidities were determined by data occurring after the study origin. Once participants had a comorbid condition diagnosis, they were assumed to have the comorbidity throughout the rest of follow-up. Specific co-morbid conditions examined in this sample included diabetes mellitus, coronary artery disease, chronic renal failure, cerebrovascular disease, hypertension, chronic obstructive pulmonary disease congestive heart failure, chronic liver disease (defined as cirrhosis, hepatic encephalopathy or hepatic coma), cancer, illicit drug use, and alcohol abuse.

HIV medication records were obtained from Maryland Medicaid pharmacy claims data (MMPCD) and were categorized by HIV medication type: protease inhibitor (PI); non-nucleoside transcriptase inhibitor (NNRTI); or nucleoside transcriptase inhibitor (NRTI). We defined HIV medication persistence as the proportion of days covered for each year, that is, the number of days when medication was available in each year divided by the total days in the one-year observation period. Because administrative data does not contain CD4 cell counts, a biomarker of HIV disease severity, we used the presence or absence of an AIDS defining illness, determined by ICD-9 diagnostic codes, as a surrogate marker of disease severity. This has been used in other HIV studies using administrative claims data (Hoover et al., 2004).

Mortality data was obtained by linking the cohort to the National Death Index (NDI) from 1994 through 2004. The NDI matched user records to death records based on twelve criteria, including social security number, first name, last name, and year of birth. We then picked the most likely matched death records based on the probabilistic scoring technique used by the NDI (Rich-Edwards et al., 1994).

Survival analysis and Cox proportional hazards regression models were used to estimate the hazard ratios for total mortality comparing persons with and without-SMI. Participants were followed from the study origin, defined as the first use of ART after July 1, 1997, until death or June 30, 2004. Progressive model adjustment (PMA) was applied. Covariates in the models were included in every fiscal year. Models were initially adjusted for age, gender, race, and further extended and adjusted for comorbidities including diabetes, coronary heart disease, chronic renal failure, cerebrovascular disease, hypertension, congestive heart failure, chronic liver disease, drug abuse, and alcohol abuse. Finally, models were adjusted for outpatient medical visits (numbers per year), disease severity, and HIV medication persistence. Covariates with a $p > 0.1$ (that is, diabetes, coronary heart disease, and hypertension) were excluded from the final model. We also determined whether the individuals with SMI were more likely to die prior to 1997 as compared to those without SMI to assess for potential bias. Data were compiled and analyzed using Stata version 10. The study was approved by the Johns Hopkins Medical Institutions and the Maryland Department of Health and Mental Hygiene Institutional Review Boards with a waiver of informed consent.

## RESULTS

### Characteristics of cohort members with and without serious mental illness

Among 623 HIV infected individuals receiving ART after 1997 in the cohort, 25% of them had SMI (Table 1). Thirty six percent of the overall sample was female, and 88% were African American with a median number of annual outpatient visits of 4 and 3 for individuals with and without SMI, respectively. Compared to individuals without SMI, those with SMI were more likely to have chronic obstructive pulmonary disease, drug abuse, and alcohol abuse. There was no difference in AIDS defining

