*Am. J. Trop. Med. Hyg.*, 85(4), 2011, pp. 782–789
doi:10.4269/ajtmh.2011.11-0187


# Neuropsychiatric and Socioeconomic Status Impact Antiretroviral Adherence and Mortality in Rural Zambia

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*Abstract.* We conducted a prospective cohort study of 496 adults starting antiretroviral treatment (ART) to determine the impact of neuropsychiatric symptoms and socioeconomic status on adherence and mortality. Almost 60% had good adherence based upon pharmacy records. Poor adherence was associated with being divorced, poorer, food insecure, and less educated. Longer travel time to clinic, concealing one's human immunodeficiency virus (HIV) status, and experiencing side effects predicted poor adherence. Over a third of the patients had cognitive impairment and poorer cognitive function was also associated with poor adherence. During follow-up (mean 275 days), 20% died—usually within 90 days of starting ART. Neuropsychiatric symptoms, advanced HIV, peripheral neuropathy symptoms, food insecurity, and poverty were associated with death. Neuropsychiatric symptoms, advanced HIV, and poverty remained significant independent predictors of death in a multivariate model adjusting for other significant factors. Social, economic, cognitive, and psychiatric problems impact adherence and survival for people receiving ART in rural Zambia.

## INTRODUCTION

Poor medication adherence results in clinical failure for patients on antiretroviral therapy (ART) and may facilitate the development of antiretroviral (ARV)-resistant strains of human immunodeficiency virus (HIV).[1,2] Several studies have established that excellent adherence is possible in resource-poor settings,[1,3,4] especially where medications are provided free of direct costs,[5] but these observations have often been made in clinics offering additional benefits to attendees such as food supplements. Adherence estimates are less optimistic when observed in the absence of these additional supports.[6–8] Resource limitations in most of sub-Saharan Africa are such that secondary benefits cannot be routinely made available.

Understanding factors that impact adherence is critical for optimizing patient care. Determinants of ART adherence in Africa have been assessed in several studies, though usually among patients who return to the clinic rather than those who have completely defaulted from treatment. Reasons for treatment defaulting might be different from reasons for poor adherence, but the difficulty presented in tracking defaulters makes this information challenging to ascertain.

Among ART patients in Nigeria, non-adherence was found to be related to side effects, inadequate medication supplies provided through the clinic, simply forgetting, stigma, and the direct selling of medications to others by patients under treatment.[9] In indigent South African populations, socioeconomic status (SES) was not found to be associated with adherence,[10] but a lack of variability in economic state (i.e., everyone was indigent) may have limited the capacity of this work to identify differences that might be more evident in broader patient populations. Furthermore, this study was conducted as part of a phase 3 clinical trial and therefore involved a relatively select population of patients.

Food insecurity and/or frank hunger may also be a barrier to ART adherence in Africa. The popular press has reported patient and healthcare worker concerns that inadequate access to food contributes to poor adherence and adverse outcomes.[11,12] For rural people, transportation costs and transport availability may be particularly important in determining access to care.[13,14] In a 2006 meta-analysis, poor adherence was found to be related to the cost of accessing medication, a lack of disclosure to one's spouse, alcohol use/misuse, and the complexity of the treatment regimen.[15] The presence of HIV-associated cognitive impairment might impact a person's capacity for good ART adherence,[16,17] but this has not been studied prospectively. Co-morbid psychiatric disorders, particularly if untreated, might adversely impact a person's capacity for adherence.[17] The United States studies of mood disorders and ARV adherence generally focus on HIV+ populations with co-morbid drug abuse problems and in Africa most studies of the impact of psychiatric symptoms on adherence have been qualitative in nature. A quantitative study in Kwa-Zulu Natal did find that depression is associated with poorer ART adherence.[18]

In 2004, the Zambian Ministry of Health began programs providing free ARV treatment. Several rural HIV clinics providing free medication were opened in 2005, including the clinic sites for this study. To better understand patient-level characteristics that impact ART adherence and mortality among people attending recently opened rural HIV clinics in Zambia, we undertook a prospective cohort study of patients commencing ART, which included assessments of cognitive function, psychiatric symptoms, social supports, SES, and food security. These and other biomedical and demographic characteristics were then evaluated with regard to their relationship to adherence and mortality.

