1. INTRODUCTION AND REVIEW OF MEETING OBJECTIVES

MEETING OBJECTIVES

1. To educate key stakeholders regarding the current status of the clinical trial evaluating the safety and effectiveness of solid organ transplantation in people with HIV infection.*

2. To define the key areas for which there is no current consensus and outline all relevant points of view, using an ethical framework when possible.

3. To identify areas where consensus can be reached, and areas where it is acceptable for individual sites to make independent decisions.

4. To draft a paper for submission in a major medical journal entitled: Key Clinical, Ethical and Policy Issues in the Evaluation of the Safety and Effectiveness of Solid Organ Transplantation in People with HIV Infection.

* Identified stakeholders include: Clinical trial site personnel, NIH personnel, Community Advisory Board members, representatives of organizations advocating for populations in need of transplants, Organ Transplant organizations, insurers, ethicists involved in issues of transplantation and/or HIV.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
Reference: Introduction and General background

1. **Braff, J.P. Solid Organ Transplantation and People with HIV – Conference Back grounder

ABSTRACT: Extensive written material concerning the ethics of solid organ transplantation exists, and there is a vast literature on ethics related to HIV and AIDS as well. There is surprisingly little written about the intersection of these two subjects.

A brief discussion of the socio-political history of HIV and AIDS, and a review of the current clinical situation regarding transplantation and people with HIV, are presented. Then, in outlining the generally-accepted ethical principles developed by Beauchamp and Childress employed in clinical decision-making in the United States, an ethics-related framework to address this lacuna at the intersection of transplantation and HIV is provided. The current situation with respect to the system of organ donation, as well as donation policy in the United States, is also discussed.
2. ETHICAL ISSUES IN THE SELECTION OF SUBJECTS
3. ARE SELECTION CRITERIA FAIR?

A. Hepatitis C (Liver, Kidney)

Liver Transplantation

Background

Transplant outcomes in HIV negative individuals with Hepatitis C (HCV) are less successful than those in patients with Hepatitis B (HBV) because re-infection of the graft is less successfully prevented, often resulting in rapid progression to cirrhosis. In addition, HCV infection is accelerated in people with HIV compared to those who are HIV negative. However, a significant proportion of people with HIV and ESLD have HCV. HCV is the leading indication for liver transplant in the over-all population.

Available data on transplant outcomes in co-infected patients are quite variable. For example,

- At the University of Pittsburgh, four of six HIV/HCV co-infected patients are alive with follow-up of greater than 42 months. The 2 deaths were related to pancreatitis (day 1) and rejection (22 months) following a HAART interruption.

- Investigators at Kings College in London have reported more disappointing outcomes, with all four HCV co-infected transplant patients dying. (Four HIV/HBV transplant patients from Kings College are all alive.)

- The first and only HCV infected liver patient transplanted at UCSF under protocol died of recurrent HCV approximately 14.5 months following transplant, although a co-infected patient transplanted in 1993 is still alive and well.

More data are needed on possible risk factors in co-infected transplant patients who survive and those who do not survive.

Question #1

Should we include HCV co-infected liver recipients if we want to adhere to our proof of concept approach of selecting patients for transplant that we are the least likely to harm and are the most likely to have a good outcome?

Note: The full text of citations marked with a double asterisk (***) can be found in the Conference Reader.
Question #2

*Does the high rate of HCV infection in the HIV+ population support inclusion of co-infected patients, particularly since we want study results to be relevant and generalizable to the target patient population?*
Kidney Transplantation

Background

Cirrhosis and survival outcomes of kidney transplants in HIV negative individuals infected with HCV have been variable. Transplant centers have individual policies regarding the eligibility of HCV co-infected patients and HCV treatment prior to transplant.

Currently, only patients with cirrhosis on biopsy are excluded from our study. HCV treatment is recommended based on results of genotype, HCV viral load and biopsy, but is not mandated.

Question #1

*Are these inclusion/exclusion criteria adequate to protect our subjects from progressive liver disease?*

Question #2

*Given the poor efficacy and side effect profile of currently available treatments, should the treatment decision continue to be left to the patient and their primary care provider(s)?*
References: Hepatitis C

General/Background


These recommendations are an expansion of previous recommendations for the prevention of hepatitis C virus (HCV) infection that focused on screening and follow-up of blood, plasma, organ, tissue, and semen donors (CDC. Public Health Service inter-agency guidelines for screening donors of blood, plasma, organs, tissues, and semen for evidence of hepatitis B and hepatitis C. MMWR 1991;40[No. RR-41;1-17). The recommendations in this report provide broader guidelines for a) preventing transmission of HCV; b) identifying, counseling, and testing persons at risk for HCV infection; and c) providing appropriate medical evaluation and management of HCV-infected persons. Based on currently available knowledge, these recommendations were developed by CDC staff members after consultation with experts who met in Atlanta during July 15-17, 1998. This report is intended to serve as a resource for health-care professionals, public health officials, and organizations involved in the development, delivery, and evaluation of prevention and clinical services.

General/HIV


The natural history of hepatitis C virus (HCV) infection in human immunodeficiency virus (HIV)-infected patients has never been studied according to the concept of liver fibrosis progression. The aim of this work was to assess the fibrosis progression rate in HIV-HCV coinfected patients and in patients infected by HCV only. A cohort of 122 HIV-HCV coinfected patients was compared with a control group of 122 HIV-negative HCV-infected patients. Groups were matched according to age, sex, daily alcohol consumption, age at HCV infection, and duration and route of HCV infection. The fibrosis progression rate was defined as the ratio between fibrosis stage (METAVIR scoring system) and the HCV duration. The prevalence of extensive liver fibrosis (METAVIR fibrosis scores 2, 3, and 4) and moderate or severe activity were higher in HIV-infected patients (60% and 54%, respectively) than in control patients (47% and 30%, respectively; P 50 g/d, P =.0002), age at HCV infection (50 g/d), CD4 count (/=200 cells/microL), and age at HCV infection (25 years old) (P .

