

# Individual and environmental correlates and predictors of early adherence and outcomes after liver transplantation

**Context**—Little is known about patients' contribution to health outcomes after liver transplantation. Yet, in other transplant recipients, nonadherent behavior is directly related to the leading causes of morbidity and mortality in liver transplant recipients.

**Objective**—To examine patient and environmental factors in relation to all aspects of adherence to the posttransplantation regimen and health outcomes in the first 6 months after transplantation.

**Design**—A descriptive analysis of individual and environmental factors in relation to adherence and health outcomes at 6 months after liver transplantation.

**Participants, Setting**—One hundred fifty-two adult liver transplant recipients at the University of Pittsburgh Medical Center.

**Main Outcome Measures**—Adherence to medication taking, appointment keeping, lifestyle changes, mood, quality of life, and clinical markers of liver function.

**Results**—Nonadherence was prevalent (47% with appointments, 73% with medication); relapse to drug/alcohol use occurred among a few recipients (5.6%), all with a history of substance abuse before transplantation. Patterns of coping, decision making, attitude, and social support were correlated with adherence, clinical markers, and psychological function ( $r = 0.22-0.45$ ). Avoidant coping, affective dysregulation, and caregiver support emerged as robust predictors of negative clinical and mental health outcomes ( $\beta = .224-.363$ ).

**Conclusion**—This information about liver transplant recipients is important for researchers and clinicians. Researchers can develop guidelines by using stable but modifiable characteristics of patients to identify transplant candidates at risk of nonadherence. Such guidelines would enable clinicians to prepare patients better to manage the posttransplant regimen. (*Progress in Transplantation*. 2010;20:58-67)

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## Notice to CE enrollees:

A closed-book, multiple-choice examination after this article tests your ability to accomplish the following objectives:

1. Discuss behaviors associated with mortality in liver transplant recipients
2. Describe social characteristics of liver recipients with a history of alcohol abuse
3. Identify factors associated with medication adherence after liver transplantation

Posttransplant adherence for liver recipients involves taking medications on a regular basis, keeping appointments, and making and sustaining recommended

lifestyle changes related to smoking, drinking, drug use, and other high-risk behaviors. Much of the research to date has been focused primarily on 1 facet of adherence in a subgroup of liver transplant recipients, namely, return to drinking among recipients who received a transplant because of alcoholic liver disease. Little is known about the contribution of patient and environmental factors to adherence or health outcomes in the general population of liver transplant recipients. Yet nonadherence affects physical and mental health in other transplant recipients.<sup>1,2</sup> Not taking medications, failure to keep appointments, and relapse to drug or alcohol use and/or smoking are directly related (among other transplant recipients) to the leading causes of late mortality (chronic rejection, de novo malignant neoplasms)<sup>3,4</sup> among liver transplant recipients.

Liver transplant patients vary widely in terms of psychiatric, behavioral, and medical history. Approximately half of the population receives a transplant because of hepatitis C and/or alcoholic cirrhosis, contracted through substance abuse and/or other risky activities; most other causes of end-stage liver disease are unrelated to behavior. The range of psychopathology and behavioral history unique to this population<sup>5,6</sup> suggests that liver transplant recipients may differ from other transplant groups with respect to patterns of behavior that affect adherence and health outcomes.

Rates and risk factors for nonadherence to the post-transplant medical regimen in the general population of liver transplant recipients were reported in a recent meta-analysis.<sup>7</sup> However, empirical evidence about adherence to medication taking, appointment keeping, lifestyle changes, and clinical outcomes among liver transplant recipients is scarce, and the methods of collecting such evidence are generally limited. No published studies have involved comprehensive assessment of psychosocial and environmental factors in relation to the full range of adherence and health outcomes. Findings about the impact of specific behaviors (eg, medication adherence) on specific health outcomes in this population are mixed.<sup>8,9</sup> Although relapse to drug and/or alcohol use does not appear to directly affect short-term outcome, rates are significant and little is known about the longer-term effects of recidivism to alcohol or other drugs of abuse on adherence to the rest of the treatment regimen or on health outcomes.<sup>10,11</sup> Some research on patients with alcoholic liver disease suggests that nonadherence with other aspects of the treatment regimen, particularly relapse to smoking, is concomitant with relapse to drinking and affects morbidity and mortality.<sup>12,13</sup>

This study is the first to prospectively focus on adherence to the entire treatment regimen by the general population of liver transplant recipients with a comprehensive assessment approach. We know that nonadherence affects health outcomes in other transplant populations<sup>1,2</sup> but, given the wide range of psychiatric disease (which underlies patterns of behavior), we hypothesized that behavior relevant to adherence would differ in liver transplant recipients.