## MATERIALS AND METHODS

**Study sites.** The three rural HIV clinics involved in this work have been described elsewhere.[19] Before the opening of these clinics, ARV treatment was not available in these clinical catchment areas. Even people with resources for purchasing medications had to travel into urban centers to do so. All HIV care including laboratory studies, are provided free of user

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fees, but at the time this study was conducted, no inducements or secondary benefits were available. Specifically, patients were not provided with food supplements or transport reimbursement. Home-based care services were also extremely limited and available to < 1% of HIV patients under care. At the time this study was conducted, the only ARV treatment available was Triomune offering a fixed dose combination tablet of stavudine (d4T), lamivudine (3TC), and nevirapine (NVP). For patients with adverse side effects from Triomune or clinical failure, second-line treatments or alternative ARVs were not available.

**Study population.** Recruitment occurred from 31 July 2006–10 Oct 2007. Before the initiation of ART, patients attended 3–5 preliminary visits for counseling, HIV testing, obtaining tests results, and CD4 count assessments. Clinic attendees were eligible for study enrollment if they were 18 years of age or older and newly initiated on ARVs with no history of prior treatment. They had to provide written informed consent.† The initial study evaluation including all baseline assessments had to be completed within 1 week of ART initiation. This study was approved by the University of Zambia's Research Ethics Committee and Michigan State University's Biomedical Institutional Review Board.

**Data collection and variables.** *At enrollment.* After providing informed consent, patients underwent an examination and interview in a private room. Data was obtained on the following: demographic information, SES including food security, perceived levels of stigma, community disclosure status, body mass index (BMI), neurocognitive status, and the presence of psychiatric symptoms. Demographic data obtained included age, gender, education level, marital status, and household composition. The SES and food security were measured using a previously developed instrument.[20] A three-item instrument previously used in Zambia with a possible score range of 0–3 was used to measure stigma.[20] Neurocognitive status was assessed using the International HIV Dementia Scale (IHDS)[21] and the Zambian mini-mental state exam (zMMSE).[22] Symptoms of anxiety and depression were quantified using the Shona Symptom Scale.[23,24] This instrument, developed and validated in Zimbabwe,‡ includes 14 questions regarding the presence or absence of specific symptoms.

At enrollment, study subjects' HIV clinic charts were reviewed to confirm demographic data. Standardized outpatient chart abstractions were completed to obtain information on World Health Organization (WHO) clinical staging, whether the study subject had a history of tuberculosis, their CD4 count, HIV disclosure status within the community, and to determine whether a clinic supporter or "clinic buddy" attended the initial visits. This abstraction method has been previously shown to have an inter-rater reliability of > 0.8 for all nonlinear variables.[19] The clinic intake data also included a single question regarding peripheral neuropathy symptoms ("Do you experience tingling, burning, or numbness in your feet or hands?"), which has been shown to have 95.7% sensitivity, 80.0% specificity, 88.2% positive predictive value, and 92.3% negative predictive value in the Zambian population for identifying HIV patients with peripheral neuropathy.[25]

*During follow-up.* Research personnel had access to HIV clinic records for all study subjects, tracked the dates of scheduled clinic follow-up visits, and alerted clinic staff if a patient was more than 1 week late for their appointment. To protect and respect patient privacy, research personnel did not track patients directly, but research resources were used to provide motorbikes and fuel to HIV clinic staff responsible for tracking defaulters.

Outcomes obtained through chart review and tracking defaulters included any symptoms experienced by patients that were attributed to ARV side effects, adherence assessments, and death. Side effects were categorized as being mild, moderate, or severe with *mild* being symptoms that required no treatment or intervention, *moderate* being symptoms that required adjunctive treatment (e.g., antiemetics), and *severe* being symptoms that resulted in hospitalization, ART discontinuation, or death. Adherence was assessed by three measures: pharmacy records, healthcare provider assessments, and patient self-assessments including a visual analog scale.

Review of the data revealed that pharmacy records provided the most comprehensive data on adherence. Any indication of an adherence problem from the healthcare worker or patient self-assessment was always associated with pharmacy data indicating a lapse in drug acquisition. Additionally, pharmacy records frequently identified adherence problems not identified in the healthcare worker or patient report. Therefore, pharmacy records were used to categorize adherence for the analyses. As such, a patient who had no documented lapses in drug acquisition per pharmacy records and no patient or healthcare worker reports of adherence problems was deemed to have "*good adherence.*" Patients with a lapse in drug acquisition which, based on pill distribution, would have resulted in greater than 1 week off ARV therapy were categorized as having "*poor adherence.*" Patients who failed to return to the clinic as scheduled for more than 3 months were termed "*defaulters*" unless tracking efforts deemed that the person had died. Patients who died during follow-up were categorized based on their adherence before date of reported death.