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0001, respectively) were associated with a higher fibrosis progression rate. HIV seropositivity accelerates HCV-related liver fibrosis progression. In coinfected patients, a low CD4 count, alcohol consumption rate, and age at HCV infection are associated with a higher liver fibrosis progression rate.


BACKGROUND: Hepatitis C virus (HCV) infection is highly prevalent among HIV-1-infected individuals, but its contribution to the morbidity and mortality of coinfected patients who receive potent antiretroviral therapy is controversial. We used data from the ongoing Swiss HIV Cohort Study to analyse clinical progression of HIV-1, and the virological and immunological response to potent antiretroviral therapy in HIV-1-infected patients with or without concurrent HCV infection. METHODS: We analysed prospective data on survival, clinical disease progression, suppression of HIV-1 replication, CD4-cell recovery, and frequency of changes in antiretroviral therapy according to HCV status in 3111 patients starting potent antiretroviral therapy. RESULTS: 1157 patients (37.2%) were coinfected with HCV, 1015 of whom (87.7%) had a history of intravenous drug use. In multivariate Cox's regression, the probability of progression to a new AIDS-defining clinical event or to death was independently associated with HCV seropositivity (hazard ratio 1.7 [95% CI 1.26-2.30]), and with active intravenous drug use (1.38 [1.02-1.88]). Virological response to antiretroviral therapy and the probability of treatment change were not associated with HCV serostatus. In contrast, HCV seropositivity was associated with a smaller CD4-cell recovery (hazard ratio for a CD4-cell count increase of at least 50 cells/microL=0.79 [0.72-0.87]). INTERPRETATION: HCV and active intravenous drug use could be important factors in the morbidity and mortality among HIV-1-infected patients, possibly through impaired CD4-cell recovery in HCV seropositive patients receiving potent antiretroviral therapy. These findings are relevant for decisions about optimum timing for HCV treatment in the setting of HIV infection.


The aims of this study were to analyze the mortality directly attributable to chronic viral hepatitis in HIV-1 infected patients and to investigate the influence of hepatitis virus infections on the survival of this population. A cohort of 328 HIV-1 infected, antiretroviral-treated patients, followed up

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from 1989 to 1996, was investigated in the study. The median follow-up period of the cohort was 120 weeks. The median baseline CD4 + cell count of the cohort was 303 cells/mm³. Hepatitis C virus, hepatitis B virus and hepatitis D virus infections were present in 214 (65%), 16 (4.9%) and 9 (2.7%) patients, respectively. Sixty-seven (20.4%) subjects died but there was no information on the vital status of 36 patients (11%). The causes of mortality were AIDS in 49 (73%), liver failure in 3 (4.5%) and other causes in 15 (22.4%). The cohort was divided into two groups for survival analysis, the groups consisting of persons infected by a hepatitis virus and persons without hepatitis virus infection. There was no difference in survival between the two groups (p = 0.31, log-rank). It is concluded that mortality among HIV-1/hepatitis virus coinfected patients with moderate to severe immunosuppression is mostly due to AIDS, and that the survival of these subjects is not influenced by the presence of hepatitis virus infections, particularly hepatitis C virus.


Hepatitis C virus (HCV) is an RNA virus of the Flaviviridae family and is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Owing to shared routes of transmission, HCV and human immunodeficiency virus (HIV) coinfection are common, affecting approximately one-third of all HIV-infected persons in the United States. In addition, HIV coinfection is associated with higher HCV RNA level and a more rapid progression of HCV-related liver disease, which leads to an increased risk of cirrhosis. HCV infection may also impact the course and management of HIV disease, particularly by increasing the risk of antiretroviral drug-induced hepatotoxicity. Thus, chronic HCV infection acts as an opportunistic disease in HIV-infected persons, because the incidence of infection is increased and the natural history of HCV infection is accelerated in coinfected persons. Strategies to prevent primary HCV infection and to modify the progression of HCV-related liver disease are urgently needed for HIV-HCV-coinfected individuals.


Highly active antiretroviral therapy has decreased human immunodeficiency virus (HIV)-associated mortality; other comorbidities, such as chronic liver disease, are assuming greater importance. We retrospectively examined the causes of death of HIV-seropositive patients at our institution in 1991, 1996, and 1998-1999. In 1998-1999, 11 (50%) of 22 deaths were due to end-stage liver disease, compared with 3 (11.5%)
of 26 in 1991 and 5 (13.9%) of 36 in 1996 (P=.003). In 1998-1999, 55% of patients had nondetectable plasma HIV RNA levels and/or CD4 cell counts of >200 cells/mm(3) within the year before death. Most of the patients that were tested had detectable antibodies to hepatitis C virus (75% of patients who died in 1991, 57.7% who died in 1996, and 93.8% who died in 1998-1999; P=NS). In 1998-1999, 7 patients (31.8%) discontinued antiretroviral therapy because of hepatotoxicity, compared with 0 in 1991 and 2 (5.6%) in 1996. End-stage liver disease is now the leading cause of death in our hospitalized HIV-seropositive population.