Specific aims of the study pertinent to this article are as follows: (1) To characterize adherence to medication taking, appointment keeping, and lifestyle changes during the first year after liver transplantation. (2) To determine the individual and environmental factors that underlie adherence and health outcomes during the first year after liver transplantation. We examined sociodemographic, clinical (factors related to medical history, psychiatric history, and transplant), individual, and environmental characteristics known to affect adherence and health outcomes in general medicine and other transplant populations<sup>14,15</sup>

shortly after transplantation. Multiple methods are being used to track aspects of posttransplant adherence (appointment keeping, medication taking, lifestyle changes) and health outcomes (physical and mental function) for the remainder of the study.

## Methods and Materials

### Study Setting and Sample

This study was focused on correlates and predictors of adherence to the posttransplant regimen and health outcomes in the first 6 months after transplantation. Early patterns of adherence have been predictive of longer term adherence and health outcomes in other transplant populations.<sup>2</sup> Approval from the University of Pittsburgh's institutional review board was obtained before recruitment; informed consent was obtained from all participants at the time of enrollment, either in the hospital or at an outpatient clinic appointment after discharge. All participants gave us permission to access their medical records for the length of the study.

First-time, English-speaking, adult liver transplant recipients were recruited from the Starzl Transplant Institute at the University of Pittsburgh Medical Center (UPMC) either before discharge from the hospital or at an early clinic visit. Stille et al,<sup>16</sup> also in this issue of *Progress in Transplantation*, offer a more complete description of the methods and the generalizability of the sample to liver transplant recipients at UPMC and nationally. This article is focused on 152 patients who received a liver transplant between October 2006 and November 2008.

### Procedure

Recipients who had received a liver transplant 1 to 3 months earlier and were managing their treatment regimens (at home or elsewhere) participated in a baseline interview with a member of the study team and completed a battery of self-report measures. Participants were provided with electronic medication monitors and diaries, detailed verbal and written directions, and a toll-free telephone number to reach study personnel.

Recipients participated in a telephone interview 6 months after the baseline session and were questioned about adherence to all aspects of the treatment regimen and about changes to their personal or environmental situations. Six participants were lost between enrollment and the baseline interview (5 withdrew because of illness, 1 died). When this article was written, 146 participants had completed the baseline interview and 130 had completed the self-reporting measures. Four participants withdrew, 1 was lost to follow-up between baseline and 6 months; 109 have, to date, completed the 6-month interview. Adherence and health outcomes are being tracked with a second

interview at 12 months and, on all enrolled recipients, across the entire study period with data from medical records. Interviews were randomly monitored by senior research staff for fidelity to the study protocol.

### Baseline Data

Three clusters of factors at baseline were examined to determine relationships between potential correlates and predictors of adherence and health outcomes at 6 months. Variables of interest are listed within those clusters; additional information about measures and scoring can be found in our other article in this issue.<sup>16</sup>

*Sociodemographic Characteristics.* Basic sociodemographic history was obtained during the baseline interview. We examined patients' age, sex, race, marital status, education, household income, and adequacy of income to meet basic needs in this analysis.

*Medical and Psychiatric History, Transplant-Related Factors.* Medical and mental health history were obtained at the baseline session from medical records and a comprehensive interview that had been developed in research with chronic medical patients and cardiothoracic transplant recipients.<sup>17</sup> The interview was modified to include additional information pertinent to liver transplant recipients (eg, drug/alcohol use, addiction rehabilitation, and length of abstinence before transplant). Documented history of substance abuse, pretransplant diagnosis and MELD (Model for End-Stage Liver Disease) score (which indicates severity of disease), and donor type (living or deceased) were obtained from a review of medical records.