**Table 1.** Descriptive statistics of sample characteristics by serious mental illness with or without SMI status.

| Characteristic variable | SMI (n = 156) | Non-SMI (n = 467) | p-value |
|---|---|---|---|
| Age-years | 38.6 (7.2) | 40.0 (8.8) | 0.08 |
| Sex-Female | 60 (38.5) | 164 (35.1) | 0.45 |
| Race-African American | 134 (85.9) | 416 (89.1) | 0.29 |
| Urban | 151 (96.8) | 451 (86.6) | 0.68 |
| AIDS defining illness | 87 (55.4) | 239 (51.0) | 0.35 |
| **Baseline medical comorbid condition** | | | |
| Diabetes | 05 (3.2) | 18 (3.9) | 0.71 |
| Coronary artery disease | 04 (2.6) | 07 (1.5) | 0.38 |
| Chronic renal failure | 02 (1.3) | 20 (4.3) | 0.08 |
| Cerebrovascular disease | 02 (1.3) | 08 (1.7) | 0.71 |
| Hypertension | 13 (8.3) | 39 (8.4) | 0.99 |
| Obstructive pulmonary disease | 17 (10.9) | 24 (5.1) | 0.01 |
| Congestive heart failure | 04 (2.6) | 19 (4.1) | 0.39 |
| Chronic liver disease | 02 (1.3) | 07 (1.5) | 0.84 |
| Cancer | 05 (3.2) | 09 (1.9) | 0.35 |
| Drug abuse | 73 (46.8) | 111 (23.8) | <0.001 |
| Alcohol abuse | 37 (23.7) | 56 (12.0) | <0.001 |
| % of days on any HIV medication during the study period | 40.1 (28.3) | 42.6 (30.629.4) | 0.37 |
| Median number of annual medical outpatient visits* | 4 (1-10) | 3 (1-8) | 0.001 |

Values are number (%) or *Median + IQR. Significant at 95% ($p \leq 0.05$).

illnesses (ADI) (SMI: 55.4% versus Non-SMI: 51.0%), or in the percentage of days on ART comparing SMI and non-SMI individuals (SMI: 40.1% versus Non-SMI: 42.6%) (Table 1).

### Mortality

Total number of deaths was 271 with 60 deaths in the SMI group (38.5%) and 211 in the non-SMI group (45%). In unadjusted analysis, there was a borderline significant difference in time to death with non-SMI individuals experiencing earlier death as compared to those with SMI (Figure 1; Log-Rank p = 0.05). In multivariable analysis, the association between SMI and risk of death was not statistically significant (Adjusted hazard ratio (AHR): 0.86, 95% CI: 0.66 to 1.12) (Table 2). Increasing age (AHR: 1.02, 95% CI: 1.01 to 1.03) and drug abuse (AHR: 1.31, 95% CI: 1.03 to 1.67) were independently associated with higher risk of death, as were ADI, renal disease, cerebrovascular disease, congestive heart failure, and chronic liver disease (Table 2). Increasing number of outpatient medical visits (AHR: 0.97, 95% CI: 0.95 to 0.99) was associated with a lower risk of death as were an increased percentage of days of HIV medication use (AHR: 0.97, 95 % CI: (0.94 to 1.00).

We also examined whether individuals with SMI were more likely to die prior to 1997 as compared to those without SMI, and found no significant difference in deaths between the two groups (p-value: ≥ 0.79).

## DISCUSSION

In this Maryland Medicaid sample of HIV infected individuals, having a serious mental illness was not associated with earlier death. Both individuals with and without SMI were engaged in outpatient clinical care, reflected by their annual number of outpatient medical visits, which was associated with a decreased risk of death. Antiretroviral therapy use was also associated with delayed death, while several co-morbid conditions including renal disease, congestive heart failure, and substance use were associated with an increased risk of death.

Our finding that SMI was not associated with earlier death is consistent with findings from an earlier study that examined 549 HIV infected patients in care at a single clinical site, 18% of whom had a psychiatric disorder. They found that individuals in treatment with a current psychiatric disorder were more likely to receive antiretroviral therapy, and more likely to survive than those without a psychiatric disorder (Himelhoch et al., 2004). Both our findings and those of Himelhoch et al. (2004) are in contrast to the literature on mortality among those with SMI in the non-HIV infected population, where SMI is associated with higher mortality rates (Daumit et al., 2010; Laursen et al., 2007). Retention in care has