OBJECTIVE: To investigate the risk of hepatotoxicity after initiation of protease inhibitor-containing highly active antiretroviral therapy (HAART) for HIV-1 infected patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection. DESIGN: Retrospective study with 394 HIV-1-infected patients initiating HAART at a single university clinic. METHODS: Liver enzyme elevation (LEE) was defined as alanine aminotransferase or aspartate aminotransferase at least five times the upper limit of normal and an absolute increase of > 100 U/l. Relative risks for time to LEE were estimated using Cox proportional hazards models. RESULTS: Of 394 patients 7% were hepatitis B surface antigen (HBsAg)-positive and 14% were anti-HCV-positive. Patients with chronic hepatitis had a higher risk for LEE compared with patients without co-infection: 37% versus 12% respectively. After adjustment for higher baseline transaminases, the presence of HBsAg or anti-HCV remained associated with an increased risk of LEE - relative risk 2.78 (95% confidence interval, 1.50-5.16) and 2.46 (95% confidence interval, 1.43-4.24) respectively. In patients with LEE, transaminases declined whether HAART was continued or modified. Of patients with chronic HBV infection 38% lost HBeAg or developed anti-HBe after initiation of HAART, and one seroconverted from HBsAg-positive to anti-HBs-positive. However, there was no clear relationship with LEE. CONCLUSIONS: HIV-1-infected patients co-infected with HBV or HCV were at considerably higher risk of developing LEE when HAART was initiated compared with patients without co-infection, but it is usually not necessary to modify antiretroviral therapy.


CONTEXT: Use of antiretroviral drugs, including protease inhibitors, for treatment of human immunodeficiency virus (HIV) infection has been

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anecdotally associated with hepatotoxicity, particularly in persons coinfected with hepatitis C or B virus. OBJECTIVES: To ascertain if incidence of severe hepatotoxicity during antiretroviral therapy is similar for all antiretroviral drug combinations, and to define the role of chronic viral hepatitis in its development. DESIGN: Prospective cohort study. SETTING: University-based urban HIV clinic. PATIENTS: A total of 298 patients who were prescribed new antiretroviral therapies between January 1996 and January 1998, 211 (71%) of whom received protease inhibitors as part of combination therapy (median follow-up, 182 days) and 87 (29%) of whom received dual nucleoside analog regimens (median follow-up, 167 days). Chronic hepatitis C and B virus infection was present in 154 (52%) and 8 (2.7%) patients, respectively. MAIN OUTCOME MEASURE: Severe hepatotoxicity, defined as a grade 3 or 4 change in levels of serum alanine aminotransferase and aspartate aminotransferase, evaluated before and during therapy. RESULTS: Severe hepatotoxicity was observed in 31 (10.4%) of 298 patients (95% confidence interval [CI], 7.2%-14.4%). Ritonavir use was associated with a higher incidence of toxicity (30%; 95% CI, 17.9% -44.6%). However, no significant difference was detected in hepatotoxicity incidence in other treatment groups, ie, nucleoside analogs (5.7%; 95% CI, 1.2%-12.9%), nelfinavir (5.9%; 95% CI, 1.2%-16.2%), saquinavir (5.9%; 95% CI, 0.15%-28.7%), and indinavir(6.8%; 95% CI, 3.0%-13.1 %). Although chronic viral hepatitis was associated with an increased risk of severe hepatotoxicity among patients prescribed nonritonavir regimens (relative risk, 3.7; 95% CI, 1.0-11.8), most patients with chronic hepatitis C or B virus infection (88%) did not experience significant toxic effects. Rate of severe toxicity with use of any protease inhibitor in patients with hepatitis C infection was 12.2% (13/107; 95% CI, 6.6%-19.9%). In multivariate logistic regression, only ritonavir (adjusted odds ratio [AOR], 8.6; 95% CI, 3.0-24.6) and a CD4 cell count increase of more than 0.05 x 10(9)/L (AOR, 3.6; 95% CI, 1.0 - 12.9) were associated with severe hepatotoxicity. No irreversible outcomes were seen in patients with severe hepatotoxicity. CONCLUSIONS: Our data indicate that use of ritonavir may increase risk of severe hepatotoxicity. Although hepatotoxicity may be more common in persons with chronic viral hepatitis, these data do not support withholding protease inhibitor therapy from persons coinfected with hepatitis B or C virus.


There has been a steady increase in the number of dialysis patients with human immunodeficiency viral (HIV) infection. HIV-associated nephropathy (HIVAN) is the most common cause of end-stage renal disease in this patient population. Although the major potential category of risk of HIV transmission is from the dialysis patient to staff, there are no data to indicate that this has occurred. Dialysis of patients with HIV...
infection is challenging and requires effective care to prolong survival.


Hepatitis B virus (HBV) resistance to lamivudine has not been extensively documented in human immunodeficiency virus (HIV)-infected patients. We studied the long-term incidence of HBV resistance to lamivudine in HIV-positive patients. Sixty-six HIV-HBV-coinfected patients were studied while receiving lamivudine (150 mg twice daily) as a part of antiretroviral therapy. All these patients had a detectable serum HBV DNA at the beginning of lamivudine therapy. Serum HBV DNA was quantified by molecular hybridization. Sequence analysis of the HBV polymerase was performed in patients who became resistant to lamivudine. After 2 months of lamivudine, HBV DNA became undetectable in 57 patients (86.4%, 95% CI: 75.7%-93.6%). After 2 years of lamivudine, 47% +/- 18.6% of the patients, had sustained HBV-DNA suppression. All the 22 tested patients with HBV resistance developed mutation at position 550 in the YMDD motif of the DNA polymerase. None of the following variables were associated with an increased risk of lamivudine resistance: age, associated protease inhibitor therapy, Center for Disease Control (CDC) stage C, known HIV-infection duration, serum HBV-DNA level at baseline, CD4 cell count and serum alanine transaminase levels at baseline and at HBV-replication suppression (2 months of lamivudine). Lamivudine (300 mg/d) is effective for the inhibition of HBV replication in HIV-infected patients. However, emergence of lamivudine-resistant HBV may occur in 20% of patients per year.