*Individual and Environmental Factors.* Coping style, as it pertains to transplant-related health problems, was assessed by using the Coping Responses Inventory. This 48-item Likert-scale instrument is used to assess 8 different types of coping responses by using the approach-avoidant framework.<sup>18</sup>

The Dysregulation Inventory, a 92-item self-report scale developed at UPMC to determine risk of substance abuse among adolescents and adults, was used to assess participants' style of decision making and self-regulatory ability (degree of impulsivity). The Dysregulation Inventory can be used to assess the 3 traits comprised by dysregulation (affect, behavior, cognition). Affective dysregulation represents degree of negative affectivity and irritability; behavioral dysregulation is impulsivity, sensation seeking, and aggression; cognitive dysregulation is less strategic thinking, problem solving, and self-monitoring.<sup>19</sup>

The Cook-Medley Hostility Scale, a measure frequently used to assess individual differences in cynical hostility in chronically ill patients, was used to

assess level of trait hostility; lower scores indicate higher levels of hostility.<sup>20</sup>

Relationship with spouse/caregiver was assessed with the 32-item Dyadic Adjustment Scale, which has been widely used in clinical and research work with couples. Items are scored from 0 to 5, with a higher score representing a closer relationship.<sup>21</sup>

Family support was assessed with the Family Relations Index from the Family Environment Scale<sup>22</sup>; this index measures positive versus negative perceptions of family support.

Recipients' social network was evaluated with the Lubben Social Network Scale, an 11-item self-report instrument that describes family and friend networks, confidence in relationships, and degree of social engagement.<sup>23</sup>

Proximity and ease of access to local physicians, visiting nurses, social service professionals, hospital, laboratory, and pharmacy and accessibility of services (transportation, affordability) were assessed with an questionnaire designed by the investigators at the baseline session.

### Six-Month Data

*Adherence: Medication Taking, Appointment Keeping, and Lifestyle Changes.* Adherence to immunosuppressant medication was monitored in 3 ways. First, patients were questioned about adherence to medications, as well as to other aspects of the regimen, during an interview that used an adaptation of a measure that was developed for cardiothoracic patients.<sup>16</sup> Second, medication taking was monitored with pill bottles fitted with electronic caps that recorded time and date of each opening to continuously track adherence to the primary immunosuppressant. Medication adherence, in these analyses, was operationalized as percentage of prescribed doses taken and percentage of days with the correct dose and with the correct interdose interval (within 2 hours of the scheduled time for twice-daily dosing) for the 6-month period. Third, medication diaries supported cap data by allowing patients to explain variance in openings (eg, for filling daily medication dispensers, pocket dosing, or for refilling the bottle). Medication orders were periodically updated with patients' reports and data from medical records in order to determine if adherence was in accordance with the physician's instructions. Seventy-four recipients (68%) used the electronic caps; recipients who used a weekly medication minder were not given caps, and no one refused to use a cap.

We assessed recipients' adherence to appointments with the physician, the clinic, and the laboratory during the interview by using the same questionnaire just described and with data extracted from medical records. Adherence to appointment

keeping was operationalized as the percentage of scheduled appointments that were kept.

Recipients were questioned about smoking and drinking; if they answered positively, frequency and quantity of use was determined. We used self-report rather than biomedical markers to assess both smoking and drinking based on our prior research with transplant recipients, which showed that patients disclose their tobacco/substance use during clinic interviews more often than when other methods are used to gather such information.<sup>24</sup> We also questioned recipients about the use of recreational/street drugs, exposure to potentially contaminated needles, and sexually transmitted disease, all of which increase risk of infection. Failure to follow any recommended lifestyle change was considered nonadherent behavior.

*Health Outcomes: Morbidity, Mood, and Quality of Life.* The latest biopsy and laboratory reports at 6 months after transplantation were extracted from medical records data. Results of the following liver function tests were monitored: aspartate aminotransferase, alanine aminotransferase,  $\gamma$ -glutamyl transpeptidase, and total bilirubin.

Recipients' level of emotional distress was assessed with the Hamilton Anxiety and Depression semistructured interviews conducted by trained study staff at 6 months after transplantation. A total score for each measure represented level of distress.<sup>25,26</sup> Health-related quality of life was assessed in an interview by using version 2 of the Medical Outcomes Study Short Form 12, which is a short multipurpose health survey that yields summary scores of physical and mental health.<sup>27</sup>

### Analytic Strategies

First, the sample and variables of interest were characterized with descriptive statistics (range, mean, standard deviation, median and interquartile ranges for continuous sociodemographic and clinical factors; numbers and percentages for categorical data). Baseline individual and environmental factors were categorized as high (above the median) or low (below the median) or as percentage endorsing a construct (eg, social connectedness). Second, relationships between baseline sociodemographic, psychosocial, and clinical factors and adherence and health outcomes at 6 months were explored to assess for statistical significance with correlations,  $\chi^2$  analysis, and one-way analysis of variance. Third, relationships between significant baseline (predictor) and 6-month (adherence, health outcomes) data were assessed with hierarchical regression analyses to determine potential predictors (sociodemographic, clinical, psychosocial/ environmental factors) of health outcomes. Differences between recipients with and without a history of alcohol and/or drug abuse, documented in medical