**Analysis.** Descriptive data on the distribution of baseline patient characteristics at the initiation of antiretroviral therapy were determined. For the outcomes of poor adherence and death, the logistic regression or a *t* test was used to assess the association between outcomes and baseline patient characteristics. With minor modifications to avoid issues of multicollinearity, all variables significant in the bivariate comparisons were included in multivariate models of adherence (poor versus good) and survival (died versus survived).

In the primary analysis, people were considered food insecure if the number of meals they reported taking was lower during the "hunger" season (1–2 months just before the harvest) compared with the number of meals taken most of the year. Two sensitivity analyses were completed for the food insecurity variable. First, we repeated the analyses with food insecurity based on the quantity of maize meal (the local staple) consumed per person per month in the household and adjusted for number of children and adults in the household. In the second, food insecurity was determined by the number of days in the past week the person had skipped a meal because of a lack of food.

†Written consent was reviewed verbally as part of the informed consent process given literacy rates in the population.

‡Note that our study population resides in southern Zambia in the region bordering Zimbabwe, so language and culture of the studied subjects are very similar to the Shona population.

## RESULTS

**Recruitment.** A total of 496 study subjects were recruited and underwent baseline assessments within 1 week of initiating ART. Ninety-eight percent underwent testing the first day ARV medications were dispensed before the patient had received a single dose. More than 95% of eligible study subjects consented to participate.

**Baseline patient characteristics.** Demographic, biomedical, socioeconomic, and neuropsychiatric patient characteristics at the time of ARV initiation are presented in Table 1. The demographic profile of the study population is very similar to

TABLE 1
Patient characteristics at initiation of antiretroviral therapy ($N = 496$)*

| Demographic | |
|---|---|
| Age (mean years) | 38.1 (range 18.0–68.0; SD 9.5) |
| Gender (n, % males) | 205 (41.3) |
| Marital status (n, %) | |
| Married† | 301 (60.7) |
| Divorced | 59 (11.9) |
| Widowed | 90 (18.1) |
| Never married | 46 (9.3) |
| No. children in household (median) | 3.0 (IQR 3–5) |
| Education (mean years) | 7.2 (range 0–20.0; SD 3.5) |
| Socioeconomic | |
| Disclosure status to community (n, %) | |
| Undisclosed | 350 (70.6) |
| Forced disclosure | 65 (13.1) |
| Voluntary disclose | 24 (4.8) |
| Do not know | 57 (11.5) |
| Wealth in household goods (median US$)[26] | $1,078 (IQR $62–$1,523) |
| Has clinic buddy (n, %) | 252 (50.8) |
| HIV clinic access | |
| Travel mode (%) | Walk 51.9; vehicle 41.5; bike 5.1; other 1.4 |
| Travel time required (median minutes) | 90 (IQR 30–180) |
| Travel cost per visit (median US$)‡ | $1.60 (IQR $0.40–$2.40) |
| Water Source (n, %) | |
| Inside tap | 88 (17.7) |
| Pump | 237 (47.8) |
| Well | 65 (13.1) |
| Stream | 44 (8.9) |
| Missing | 62 (12.5) |
| Human waste management (n, %) | |
| Bush | 91 (18.3) |
| Pit latrine | 283 (57.1) |
| Flush toilet | 35 (7.1) |
| Missing | 61 (12.3) |
| Food insecure (%, n)§ | 220 (44.4) |
| Medical | |
| WHO clinical stage (n, %) | |
| Stage 1: | 26 (5.2) |
| Stage 2: | 172 (34.7) |
| Stage 3: | 242 (48.8) |
| Stage 4: | 31 (6.3) |
| Not documented: | 25 (5.0) |
| Body mass index (median BMI) | 20.5 (IQR 18.8–23.1) |
| TB history (n, %) | 102 (20.6) |
| Peripheral neuropathy symptoms¶ (%, n) | 375 (75.6) |
| Neuropsychiatric Profile | |
| International HIV Dementia Scale (IHDS)[21] ($N = 440$) | Mean 9.0 (range 2.0–12.0; SD 2.3)<br>Median 9.0 (IQR 8.0–11.0)<br>Below norms‖ 230 (42.1%)[21] |
| Zambian Mini-Mental State Examination (zMMSE)[22] ($N = 471$) | Mean 21.6 (range 8–24; SD 2.6)<br>Median 22.0 (IRQ 21.0–23.0)<br>Below norms** 245 (34.4%)[22] |
| Shona Symptom Scale[23] ($N = 469$) | Mean 8.0 (range 0–14; SD 3.7)<br>Median 8.0 (IQR 5.0–11.0)<br>Require psychiatric support 380†† (81.0%)[23] |
| Stigma Score ($N = 494$) | Mean 0.5 (range 0–3; SD 1.0)<br>Median 0.5 (IQR 0–0) |