General/Transplant


Hepatitis C virus (HCV)-associated end-stage liver disease is a leading diagnosis in patients undergoing liver transplantation, accounting for approximately 20-25% of transplantations in many centres. In spite of universal viral recurrence, early post-transplantation infection generally results in indolent disease with good graft and patient survival, at least for the first 5-7 years, comparable to those observed in other patients.

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undergoing transplantation for non-viral end-stage liver disease. The full consequences of HCV recurrence are however beginning to be delineated with development of progressive liver failure observed with longer follow-up in a still unknown proportion of patients. Factors which may influence the outcome include viral load at transplantation and the type/amount of immunosuppression. Currently, the only available drugs are interferon and ribavirin, alone and in combination, used either therapeutically when the disease has fully developed, or prophylactically early after transplantation. Unfortunately, interferon has been used with limited success and with concerns about toxicity. Ribavirin monotherapy has been ineffective in producing meaningful results. Preliminary results on combination therapy are promising, both when administered before hepatitis develops or when histologic disease is present. Current antiviral therapy is however unable to eliminate HCV in the liver transplant setting, suggesting that indefinite treatment designed to suppress the effects of virus may be necessary. Major therapeutic advances for HCV infection are awaited.


ABSTRACT: The natural history of clinically compensated hepatitis C virus (HCV) cirrhosis after liver transplantation is unknown. This information is relevant to transplant centers to improve the management of these patients and decide the optimal timing for retransplantation. The aims of the study were (1) to describe the natural history of patients with HCV-cirrhosis transplants in a center with annual liver biopsies, and (2) to determine predictors for clinical decompensation, retransplantation, and mortality rates. A total of 49 patients with HCV-graft cirrhosis, 39 clinically compensated at histologic diagnosis of cirrhosis (post-liver transplantation cirrhosis) were included and followed up for 1 year (15 days-3.5 years). All patients tested were infected with genotype 1b. Predictive variables included histologic activity index (HAI) at post-liver transplantation cirrhosis, liver function tests, age, sex, and maintenance immunosuppression. Eighteen of 39 patients developed at least 1 episode of decompensation after a median of 7.8 months (4 days-2.6 years; 93% ascites). The cumulative probability of decompensation was 8%, 17%, and 42% at 1, 6, and 12 months, respectively. Graft and patient survival rates were 100%, 85%, and 71% and 100%, 92%, and 74% at 1, 6, and 12 months, respectively. Patient survival rates dropped significantly once decompensation developed (93%, 61%, and 41% at 1, 6, and 12 months, respectively). Variables associated with decompensation, retransplantation, and mortality rate included a high Child-Pugh score (>A), low levels of albumin at post-liver transplantation cirrhosis, and a short interval between liver transplantation and post-liver transplantation cirrhosis. The natural history of clinically compensated HCV-graft cirrhosis is shortened.
when compared with immunocompetent patients. If retransplantation is considered, it should be performed promptly once decompensation develops.

**General/Transplant Policy**


Abstract: Whether hepatitis C virus (HCV)-positive candidates or donor organs should undergo transplantation remains controversial. Seventy-two thoracic transplantation centers responded to a survey soliciting specific information about policies regarding the listing of HCV-positive candidates and the use of HCV-positive donor organs. Most centers (64%) list HCV-positive candidates for heart transplantation. Twenty-six percent of centers refuse to use HCV-positive organs, whereas the remainder restrict the use of HCV-positive organs to status 1 recipients or HCV-positive candidates. More information is needed regarding the clinical outcomes of HCV-positive candidates and recipients of HCV-positive organs before clear-cut candidate selection and organ allocation policies can be established.

**Transplantation in People with HIV and HCV**


Introduction: The presence of HIV in a patient with ESLD has been considered a contraindication to transplantation at most centers. Early studies suggested that transplantation and immunosuppression accelerated the demise of these patients. However, objective measurements such as viral load, CD4 counts, and opportunistic infections were not reported. With the advent of effective antiretroviral therapy (HAART), HIV has now become a chronic disease. As a result, more patients present with complications of organ failure. Cirrhosis from HCV is increasingly prevalent in the HIV population. We examined the impact of OLT in patients with HIV. Methods: Six patients underwent OLT between March 1997 to present. We evaluated the impact of OLT on progression of HIV, patient and graft survival, and interactions between immunosuppressive drugs and HAART. Results: Five patients had cirrhosis secondary to HCV, and one had fulminant hepatic failure from protease inhibitors (PI). At time of OLT, total CD4 counts ranged from 108-660/ul, and viral loads ranged from undetectable to 175559 copies/ml. No patient had active opportunistic infections. One patient with advanced
liver disease, respiratory and renal failure died 12 days after OLT from bacterial sepsis unrelated to HIV. A second patient died 20 months after OLT of liver failure secondary to chronic rejection after tacrolimus levels fell on stopping HAART. The remaining 4 patients are alive with a mean follow-up of 17.8 months. OLT corrected the complications of liver failure, and all patients have excellent liver function. Patients were placed on HAART with return of normal liver function. CD4 counts have maintained above 200, and viral loads remain undetectable. Two patients developed recurrent HCV, but responded to therapy with IFN and ribavirin. Two patients developed CMV (1 asymptomatic, 1 pneumonitis) responsive to DHPG. The use of PI was associated with significant drug interactions. Tacrolimus dosing was dramatically reduced to maintain normal levels (1-2 mg/week). Cessation of HAART in one patient led to a fall in tacrolimus levels, resulting in severe rejection that led to liver failure and death. Conclusions: This experience suggests that OLT may be performed safely in selected patients with HIV. Postoperative care requires careful coordination of medical and surgical care, with close attention to maintenance of adequate immunosuppression and HAART. Disclosure: No disclosure information to disclose.