Table 1 Sociodemographic characteristics of the sample (N = 152)

| Characteristic  | Value                       |
|---|-----------------------------|
| Male, No. (%)   | 102 (67.1)                  |
| White, No. (%)  | 144 (94.7)                  |
| Currently married, No. (%)  | 101 (66.4)                  |
| Age, years, mean (SD); median (interquartile range)                 | 55.3 (9.8); 55 (11)         |
| Education, years, mean (SD); median (interquartile range)           | 14 (3.1); 14 (4)            |
| Retired or disabled, No. (%) <sup>a</sup>                           | 81 (58.7)                   |
| Household income, US\$1000, mean (SD); median (interquartile range) | 30-39 (3145); 40-49 (40-49) |
| Income adequate for needs, No. (%)                                  | 114 (75.0)                  |

<sup>a</sup> Percentage based on N = 138.

records, on baseline, adherence, and health outcome factors were assessed with independent sample *t* tests and  $\chi^2$  analyses.

## Results

### Descriptive Baseline (Predictors) Factors

*Sociodemographics.* The sample was predominantly male. Most recipients were white, middle aged, and married; most had completed some education after high school. Most recipients were either retired or disabled, and most reported that their household income was adequate to meet basic needs (Table 1). The 6 recipients who were lost before the baseline assessment and those who remained in the study did not differ significantly in any sociodemographic or pretransplant clinical characteristics.

The majority of recipients with a history of substance abuse (62; 43.1% of the sample) were male, fewer were currently married, and most were white. Recipients with a history of substance abuse were also younger than other participants, with fewer years of education and lower income levels.

*Medical/Psychiatric History, Transplant-Related Characteristics.* Pretransplant clinical characteristics of the sample are illustrated in Table 2. Number of comorbid (with liver disease) medical diagnoses ranged from 0 to 12 with a mean of 4.43 (SD, 2.5; median, 4.0; interquartile range, 3); number of psychiatric diagnoses (except substance abuse) ranged from 0 to 4 with a mean of 0.78 (SD, 0.94; median, 0.00; interquartile range, 2). Aside from substance abuse, psychiatric history was unrelated to pretransplant diagnosis of liver disease. Thirty-nine recipients had a history of alcohol abuse, 4 had a history of drug abuse, and 19 had a history of both alcohol and drug abuse

Table 2 Medical/psychiatric history, transplant-related characteristics of the sample

| Characteristic <sup>a</sup>          | No. (%)    |
|--------------------------------------|------------|
| Pretransplant diagnosis              |            |
| Alcoholic cirrhosis                  | 32 (21.1)  |
| Hepatitis C                          | 42 (27.6)  |
| Alcoholic cirrhosis with hepatitis C | 11 (7.2)   |
| Cryptogenic cirrhosis                | 12 (7.9)   |
| Nonalcoholic steatohepatitis         | 23 (15.1)  |
| Primary biliary cirrhosis            | 8 (5.3)    |
| Primary sclerotic cholangitis        | 14 (9.2)   |
| Other                                | 10 (6.6)   |
| Medical history                      |            |
| Diabetes <sup>b</sup>                | 62 (43.1)  |
| Cardiovascular disease <sup>b</sup>  | 33 (22.9)  |
| HIV positive <sup>c</sup>            | 3 (2.2)    |
| Psychiatric history                  |            |
| Depression <sup>d</sup>              | 58 (42.0)  |
| Anxiety <sup>d</sup>                 | 52 (37.4)  |
| Bipolar disorder <sup>d</sup>        | 3 (2.2)    |
| Substance abuse <sup>e</sup>         | 62 (43.1)  |
| Donor type: deceased                 | 126 (87.5) |

<sup>a</sup>The mean (SD) score on the Model for End-Stage Liver Disease scale before transplant was 17.5 (8.6), the median (interquartile range) was 15 (11), and the range was 6 to 44.

<sup>b</sup>Percentage based on N = 144.

<sup>c</sup>Percentage based on N = 139.

<sup>d</sup>Percentage based on N = 139.

<sup>e</sup>Percentage based on N = 144.

documented in medical records. Length of abstinence from alcohol prior to transplantation was from 1 month to 25 years with a median of 23.6 months (interquartile range, 36 months); duration of abstinence from drug use was from 1 month to 30 years; 14 recipients had abstained for less than 3 years. Twenty-two recipients went through alcohol rehabilitation treatment before transplant, and 11 recipients participated in a drug rehabilitation program (Table 2).