* IRQ = interquartile range.
† 5.8% of women and 6.8% of men were in a polygamous marriage.
‡ In 2006, 73% of households in the Southern Province lived below the poverty line with an income of < $2.00 per year.
§ Subjects were considered food insecure if they reported taking fewer meals per day in the months before harvest (i.e., the hunger season).
¶ Present at enrollment (i.e., before antiretroviral [ARVs] were initiated) based on single question neuropathy screen (SQNS).
‖ Score ≤ 10 considered abnormal based on prior studies.
** Scores < 22 considered abnormal based on previous Zambian norms.
†† Validation of Shona Symptom Scale suggested that scores of > 5 warranted further assessment.

Table 2
Neuropsychiatric symptoms per the Shona Symptom Scale ($N = 496$)

| Question (*During the course of the past week…*) | Yes (n, %) |
|---|---|
| Did you have times in which you were thinking deeply or thinking about many things? | 355 (71.6) |
| Did you find yourself sometimes failing to concentrate? | 276 (55.6) |
| Did you lose your temper or get annoyed over trivial matters? | 326 (65.7) |
| Did you have nightmares or bad dreams? | 303 (61.1) |
| Did you sometimes see or hear things that others could not see or hear? | 145 (29.2) |
| Was your stomach aching? | 291 (58.7) |
| Were you frightened by trivial things? | 213 (42.9) |
| Did you sometimes fail to sleep or lose sleep? | 323 (65.1) |
| Were there moments when you felt life was so tough that you cried or wanted to cry? | 314 (63.3) |
| Did you feel run down (tired)? | 365 (73.6) |
| Did you at times feel like committing suicide? | 48 (9.7) |
| Were you generally unhappy with things you were doing each day? | 341 (68.8) |
| Was your work lagging behind? | 346 (69.8) |
| Did you feel you had problems in deciding what to do? | 306 (61.7) |

that of the overall adult population accessing care in the study clinics.[19] Almost 40% of patients ($N = 193$) had not completed primary school, 41.5% ($N = 206$) came from homes where the head of the household was a subsistence farmer, and 50% resided in a mud brick hut with thatched roof and dirt floor.

Approximately half of the subjects walked to their clinic appointments with a median travel time of 90 minutes and half had a clinic buddy. Most study subjects did not get a CD4 count before ART initiation because of problems with local laboratory equipment at all three study sites. One in five participants had a history of tuberculosis and peripheral neuropathy symptoms were extremely common. Overall, 17.9% ($N = 89$) of patients lived in communities where their HIV status was generally unknown at the time ARVs were initiated.

Neurocognitive dysfunction was evident in 42.1% and 34.4% of study subjects based on the IHDS and the zMMSE, respectively. The median Shona Symptoms Score was eight, indicating that 81% of patients warranted further psychiatric assessment and support based on previously published recommendations for use of this instrument in the general population.[24] The distribution of positive responses to the 14 questions in the Shona Symptom Scale is provided in Table 2. Of note, almost 10% of patients reported suicidal ideation in the prior week.

Almost 60% of patients had good adherence throughout the observation period. One in five deaths occurred within 3 months of ART initiation. Outcomes are presented in Table 3. Less than 3% of subjects were lost to follow-up with a median follow-up of 275 days. Forty percent of patients had moderate-to-severe ARV side effects including five fatal drug reactions (anemia, hepatic failure, and toxic epidermal necrosis).

Predictors of poor adherence are provided in Table 4. In the bivariate analysis, being female, divorced, less educated, and food insecure were all associated with poor adherence. Longer travel time to clinic, ARV side effects, and baseline cognitive dysfunction were also barriers to adherence. Food insecurity remained significant in the two sensitivity analyses using other definitions of food insecurity. In the multivariate model, containing all variables significant in the bivariate analysis, ARV side effects remained a significant independent predictor of poor adherence.