Background: Liver Transplantation in HIV-positive patients is controversial. The presence of HIV was previously considered a contraindication to any form of transplantation. Reported cases are few and mostly refer to patients who tested HIV positive after transplantation or seroconverted in the post-transplant period. Methods: A retrospective case note review of all HIV-positive patients who underwent orthotopic liver transplantation at King’s College Hospital, London, UK between 1995-2000 was performed. 7 patients were identified, all of whom were known to be HIV positive at the time of transplantation. 4 had end-stage liver disease due to hepatitis C, 3 of whom had haemophilia A. 2 patients had acute liver failure, one from hepatitis B and the other non-A-non-B hepatitis, with co-existing hepatitis B infection. One had end-stage chronic liver disease due to hepatitis B. The mean age was 34 years. 6 were CDC stage A and one CDC stage C. Results: All patients survived the immediate post-transplant period, receiving prednisolone and either tacrolimus or cyclosporin as primary immunosuppression. All patients with hepatitis C died of complications of recurrent hepatitis C between 3-25 months post-transplant, despite the introduction of interferon alpha and ribavirin in 2 of the cases. The 3 patients with hepatitis B received lamivudine and hepatitis B immunoglobulin and are alive with good graft function at 33, 13

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and 3 months post-transplant. They are all on antiretroviral therapy with CD4 counts >200/mm3 and HIV viral loads of <400 cp/ml. None of the patients have developed complications related to HIV infection. Conclusions: HIV infection should not be an absolute contraindication for liver transplantation. In the setting of co-infection with viral hepatitis, it is likely to be successful only if there is effective therapy to prevent graft reinfection. Developments in the treatment of viral hepatitis may extend the application of this therapeutic intervention, particularly to patients with end-stage liver disease secondary to hepatitis C.

(HIV Negative) HCV Co-Infected Kidney Recipients: Improved Outcome


Hepatitis C virus (HCV) infection is common in end-stage renal failure patients. It is not known whether the prognosis of HCV-positive patients differs depending on whether they remain on dialysis or receive a kidney transplant. To address this question, we compared the outcomes of HCV-positive renal transplant recipients and HCV-positive patients who were acceptable candidates but had not yet received transplants. We reviewed all patients referred to our institution for renal transplantation evaluation between January 1992 and December 1995. Anti-HCV antibody was detected in 151 of 2,053 (7.4%) patients. HCV-positive patients were more often male (74% v 56%; P < 0.0001), black (68% v 49%; P = 0.001), unemployed (87% v 74%; P = 0.0004), on dialysis (88% v 78%; P = 0.0026), and on dialysis longer (30 +/- 44 months v 13 +/- 23 months; P = 0.0001) than HCV-negative patients. We determined the outcomes of HCV-positive patients who had at least 2 years' follow-up. Thirty-three HCV-positive patients received kidney transplants (group I); 25 HCV-positive patients were acceptable transplant candidates but had not yet received transplants. Group I and II HCV-positive patients were similar with respect to age, race, duration of dialysis, cause of renal failure, prevalence of heart disease, and results of liver function tests. Survival was significantly decreased in group II versus group I (P = 0.043). Our study showed that HCV-positive renal transplant recipients had a better survival than similar HCV-positive patients awaiting transplantation.


The impact of hepatitis B (HBV) and C (HCV) on patient survival after kidney transplantation is controversial. The aims of this study were (1) to
assess the independent prognostic values of HBsAg and anti-HCV in a large renal transplant population, (2) to compare infected patients with noninfected patients matched for factors possibly associated with graft and patient survival, and (3) to assess the prognostic value of biopsy-proven cirrhosis. Eight hundred thirty-four transplanted patients were included: 128 with positive HBsAg (group I), 216 with positive anti-HCV (group II), and 490 without serological markers of HBV and HCV (group III). Fifteen percent and 29% of patients were HBsAg-positive and anti-HCV-positive, respectively. Ten-year survivals of group I (55 +/- 6%) and group II (65 +/- 5%) were significantly lower than survival of group III (80 +/- 3%, P <.001). At 10 years, among overall patients with HCV screening (n = 834), four variables had independent prognostic values in patient survival: age at transplantation (P <.0001), year of transplantation (P =.02), biopsy-proven cirrhosis (P =.03), and presence of HCV antibodies (P =.02). In the case control study, comparison of infected patients with their matched control patients showed that age at transplantation (P <.05), HBsAg (P =.005), and anti-HCV (P =.005) were independent prognostic factors. HCV, biopsy-proven cirrhosis, and age are independent prognostic factors of 10-year survival in patients with kidney grafts. The case-control study showed that anti-HCV and HBsAg were independently associated with patient and graft survivals. In infected patients, a routine liver histological analysis would improve selection of patients for renal transplantation.


Hepatitis C virus (HCV) infection is common among patients with end-stage renal disease (ESRD). However, the effect of HCV infection on survival among ESRD patients, and the impact of renal transplantation on the course of HCV infection has not been adequately defined. Sera from patients on the renal transplant waiting list at the New England Organ Bank between November 1986 and June 1990 were tested for anti-HCV using a third generation ELISA. All anti-HCV positive patients and a 1:1 ratio of randomly selected anti-HCV negative patients comprised the study sample. Duration of follow-up was calculated from the date of the first available serum specimen until death, loss to follow-up or December 31, 1995, whichever occurred earlier. Multivariate analysis of risk factors for mortality was performed using a Cox proportional hazards model which included anti-HCV as a time-independent (baseline) variable, transplantation as a time-dependent (follow-up) variable, and