*Individual and Environmental Factors.* Most recipients (98.4%) used primarily an approach (actively dealing with rather than avoiding a situation) or balanced (less than 5-point difference between approach and avoidant scales) style of coping with transplant-related problems. Slightly less than half of the sample (46.1%) reported low levels of trait hostility. Half (49.6%) of the sample endorsed items suggestive of good impulse control or low overall dysregulation. Most recipients who completed the caregiver support measure were married, and approximately half reported high levels of support. A slight majority (55.6%) of recipients endorsed a positive perception of family support. Most recipients (72.7%) were socially connected within the community, as evidenced by helping others very often or daily. Access to medical, nursing, social service, laboratory, hospital, and pharmaceuti-

cal services was relatively easy for all but a few (6) of the recipients. The 5 recipients who were lost to follow-up before the 6-month assessment did not differ from those who remained in the study on any of the baseline psychosocial or environmental measures.

Recipients with a pretransplant history of substance abuse endorsed significantly higher levels of avoidant coping ( $P = .02$ ), affective ( $P < .001$ ), behavioral ( $P < .001$ ), and cognitive dysregulation ( $P < .001$ ); they were less socially connected ( $P = .02$ ) within the community.

### Descriptive 6-Month Adherence Factors

*Appointment Keeping.* Six recipients reported missing or canceling at least 1 clinic or laboratory appointment. Data from the medical records indicate that 58 recipients (of 124 subjects, 47%) missed or cancelled appointments. Recipients missed or cancelled from 0% to 100% of scheduled appointments; 9 recipients missed half or more of their appointments.

*Medication Taking.* Twenty-two recipients reported missing a dose of immunosuppressant medication at some time during the 6-month period; 19 of those recipients said they had missed a dose less often than once a month. Medication adherence was also tracked with electronic monitoring, supplemented by diaries, for the first 6 months after transplant (mean, 159 days). Fifty-four recipients (72.9%) took less than 100% of the prescribed doses, 20 took more than 100% of prescribed doses. Thirty-three recipients (44.6%) took the correct dose less than 90% of the days monitored, 42 recipients (56.8%) took medication during the allowed interdose interval less than 90% of the time.

*Lifestyle Changes.* Four recipients reported having had an alcoholic drink since transplantation, 15 reported having used tobacco, and 2 reported having used street or recreational drugs since transplant. Two of the recipients who reported using alcohol had a pretransplant history of alcohol abuse. One of those recipients had been abstinent for 6 months before transplant, the other for 3 years; neither had participated in substance abuse rehabilitation.

All recipients who used tobacco after transplant had smoked before transplant; one had been a cigar smoker, others had used cigarettes. One recipient who used street/recreational drugs had a documented history of alcohol abuse but reported no pretransplant drug use and had abstained from drinking for 3 months before transplant. The other recipient also had a documented history of alcohol abuse and had reported using marijuana and cocaine before transplant. He had been in outpatient alcohol rehabilitation and abstained from drinking for 10 months before transplant; he had not been in drug rehabilitation and had been abstinent from drugs for 2 years before transplantation. None of

Table 3 Relationships<sup>a</sup> between psychosocial and health outcome variables

| Psychosocial variable    | Bilirubin          | Alanine aminotransferase | Aspartate aminotransferase | $\gamma$ -Glutamyl transpeptidase | Depression         | Anxiety           | Quality of life |                    |
|--------------------------|--------------------|--------------------------|----------------------------|-----------------------------------|--------------------|-------------------|-----------------|--------------------|
|                          |                    |                          |                            |                                   |                    |                   | Physical        | Mental             |
| Approach coping          | .133               | .176                     | .222 <sup>b</sup>          | -.017                             | -.029              | .083              | .041            | .097               |
| Avoidant coping          | .254 <sup>c</sup>  | .152                     | .245 <sup>c</sup>          | .017                              | .367 <sup>c</sup>  | .377 <sup>c</sup> | -.152           | -.291 <sup>c</sup> |
| Affective dysregulation  | -.015              | -.120                    | -.041                      | -.107                             | .366 <sup>c</sup>  | .283 <sup>c</sup> | -.018           | -.453 <sup>c</sup> |
| Behavioral dysregulation | -.056              | -.186                    | -.080                      | -.222 <sup>b</sup>                | .278 <sup>c</sup>  | .209 <sup>b</sup> | .069            | -.384 <sup>c</sup> |
| Cognitive dysregulation  | -.104              | -.129                    | -.122                      | -.120                             | .100               | .106              | .042            | -.235 <sup>c</sup> |
| Hostility                | -.220 <sup>c</sup> | .028                     | -.167                      | .082                              | -.276 <sup>c</sup> | -.168             | .012            | .279 <sup>c</sup>  |
| Community involvement    | .039               | .073                     | .074                       | -.024                             | -.140              | -.083             | .000            | -.102              |
| Family environment       | .033               | -.051                    | .065                       | .035                              | .196               | .148              | -.080           | -.241 <sup>b</sup> |
| Caregiver relationship   | .087               | .312 <sup>c</sup>        | .232 <sup>b</sup>          | .309 <sup>c</sup>                 | .054               | -.048             | .043            | -.057              |