Table 3
Clinical outcomes ($N = 496$)

| Outcome | |
|---|---|
| Length of follow-up (days) | Mean 265 (15–723; SD 133)<br>Median 275 (IQR 147–377) |
| ARV side effects (n, %) | |
| None-to-mild | 342 (69.0) |
| Moderate-to-severe | 149 (30.0) |
| Fatal | 5 (1.0) |
| Adherence (n, %) | |
| Good | 295 (59.5) |
| Poor | 195 (39.3) |
| Missing data | 8 (1.6) |
| Mortality | |
| Died (n, %) | 101 (20.4) |
| Time to death (median days) | 81.0 (IQR 44–139) |
| Lost to follow-up (n, %) | 14 (2.8) |

Our finding that having a clinic buddy was associated with poor adherence was unexpected and on the surface appeared paradoxical. In our retrospective chart review completed 1 year before this study's enrollment commenced, 36.5% of HIV patients had a buddy and having a clinic buddy was found to be associated with better adherence.[19] These findings were disseminated to the clinic staff that then began to encourage clinic attendees to bring a clinic buddy to their visits. Over the intervening year, the proportion of patients with clinic buddies increased from 36% to 51%. One can surmise that by targeting those patients with potential adherence problems and persuading them to get a buddy, having a buddy became a marker for non-adherence. As such, this variable was not included in the multivariate model.

Predictors of death are provided in Table 5. The more advanced HIV stage, the presence of peripheral neuropathy symptoms at the time of ART initiation, food insecurity, less wealth, and a greater burden of psychiatric symptoms as measured by the Shona Symptom Scale all predicted death in the bivariate analysis. In the multivariate model, HIV clinical stage, burden of psychiatric symptoms, and poverty remained significant predictors of death.

## DISCUSSION

In this prospective cohort study of rural Zambian patients initiating ART, we identified an early mortality rate of ~ 20%, which is congruent with reports in similar settings.[5,27–29] The overall mortality rate in this prospective study corresponded to the mortality plus default rate identified in an earlier retrospective cohort study conducted in the region and suggests that most of the patients thought to be defaulters in the retrospective assessment probably died.[19] Tracking of patients who are lost to follow-up from ARV clinics is challenging and yet understanding the reasons for defaulting and the long-term outcomes of defaulters are critical. In one South African study, among patients who failed to attend the clinic, follow-up assessments indicated that transportation costs and user fees were the primary barrier to clinic attendance and that loss to follow-up was associated with a high mortality rate.[30] A Malawian study of clinic defaulters found that 50% had died with most of these deaths occurring within 3 months.[31]

Most ART adherence research in Africa has found high early mortality rates (meaning death within 90 days of initiating ART) reported to be 8–26% when clinics initially

TABLE 4
Patient characteristics associated with poor adherence ($N = 488$)

| Characteristic | Adherence | Bivariate analysis OR (95% CI) or $P$ value | Full model |
|---|---|---|---|
| Age (mean) | Poor adherence, 37.8<br>Good, 38.3 | $P = 0.58$ | – |
| Gender (1 = male) | % Poor<br>Men, 34.5%<br>Women, 44.2% | 0.67 (0.46–0.97) | 0.70 (0.43–1.14) |
| Marital status (1 = married) | % Poor<br>Married, 38.2<br>Widowed, 45.1<br>Never, 25.5<br>Divorced, 59.3 | 1.08 (0.66–1.77)<br>0.56 (0.27–1.16)<br>2.10 (1.16–3.81) | 1.04 (0.78–1.92)<br>0.36 (0.13–1.01)<br>0.56 (0.26–1.22) |
| Education (mean years) | Poor adherence, 6.4<br>Good, 7.8 | $P < 0.001$ | 0.96 (0.89–1.03) |
| Community disclosure (1 = voluntary) | % Poor<br>Yes, voluntary 31.3<br>Do not know, 21.4<br>No, 44.2<br>Yes, forced 41.7 | 0.55 (0.24–1.30)<br>1.86 (1.02–3.38)<br>1.31 (0.48–3.62) | 0.79 (0.31–2.02)<br>1.22 (0.97–4.23)<br>1.08 (0.23–4.54) |
| Wealth (mean US$) | Poor $838<br>Good $1237 | $P = 0.0075$ | 1.00 (0.9998–1.0001) |
| Has clinic buddy | Poor, 62.1%<br>Good, 45.0% | 2.00 (1.38–2.89) | – |
| HIV clinic access<br>Travel time required (median)<br>Travel cost per visit (median US$) | Poor, 124 min.<br>Good, 103<br>Poor, $1.97<br>Good, $2.04 | $P = 0.016$<br>$P = 0.07$ | 1.00 (0.998–1.003) |
| Food insecure | Poor, 51.3%<br>Good, 38.5% | 1.68 (1.17–2.43) | 1.08 (0.68–1.70) |
| ARV side effects | Poor, 67.6%<br>Good, 32.4% | 2.63 (1.78–3.90) | 2.49 (1.54–4.03) |
| IHDS (mean) | Poor, 8.6<br>Good, 9.3 | $P = 0.001$ | 0.97 (0.88–1.08) |
| zMMSE (mean score) | Poor, 21.2<br>Good, 21.9 | $P = 0.001$ | – |
| Shona EQ-5D (mean) | Poor, 8.2<br>Good, 7.7 | $P = 0.09$ | – |
| Stigma score (mean) | Poor, 0.56<br>Good, 0.47 | $P = 0.34$ | – |