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independently significant baseline covariates. Anti-HCV was detected in 287 (19%) of 1544 patients in whom sera were available, and 286 anti-HCV negative patients served as controls. Complete information was available in 496 (87%) of these 573 patients. Median follow-up was 73 months (range 1 to 110 months), during which time 302 (61%) patients underwent renal transplantation and 154 (31%) patients died. For anti-HCV positive patients compared to anti-HCV negative patients, the relative risk of death (and 95% confidence intervals) from all causes was 1.41 (1.01 to 1.97) and due to liver disease or infection was 2.39 (1.28 to 4.48). For patients who underwent transplantation compared to those who remained on dialysis, the relative risk of death from all causes between 0 to 3 months, 3 to 6 months, seven months to four years, and after four years was 4.75 (2.76 to 8.17), 1.76 (0.75 to 4.13), 0.31 (0.18 to 0.54) and 0.84 (0.51 to 1.37), respectively. There was no interaction between the effect of anti-HCV status as baseline and subsequent transplantation (P = 0.93), meaning that the association between treatment modality and survival was similar among anti-HCV positive and negative patients, at all intervals after transplantation. We conclude that HCV infection at the time of referral for transplantation is associated with an increased risk of death, irrespective of whether patients remain on dialysis or undergo transplantation. Transplantation has a beneficial rather than adverse effect on long-term survival in anti-HCV positive patients. Hence, anti-HCV positive status alone is not a contraindication for renal transplantation.


BACKGROUND AND METHODS: The extent to which renal allotransplantation - as compared with long-term dialysis - improves survival among patients with end-stage renal disease is controversial, because those selected for transplantation may have a lower base-line risk of death. In an attempt to distinguish the effects of patient selection from those of transplantation itself, we conducted a longitudinal study of mortality in 228,552 patients who were receiving long-term dialysis for end-stage renal disease. Of these patients, 46,164 were placed on a waiting list for transplantation, 23,275 of whom received a first cadaveric transplant between 1991 and 1997. The relative risk of death and survival were assessed with time-dependent nonproportional-hazards analysis, with adjustment for age, race, sex, cause of end-stage renal disease, geographic region, time from first treatment for end-stage renal disease to placement on the waiting list, and year of initial placement on the list. RESULTS: Among the various subgroups, the standardized mortality ratio for the patients on dialysis who were awaiting transplantation (annual death rate, 6.3 per 100 patient-years) was 38 to 58 percent lower than that.
for all patients on dialysis (annual death rate, 16.1 per 100 patient-years). The relative risk of death during the first 2 weeks after transplantation was 2.8 times as high as that for patients on dialysis who had equal lengths of follow-up since placement on the waiting list, but at 18 months the risk was much lower (relative risk, 0.32; 95 percent confidence interval, 0.30 to 0.35; P<0.001). The likelihood of survival became equal in the two groups within 5 to 673 days after transplantation in all the subgroups of patients we examined. The long-term mortality rate was 48 to 82 percent lower among transplant recipients (annual death rate, 3.8 per 100 patient-years) than patients on the waiting list, with relatively larger benefits among patients who were 20 to 39 years old, white patients, and younger patients with diabetes. CONCLUSIONS: Among patients with end-stage renal disease, healthier patients are placed on the waiting list for transplantation, and long-term survival is better among those on the waiting list who eventually undergo transplantation.

(HIV Negative) HCV Co-Infected Kidney Recipients: Poor Outcome


BACKGROUND: The majority of chronic hepatitis is ascribable to hepatitis C virus (HCV) infection, whereas the clinical impact has not been understood in kidney transplant recipients. Our current study was carried out to assess the impact of HCV infection on kidney recipients over the long-term, and to investigate the effect and risk of interferon-alpha (IFN-alpha) therapy for chronic active hepatitis C. METHODS: Hepatitis B surface antigen (HBsAg) and antibody to HCV (HCVAb) were examined prospectively and retrospectively in 280 patients, who underwent kidney transplants in the period from 1973 to 1996. The patient survival rate, the graft survival rate, the incidence of liver dysfunction and the cause of mortality among the HCV infected and noninfected groups were analyzed. IFN-alpha therapy was performed on 10 patients with chronic active hepatitis C. RESULTS: Prevalence of the hepatitis virus was quite high at 34.3% (96/280): the frequency of the HBsAg carrier was 3.2% (9/280), that of the HCVAb carrier was 28.6% (80/280) and that of the both carriers was 2.5% (7/280). The other 184 cases (65.7%) were negative for both HBsAg and HCVAb. Liver dysfunction developed at the significantly higher incidence of 55% in HCVAb carriers compared to the 9.2% of the noninfected group (P<0.01). HCVAb carriers had a poor survival rate in the second decade compared to the noninfected group: 83.7% vs. 88.91% for 10-year survival (P=0.44) and 63.9% vs. 87.9% for 20-year survival (P<0.05). The poor survival rate was a result of the mortality from liver disorder. Five patients died of such disease in the infected groups whereas no noninfected patient died in the same period (p<0.01). As the

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
result of IFN-alpha therapy, biochemical activity normalized or improved in eight cases, whereas the HCV-RNA titer was reduced only in three patients. Only one patient maintained normal biochemical markers and undetectable levels of HCV-RNA for 2 years after treatment. The therapy was discontinued for five patients with the adverse effects of acute rejection, deterioration of diabetes, and depression. CONCLUSIONS: HCV infection has a significant impact on kidney transplant recipients over the long term and in particular affects them in the second decade. Our pilot study revealed only partial efficacy of IFN-alpha therapy for HCV-infected recipients, but with the high risk of acute rejection.