<sup>a</sup> Pearson correlations.

<sup>b</sup>  $P < .05$ .

<sup>c</sup>  $P < .001$ .

the recipients reported having gotten a tattoo, body piercing, or possible exposure to a sexually transmitted disease since transplantation.

The only aspect of adherence that differed according to history of substance abuse was that recipients with a positive history were more likely to resume smoking.

### Descriptive 6-Month Health Outcome Factors

**Morbidity.** According to the most recent biopsy report extracted from medical records at 6 months, 12 recipients had evidence of acute rejection and 8 recipients had evidence of steatosis 6 months after transplant. Data in the medical records indicated elevations in all liver enzyme levels on liver function tests: 21 recipients had high bilirubin levels (>1.5 mg/dL), 47 recipients had high alanine aminotransferase levels (>40 IU/mL), 34 had high aspartate aminotransferase levels (>40 IU/mL), and 43 had high  $\gamma$ -glutamyl transpeptidase levels (>65 IU/mL).

**Mood and Quality of Life.** Sixty-two recipients (57% of the 109 who completed the 6-month interview) indicated high (above the median) levels of depression 6 months after transplant; 64 recipients (59%) indicated high levels of anxiety. Thirty-eight recipients (35%) reported average or better (T scores  $\geq 50$ ) physical quality of life, 80 recipients (73%) reported average or better mental quality of life at 6 months after transplant.

Recipients with a history of substance abuse reported higher levels of depression and lower levels of mental quality of life.

### Relationships Between Baseline and 6-Month Adherence Variables

Sociodemographic factors (sex, age, race, marital status, education, income level) were not related to patterns of adherence (appointment keeping, medication taking, alcohol, drug, or tobacco use) at 6 months after transplant. Neither were any of the preoperative transplant-related or medical/psychiatric factors (MELD score, type of transplant, or medical/psychiatric history) related to adherence at 6 months.

Avoidant coping was significantly related ( $r = 0.34$ ) to percentage of days when prescribed doses were taken on schedule during the 6-month posttransplant period. Behavioral dysregulation was significantly related ( $r = 0.26$ ) to percentage of prescribed doses taken over the period.

### Relationships Between Baseline and 6-Month Health Outcome Variables

Younger recipients had higher levels of depression and scored higher on 1 test of liver function (aspartate aminotransferase level) at 6 months. Recipients with fewer years of education scored higher on tests of depression and anxiety 6 months after transplantation. Neither MELD score, pretransplant diagnosis, type of transplant, nor number of medical or psychiatric comorbid diseases was significantly related to results of liver function tests, emotional function, or quality of life at 6 months.

Relationships between psychosocial and health outcome variables are illustrated in Table 3. Coping style is significantly related to higher liver enzyme

Table 4 Hierarchical regression analysis: potential predictors of health outcomes