Full Model: Adherence (poor = 1) = gender + marital status + years of education + community disclosure status + mean wealth + travel time + food insecurity + ARV side effects + IHDS.

open.[5,27–29] In urban Zambia, during the rapid scale-up of ARV treatment, most deaths occurred within 90 days of treatment initiation with risk factors for death being a low CD4 count, higher WHO clinical stage, lower hemoglobin, lower BMI at the time of initiating ART, and poor adherence.[32] Death within 90 days after initiating ARVs was also common in this rural population. High early mortality rates may be caused by immune reconstitution inflammatory syndrome. Alternatively, consideration should be given to the possibility that patients with advanced HIV who lack adequate resources to meet their basic biological needs (i.e., those who are food insecure with low BMI) are at increased risk of death possibly because of their generally weak state being worsened by the side effects associated with ART initiation. In our study, in addition to the HIV clinical stage, a greater burden of psychiatric symptoms and key socioeconomic factors were associated with mortality. In this rural Zambian population a higher burden of psychiatric symptoms was associated with higher mortality rates, but this does not appear to be mediated through poor adherence. If these findings are replicable, then the underlying biomedical basis for this deserves further study.

Women may have better opportunities to access HIV care early through their maternity-related health services,[33] but our study found that gender differences favoring men were evident in adherence. In South Africa, men have been noted to access services later in the course of their infection,[34] but our data suggest that at least in rural Zambia men may be better able to adhere to treatment once initiated. Previous reports from rural Zambia suggest childcare responsibilities may contribute to this gender-specific adherence differential.[19] The burden of divorce and/or spousal abandonment and lack of disclosure possibly secondary to hearing of these consequences also differentially affect women.

Longer travel time to the clinic was associated with poor adherence in our cohort. In a previous study conducted in rural southern Zambia, travel times were not predictive of adherence,[13] however travel time in this earlier study was estimated using global positioning systems while we ascertained this information directly from patient interviews.

Previous qualitative reports indicate that stigma plays a role in adherence problems.[35] Although measured felt stigma did not predict adherence, community disclosure status—specifically, a lack of disclosure to the community, was associated with poor adherence suggesting the stigma does indeed impact adherence indirectly.

Previous qualitative work in Kenya[36] and other African settings have indicated that food insecurity may be a barrier to adherence. Baseline food insecurity was a strong predictor