Controversy exists regarding the impact of pretransplantation HCV infection on the outcome of renal transplantation. We compared the prevalence of posttransplantation liver disease and graft and patient survival among kidney transplant recipients with and without anti-HCV at the time of transplantation. Pretransplantation sera from 103 randomly selected recipients of kidneys from anti-HCV-negative donors were tested for anti-HCV using a second generation ELISA. Twenty-three (22%) were positive for anti-HCV and 80 (78%) were negative. Anti-HCV-positive recipients had a longer time on dialysis (P = 0.003) and had a higher number of previous transplants (P = 0.01). Further, 61% of anti-HCV-positive patients had a history of liver disease compared with 13% of anti-HCV-negative patients (P < 0.001). HCV RNA was detected in the pretransplantation serum in 61% of anti-HCV positive recipients compared with 5% of anti-HCV-negative recipients (P < 0.001). Clinical follow-up on both anti-HCV-positive and -negative patients was obtained until December, 1993. Median posttransplantation follow-up among recipients with anti-HCV prior to transplantation (45 months) was shorter (P = 0.05) than that for recipients without anti-HCV (66 months). For recipients with anti-HCV prior to transplantation, the relative risk of posttransplantation liver disease was 5.0 (95% confidence intervals of 2.4 to 10.5); the relative risk of graft loss was 1.3 (95% confidence intervals of 0.6 to 2.6); the relative risk of death was 3.3 (95% confidence intervals of 1.4 to 7.9), and the relative risk of death due to sepsis was 9.9 (95% confidence intervals of 2.6 to 38.3). The results of this study demonstrate that pretransplantation HCV infection is associated with an increased risk of liver disease and death after renal transplantation. These results raise the question of whether anti-HCV-positive patients on dialysis should be offered renal transplantation as opposed to continuing dialysis.


Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
BACKGROUND: The long-term impact of hepatitis C virus (HCV) infection in renal transplant recipients remains controversial. We report here our experience, in a homogeneous single center, of 499 patients with a fairly long follow-up. METHODS: We retrospectively studied 499 hepatitis B virus-negative patients who received an initial cadaver donor kidney transplantation at Necker Hospital between January 1, 1979 and December 31, 1994, with a graft or patient survival of at least 6 months. Anti-HCV antibodies were detected at time of transplantation in 112 patients (22%). Patient survival and causes of death were compared among anti-HCV-positive and -negative patients.

RESULTS: Our results clearly indicate that first cadaver kidney transplant recipients with anti-HCV antibodies had a significantly shorter patient and graft long-term survival than recipients without anti-HCV antibodies (P<0.01 and P<0.0001 respectively). Mean follow-up time after transplantation was 79+/−2 months in the former group and 81+/−5 months in the latter (NS). Increased mortality was primarily caused by liver disease (P<0.001) and sepsis (P<0.01). In a multivariate analysis, HCV infection significantly affected the mortality rate (odds ratio: 2.8).

CONCLUSIONS: These results suggest that HCV infection has a harmful long-term impact on the survival of kidney transplant recipients.


BACKGROUND: The impact of infection with hepatotropic viruses (hepatitis B virus [HBV] and hepatitis C virus [HCV]) on morbidity and mortality, and allograft function in renal transplant recipients with allografts functioning for >20 years is not known. METHODS AND RESULTS: Seventy-nine of 511 renal transplants performed at the Cleveland Clinic Foundation from January 1963 to January 1978 are known to have functioned for at least 20 years (level 5A). Fifty-four of these patients had hepatitis testing updated after their 19th year of transplantation. Fifteen patients had evidence of ongoing viral infection: persistent hepatitis B surface antigen in three (6%), HCV antibody (enzyme-linked immunosorbent assay II supplemented by recombinant immunoblot assay) in 11 (20%), and both viruses in one (2%). Of the 10 surviving patients, 8 were tested further for viral replication. HCV RNA (polymerase chain reaction; Amplicore) was positive in 6/7 (86%), and HBV DNA (hybridization) was positive in 1/2 (50%). An elevated alanine aminotransferase (>35 U/L) was present in all hepatitis patients, alphafetoprotein >10 ng/ml in 2/8 (25%), and cryoglobulins >50 microg/ml in 3/6 (50%) infected with HCV. No hepatocellular carcinoma was detected by hepatic ultrasound. In patients with chronic viral hepatitis, probable...
cirrhosis developed in 20% (3/15) compared to one patient in the group without hepatitis, but there was no mortality from liver failure in either group. Diabetes mellitus was significantly more common in those with than without hepatitis (11/15 vs. 10/39; P=0.002), but severe infection was not (9/15 vs. 15/39). Five hepatitis patients (33%) have died of non-hepatic causes (one from meningitis, one from unknown cause, and three from coronary heart disease [CHD] vs. only two individuals without hepatitis [5%]; P= 0.014). Although the more frequent occurrence of CHD among those with hepatitis was not significant (7/15 vs. 8/39; P=0.09), CHD as a cause of death in those with HCV was significantly increased (P=0.03).

CONCLUSIONS: Twenty-year renal transplant recipients infected with hepatotropic viruses (HBV and HCV) have a high rate of active viral replication (88%), a greater frequency of diabetes (P=0.01), and a higher overall mortality (P=0.014).
B. Viral Load Criteria for Liver Transplant Subjects

Background

In a January 2001 conference call of study investigators, a decision was made to enable flexibility for sites to determine whether to accept liver transplant candidates with detectable HIV viral load (VL). Investigators decided to offer two sets of inclusion criteria from which each site could choose: 1) patients with detectable VL off treatment due to hepatotoxicity of antiretrovirals if the HIV specialist felt HIV VL could be suppressed post transplant with treatment, or 2) undetectable VL but exceptions would be considered. There have been physician and community requests to reconsider these restrictions in cases where full HIV suppression is expected post-transplant.

Question #1

Do these inclusion criteria need to be re-addressed?