|                          | Bilirubin |                   | Alanine aminotransferase |         | Aspartate aminotransferase |                   | $\gamma$ -Glutamyl transpeptidase |         | Depression |         | Anxiety           |         | Mental quality of life |         |
|--------------------------|-----------|-------------------|--------------------------|---------|----------------------------|-------------------|-----------------------------------|---------|------------|---------|-------------------|---------|------------------------|---------|
|                          | F         | $\beta$           | F                        | $\beta$ | F                          | $\beta$           | F                                 | $\beta$ | F          | $\beta$ | F                 | $\beta$ | F                      | $\beta$ |
| Age                      |           |                   |                          |         |                            | -.072             |                                   |         |            | -.153   |                   |         |                        |         |
| Education                |           |                   |                          |         |                            |                   |                                   |         |            | -.182   |                   | -.081   |                        |         |
| Approach coping          |           |                   |                          |         |                            | .226              |                                   |         |            |         |                   |         |                        |         |
| Avoidant coping          | 7.362     | .250 <sup>a</sup> |                          |         |                            | .292 <sup>a</sup> |                                   |         |            | 6.907   | .220 <sup>b</sup> | 9.220   | .377 <sup>a</sup>      | -.132   |
| Affective dysregulation  |           |                   |                          |         |                            |                   |                                   |         |            | 6.907   | .224 <sup>b</sup> |         | .158                   | 7.445   |
| Behavioral dysregulation |           |                   |                          |         |                            |                   |                                   |         | -.142      |         | .202              |         | .103                   | -.160   |
| Cognitive dysregulation  |           |                   |                          |         |                            |                   |                                   |         |            |         |                   |         |                        | .140    |
| Hostility                |           |                   |                          |         |                            |                   |                                   |         |            | -.252   |                   |         |                        | .015    |
| Community involvement    |           |                   |                          |         |                            |                   |                                   |         |            |         |                   |         |                        |         |
| Family environment       |           |                   |                          |         |                            |                   |                                   |         |            |         |                   |         |                        | -.072   |
| Caregiver relationship   |           |                   | 3.558                    | .206    |                            | .183              | 4.004                             |         |            |         |                   |         |                        |         |

<sup>a</sup>  $P < .001$ <sup>b</sup>  $P < .05$ 

levels, emotional distress, and quality of life; dysregulation is most consistently related to emotional distress and mental quality of life. It is important to note that a lower score on the Cook Medley Scale indicates a higher level of hostility in interpreting those relationships. Caregiver support is significantly related to higher liver enzyme levels but not to emotional distress or quality of life.

#### Predictors of Health Outcomes at 6 Months After Transplant

Significant sociodemographic and psychosocial correlates of health outcomes were entered into hierarchical regression analyses (Table 4). Avoidant coping was a predictor of higher levels of bilirubin, aspartate aminotransferase, depression, and anxiety at 6 months. Affective dysregulation was a predictor of depression and poorer mental quality of life; stronger caregiver support was a predictor of higher  $\gamma$ -glutamyl transpeptidase levels at 6 months.

#### Discussion

This is the first known study to prospectively examine patterns of behavior, decision making, attitudes, social supports, adherence, and health outcomes in a sample of liver transplant recipients with various preoperative diagnoses. Much of the previous research in this population has focused on patients who received a transplant for alcoholic liver disease;

known predictors of relapse to drinking are historical (pretransplant) and not amenable to modification after transplant. The significant correlates and predictors of adherence and health outcomes examined in this study are relatively stable but modifiable with targeted interventions. This evidence is important to clinicians in that patterns of behavior, decision making, attitudes, and social support are amenable to change and can be assessed early in the transplant process.

More than half of the sample ( $n = 85$ ) received a transplant because of alcoholic liver disease and/or hepatitis C; 62 (73%) of those recipients had a history of substance abuse. Alcoholic liver disease develops in a small percentage of patients without meeting the diagnostic criteria for alcohol abuse. Most of those recipients had either a genetic predisposition to developing the disease and/or other underlying liver disease (M. E. dV., unpublished data).

We examined coping as a continuous variable (approach or avoidant) in correlational and regression analyses but found that many of our recipients used both styles with nearly equal frequency in most situations. That evidence deserves further study; a balanced mix of approach and avoidant strategies may be advantageous in stressful situations like the posttransplant experience.

We used multiple measures of adherence to appointment keeping and medication taking but relied on self report for lifestyle changes. Previous work with

liver transplant recipients has shown that interview is the most successful method of identifying posttransplant use of alcohol.<sup>24</sup> The percentage of missed or cancelled appointments and nonadherence to immunosuppressant medications was considerably more prevalent, according to medical records and electronic monitoring, than reported by patients. Measurement of medication taking is a persistent challenge in adherence research; this study is one of the few to use multiple methods to assess medication adherence.<sup>28</sup> Self-reported medication adherence is consistently lower than the level of adherence indicated by electronic monitoring; none of the 15 studies reviewed in a 2004 publication<sup>29</sup> found concordance between interview and electronic monitored adherence to medications. To increase the accuracy of electronic monitoring, electronic data about medication-taking events were supplemented by diaries and medical records. If a patient was hospitalized or indicated a reason for not opening the cap on schedule (eg, pocket dosing, daily pill minders), or opening it more often than necessary (eg, to refill the bottle), a missed or extra event was not entered into the database.