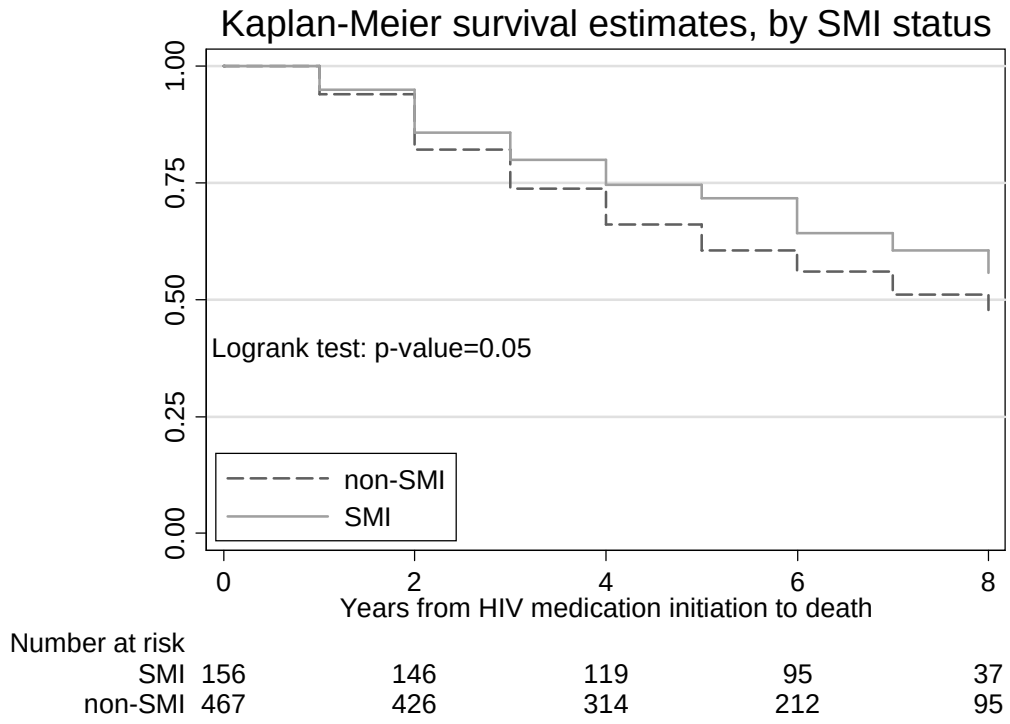


**Figure 1.** Kaplan-Meier survival estimates, by SMI status.

been associated with improved outcomes and may partially account for our findings. In a recent study among attendees of Veterans Affairs (VA) hospitals or clinics, poor retention in care, defined as fewer than four visits per year, predicted poorer survival among Veterans with HIV (Giordano et al., 2007). HIV-infected individuals with SMI may be accessing mental health and substance abuse treatment, as well as ancillary services, including case management, more than persons with SMI alone.

Studies have also demonstrated that the presence of SMI alone (without concurrent substance abuse) among HIV infected persons engaged in care is not associated with decreased ART persistence (Himelhoch et al., 2009). ART persistence is associated with survival among persons with HIV. These results imply that SMI should not be a reason to delay treatment with ART, and in fact, as our results suggest, persons with SMI can have equal survival to those without SMI. Extending these findings from HIV and use of HAART to diabetes and use of oral hypoglycemics, in a United States Veterans Administration (VA) sample, diabetics with schizophrenia were more likely to be adherent their medications as compared to those with diabetes alone. (Kreyenbuhl et al., 2008). These studies all suggest that individuals with SMI can achieve levels of adherence equal or greater than those without SMI.

This study's results are in contrast to a recent study among HIV-infected veterans, where the presence of either schizophrenia or bipolar disorder was associated with an increased risk of mortality (Nurutdinova et al., 2012). Differences in present findings may reflect the differences in study populations. This sample of HIV infected Medicaid beneficiaries without SMI may be more disadvantaged and medically ill than the HIV-infected VA samples without SMI. In addition, the relationship between SMI and mortality among persons with HIV may vary by study sample, geographic variability, and available ancillary services.