TABLE 5
Patient characteristics associated with death ($N = 488$)*

| Characteristic | Mortality | Bivariate OR (95%CI) or $P$ value | Full model |
|---|---|---|---|
| Age (mean age years)† | Died 37.8 Survived 38.2 | $P = 0.68$ | – |
| Gender (1 = male) | Mortality (%) | | |
| | Men 17.6% | 0.72 (0.47–1.15) | – |
| | Women 22.5% | | |
| WHO stage (% died; 1 = stage 1) | Mortality (%) | | |
| | Stage 1: 3.8% | 7.80 (0.95–56.0) | 4.99 (0.63–39.16) |
| | Stage 2: 23.6% | 5.44 (0.71–41.50) | 3.73 (0.48–29.29) |
| | Stage 3: 18.6% | 10.5 (1.23–89.72) | 9.85 (1.14–85.34) |
| | Stage 4: 35.5% | | |
| BMI (mean) | Died 20.8<br>Survived 21.2 | $P = 0.29$ | – |
| Tuberculosis history | Died 18.6%<br>Survived 21.0% | 1.16 (0.67–2.02) | – |
| Peripheral neuropathy sxs | Died 22.7%<br>Survived 14.0% | 1.72 (1.08–2.36) | 1.08 (0.55–2.12) |
| Food insecure | Died 53.9%<br>Survived 41.1% | 1.64 (1.06–2.54) | 1.25 (0.77–2.05) |
| Wealth (median $US) | Died $632<br>Survived $1,195 | $P = 0.004$ | 0.9997 (0.9995–1.000) |
| IHDS (mean score) | Died 8.8<br>Survived 9.1 | $P = 0.20$ | – |
| zMMSE (mean score) | Died 21.4<br>Survived 21.7 | $P = 0.40$ | – |
| Shona Symptom Score (mean) | Died 9.2<br>Survived 7.7 | $P = 0.0003$ | 1.09 (1.01–1.18) |
| Stigma score | 0.67 in deaths vs. 0.44 in survivors | $P = 0.07$ | – |

* Given that the vast majority of deaths were too early to be related to antiretroviral (ARV) adherence this was not evaluated. Also, because experiencing side effects was highly associated with duration of follow-up and was therefore not included.
† Remained with $P > 0.05$ if age analyzed by 10-year increments in categories.
Full Model: Mortality = WHO stage + peripheral neuropathy symptoms + food insecurity + wealth + Shona symptoms.

of poor adherence among people attending HIV clinics in rural Zambia. Advanced HIV with associated chronic illness can contribute to a downward SES drift for affected families, especially if the infected individual is the primary earner and might further contribute to food insecurity. Food insecurity affected 71% of people without neuropathy symptoms versus 84% of people with neuropathy symptoms—odds ratio (OR) 2.15 (1.37–3.67). In a post hoc logistic regression model with the presence of peripheral neuropathy (present/absent) as the dependent variable, both food security and clinical HIV stage were significant independent predictors of peripheral neuropathy. This may explain the high rates of neuropathy seen in this population and suggests that the high rate of neuropathy symptoms in HIV+ African populations may be related to some underlying nutritional deficiency or deficiencies. Similarly high rates of pre-treatment HIV neuropathies have been reported from Kenya.[37] The use of d4T is contraindicated in patients with pre-existing peripheral neuropathy in the United States. As ART options expand in resource-limited settings beyond a single combination treatment, such comorbid limitations can be taken into consideration.

Strengths of this study include the relatively comprehensive socioeconomic and neuropsychiatric baseline assessments made and very complete follow-up data with < 3% of patients lost to follow-up. Furthermore, the clinics involved in care had no additional resources for patient retention (e.g., food supplements) and thus the data obtained likely provide a representative estimate of patient outcomes under conditions of routine care. Limitations include the lack of biomedical markers (CD4 counts) and the lack of normative data for the Shona Symptom Score in the study community. Drug acquisition/pharmacy data provided the adherence estimates without recourse to viral load measurements to validate this adherence measure, but several studies have shown that pharmacy-based data offer a reasonably valid proxy for assessing patient adherence.[38–40]

The advent of free ARVs have led to discussion in the popular press about the problems of ARV adherence for people without sufficient access to food,[11,12] but to our knowledge ours is the first study to provide quantitative, prospective data indicating that inadequate access to food may worsen adherence and increase mortality among people receiving ARVs. As evidenced by the baseline SES data acquired in this study, many people with HIV/AIDS in Zambia lack the resources needed for basic survival. Add to this the biomedical and psychosocial burden of HIV and the provision of free medications alone will not be sufficient to reverse the morbidity and mortality of HIV in much of Africa.

Received March 29, 2011. Accepted for publication June 27, 2011.

Note: Supplemental appendix is available at www.ajtmh.org.

Acknowledgments: Many thanks to the HIV clinic staff at all study sites whose enthusiastic support of this project made it possible.

Financial support: Funding for this work was provided by the Doris Duke Charitable Foundation through their program for Operational Research for AIDS Care and Treatment in Africa (ORACTA).

Disclaimer: The authors have no conflicts of interest.

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