We limit analyses in this report to relationships between baseline factors and adherence or health outcomes because the period soon after transplantation is clinically unstable. Immunosuppressant dose is usually being regulated, so optimal therapeutic level is difficult to determine during the period soon after transplantation (M. E. dV., unpublished data). Although we hypothesize that the links between psychosocial factors and serum levels of liver enzymes will be explained by behavior, we believe it would be misleading to attribute that outcome to patterns of medication adherence during the volatile period soon after transplantation.

Significant differences according to history of substance abuse were apparent in each cluster of variables examined; this finding supports our earlier work with liver transplant candidates.<sup>30</sup> It is important to note, however, that (1) history of abuse was not a predictor of health outcomes, aside from return to smoking and emotional function, in this study and (2) recipients with a history of abuse indicated psychosocial factors (higher levels of avoidant coping and dysregulation, lower social connectedness) that were significantly related to both adherence and outcomes.

### Limitations

The primary limitation of this report is the short period of follow-up; we continue to follow up on adherence and health outcomes in this study and will run further analyses when more long-term data are available. We deem it important to report these findings now because early adherence is a predictor of long-term adherence and health outcomes in other

transplant populations<sup>2</sup> and medication nonadherence in the first 6 months has been reported as an independent risk factor for chronic rejection in liver transplant recipients.<sup>9</sup> Another limitation is the relatively small sample from a statistical perspective that will be addressed as enrollment and monitoring continue. Although our sample closely resembles the liver transplant population at UPMC, there may also be some sample bias related to recruitment difficulties due to poor health in the immediate posttransplant period, as discussed in the preceding manuscript.<sup>16</sup>

### Future Directions

Future directions for research are to continue collecting these data to determine relationships between baseline characteristics and longer term adherence and health outcomes. Results reported here suggest that it may be feasible to develop evidence-based guidelines to help clinicians identify liver transplant recipients at risk of nonadherence and poor outcomes early in the transplant process. Interventions to help such recipients gain insight into how behaviors, attitudes, and social supports affect future health and how those factors can be modified could increase the benefit of transplantation for patients, patients' families, and health care providers.

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**CE Test** Test ID 4000-137: Individual and environmental correlates and predictors of early adherence and outcomes after liver transplantation

**Learning objectives:** 1. Discuss behaviors associated with mortality in liver transplant recipients 2. Describe social characteristics of liver recipients with a history of alcohol abuse 3. Identify factors associated with medication adherence after liver transplantation

1. The usual treatment regimen for liver transplant recipients includes which of the following?

- a. Taking medications
- b. Abstaining from alcohol and recreational drug use
- c. Diet and exercise
- d. a and b

2. What behaviors are directly related to late term mortality among transplant recipients?

- a. Not taking medications
- b. Missing appointments
- c. Smoking and/or alcohol use
- d. All of the above

3. Most of the research with liver transplant patients to date has involved patients transplanted for which disorder?

- a. Hepatitis B
- b. Hepatitis C
- c. Alcoholic liver disease
- d. Cryptogenic cirrhosis

4. Relapse to drug and/or alcohol use following liver transplantation...

- a. ...is infrequent.
- b. ...may affect adherence to other aspects of the treatment regimen.
- c. ...does not affect long-term morbidity and mortality.
- d. ...increases the recipient's risk for infection and rejection.

5. Which of the following was *not* used to assess medication taking in this study?

- a. Self-report (interview questionnaire)
- b. Prescription refills
- c. Electronic medication monitors
- d. Diaries

6. Which of the following environmental or social factors were assessed in this study?

- a. Family support and social network
- b. Hostility
- c. Access to a hospital and pharmacy
- d. a and c

7. Which of the following best describes subjects with a pretransplant history of substance abuse?

- a. Less socially connected
- b. More likely to use an impulsive style of decision making
- c. More likely to resume smoking
- d. All of the above

8. Which of the following factors were most strongly related to medication adherence?

- a. Avoidant coping
- b. Hostility
- c. Caregiver support
- d. Strong social support system

9. Which of the following factors were predictors of health outcomes 6 months after transplantation?

- a. Caregiver support
- b. Hostility
- c. Coping style
- d. All of the above

10. Which of the following best describes why the results of this study are important to transplant clinicians?

- a. Posttransplant adherence affects health outcomes
- b. Factors identified as predictive of health outcomes are stable but amenable to change
- c. Findings can be included as selection criteria
- d. All of the above

Test answers: Mark only one box for your answer to each question. You may photocopy this form.

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