There are limitations to this study. Analyses of claims data are limited by their lack of clinical data. Specific to this study, CD4 cell count and HIV viral load, laboratory markers of HIV disease progression, were not available and thus we were unable to adjust for degree of immune suppression or response to antiretroviral therapy. We addressed this by creating an indicator for disease severity defined by the presence or absence of an opportunistic infection, an approach used by other studies among HIV infected individuals using claims data (Hoover et al., 2004). Despite this, there may still have been residual confounding. Second, entry into our cohort required two years of continuous enrollment in Maryland Medicaid. This implies a certain degree of stability in healthcare access among those enrolled in this cohort. Studies have shown that individuals with gaps in their insurance coverage have lower access to care overall (Schoen and DesRoches, 2000; Hoffman et al., 2001; Kasper et al., 2000). Thus, our results may not generalize to persons with HIV on Maryland Medicaid with

**Table 2.** Adjusted hazard ratios (HR) of mortality among 623 Maryland Medicaid recipients with HIV (HR and 95% CI).

| Characteristic | HR (95% CI) | p-value |
|---|---|---|
| **Age (years)** | 1.02 (1.01, 1.03) | <0.01 |
| **Sex** | | |
| Male | 1.0 (Ref) | - |
| Female | 1.10 (0.87, 1.39) | 0.41 |
| **Race** | | |
| Caucasian/Other | 1.0 (Ref) | - |
| African American | 0.96 (0.67, 1.39) | 0.86 |
| **Serious mental illness** | | |
| No | 1.0 (Ref) | - |
| Yes | 0.86 (0.66, 1.12) | 0.26 |
| **AIDS defining illness** | | |
| No | 1.0 (Ref) | - |
| Yes | 2.84 (2.24, 3.59) | <0.01 |
| **Chronic renal failure** | | |
| No | 1.0 (Ref) | - |
| Yes | 3.52 (2.54, 4.90) | <0.01 |
| **Cerebrovascular disease** | | |
| No | 1.0 (Ref) | - |
| Yes | 1.92 (1.21, 3.05) | <0.01 |
| **Congestive heart failure** | | |
| No | 1.0 (Ref) | - |
| Yes | 1.46 (1.02, 2.10) | 0.04 |
| **Chronic liver disease** | | |
| No | 1.0 (Ref) | - |
| Yes | 2.65 (1.91, 3.67) | <0.01 |
| **Drug abuse** | | |
| No | 1.0 (Ref) | - |
| Yes | 1.31(1.03, 1.67) | 0.04 |
| **Alcohol abuse** | | |
| No | 1.0 (Ref) | - |
| Yes | 1.28 (0.99, 1.66) | 0.06 |
| **Antiretroviral therapy use**[a] | 0.97 (0.94, 1.00) | 0.04 |
| **Annual outpatient visits** | 0.97 (0.95, 0.99) | 0.01 |

[a]Antiretroviral therapy use was calculated as total days on any HIV medication divided by total days eligible for medication in each year, and then multiplied by 10. 1 unit increase in HIV medication use corresponds to 10% increase in percentage of days on medication.

insurances lapses. These individuals with insurance lapses may have had poorer health outcomes, which would not be reflected by our study. In addition, our sample did not include privately insured individuals. This also limits our generalizability. However, in the United States, less than 20% of HIV infected individuals have private insurance (Fleishman et al., 2005) and greater than 85% of individuals with SMI have public insurance (Khaykin et al., 2010).

Despite these limitations, our study has several important strengths. First, we examined and adjusted for other chronic conditions associated with death in our

study, and found that renal disease, cardiovascular disease, liver disease, and substance abuse were all associated with earlier death in our sample. These results are consistent with causes of death among persons with HIV and SMI in the modern ART era, thus adding external validity to our findings. In addition, we were able to adjust for ART persistence through the use of comprehensive Medicaid pharmacy data, which is a significant predictor of survival.

This study has several implications. Efforts to seek out individuals with SMI, routinely test them for HIV, and subsequently engage and retain them in HIV and mental health care is essential. Furthermore, given that active substance abuse is independently associated with poorer antiretroviral and appointment adherence and also a risk factor for HIV among persons with SMI, efforts to engage, treat and retain these triply diagnosed individuals with HIV, substance use and SMI may be an important component of a comprehensive program. Finally, among HIV infected persons in care, screening for, diagnosing, and treating mental health disorders may improve outcomes.

## ACKNOWLEDGEMENTS

The authors acknowledged the support from NIAAA K23 AA015313 and NIMH R01MH07470.

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