Question #2

How does the relative risk of transmission of HIV and the Hepatitis viruses to the surgical staff influence this decision? Does being a research study rather than a standard of care procedure influence this decision?

Question #3

A tenet underlying this research study has to select patients we believe are most likely to do well clinically in order to prove the principle that transplantation in the HIV positive population is safe. Would enrolling patients with VL that is deemed suppressible by the HIV physician be consistent with this approach? Or is it too great a risk to accept for the over-all good of the study?

Question #4

The study results should be relevant to the HIV positive population needing organ transplants. Does this value argue for inclusion of patients with suppressible VL? It is difficult (and at times dangerous) to maintain HIV therapy when patient has decompensating end stage liver disease. How should this risk affect our thinking about VL and inclusion criteria?

Question #5

Is there a point at which we would decide to liberalize these criteria?

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
References: Viral Load Criteria for Liver Transplant Subjects

Transmission Risk


BACKGROUND: The average risk of human immunodeficiency virus (HIV) infection after percutaneous exposure to HIV-infected blood is 0.3 percent, but the factors that influence this risk are not well understood. METHODS: We conducted a case-control study of health care workers with occupational, percutaneous exposure to HIV-infected blood. The case patients were those who became seropositive after exposure to HIV, as reported by national surveillance systems in France, Italy, the United Kingdom, and the United States. The controls were health care workers in a prospective surveillance project who were exposed to HIV but did not seroconvert. RESULTS: Logistic-regression analysis based on 33 case patients and 665 controls showed that significant risk factors for seroconversion were deep injury (odds ratio= 15; 95 percent confidence interval, 6.0 to 41), injury with a device that was visibly contaminated with the source patient's blood (odds ratio= 6.2; 95 percent confidence interval, 2.2 to 21), a procedure involving a needle placed in the source patient's artery or vein (odds ratio=4.3; 95 percent confidence interval, 1.7 to 12), and exposure to a source patient who died of the acquired immunodeficiency syndrome within two months afterward (odds ratio=5.6; 95 percent confidence interval, 2.0 to 16). The case patients were significantly less likely than the controls to have taken zidovudine after the exposure (odds ratio=0.19; 95 percent confidence interval, 0.06 to 0.52). CONCLUSIONS: The risk of HIV infection after percutaneous exposure increases with a larger volume of blood and, probably, a higher titer of HIV in the source patient's blood. Postexposure prophylaxis with zidovudine appears to be protective.

Viral Load and Patient Outcome


Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
OBJECTIVES: It is predicted that HIV-infected individuals in early HIV disease are the most likely group to achieve immune reconstitution following highly active antiretroviral treatment. We assessed whether suppression of HIV replication in this group would improve immune function. METHODS: Seventeen antiretroviral-naïve patients in early HIV disease were evaluated for immune function and lymphocyte phenotyping using standard immunological assays. RESULTS: Absolute CD4+ T-cell number increased from a median of 550 to 800 x 10(6) cells/l while CD8+ T-cell numbers were reduced. The decrease in CD8+ cells correlated with a decrease in the CD8+ memory phenotype. Kinetics of CD4+ naïve and memory T-cell rise indicated that 80% of the maximum CD4+ naïve increase was achieved within 18 weeks whereas maximum CD4+ memory T-cell rise was achieved within 36 weeks. Activation markers (HLA-DR, CD38) and an apoptosis-related marker (CD95) were reduced on CD4+ and CD8+ T cells. Lymphocyte proliferation responses to tetanus toxoid, alloantigen, and anti-CD3/CD28 were restored in patients that were initially unresponsive. At baseline, 31% of the patients responded to HIV p24, which increased to 69% post-therapy. The inducible RANTES response was normalized following therapy whereas inducible interferon-gamma, interleukin (IL)-12, and MIP1beta were elevated. The depressed inducible IL-10 response, however, was not altered after therapy. CONCLUSIONS: This is one of the first studies to demonstrate the restoration of HIV-1 specific responses in non-acute HIV infection, suggesting early intervention with potent antiretroviral therapy may reverse immune-mediated damage not seen with treated patients who have more advanced disease.


BACKGROUND: In many patients with human immunodeficiency virus (HIV) infection, therapy with potent antiretroviral drugs does not result in complete suppression of HIV replication. The effect of cessation of therapy in these patients is unknown. METHODS: Sixteen patients who had a plasma HIV RNA level of more than 2500 copies per milliliter during combination antiretroviral-drug therapy were randomly assigned, in a 2:1 ratio, to discontinue or continue therapy. Plasma HIV RNA levels, CD4 cell counts, and drug susceptibility were measured weekly. Viral replicative capacity was measured at base line and at week 12. RESULTS: Discontinuation of therapy for 12 weeks was associated with a median decrease in the CD4 cell count of 128 cells per cubic millimeter and an increase in the plasma HIV RNA level of 0.84 log copies per milliliter. Virus from all patients with detectable resistance at entry became susceptible to
HIV-protease inhibitors within 16 weeks after the discontinuation of therapy. Drug susceptibility began to increase a median of six weeks after the discontinuation of therapy and was temporally associated with increases in plasma HIV RNA levels and decreases in CD4 cell counts. Viral replicative capacity, measured by means of a recombinant-virus assay, was low at entry into the study and increased after therapy was discontinued. Despite the loss of detectable resistance in plasma, resistant virus was cultured from peripheral-blood mononuclear cells in five of nine patients who could be evaluated. Plasma HIV RNA levels, CD4 cell counts, and drug susceptibility remained stable in the patients who continued therapy. CONCLUSIONS: Despite the presence of reduced drug susceptibility, antiretroviral-drug therapy can provide immunologic and virologic benefit. This benefit reflects continued antiviral-drug activity and the maintenance of a viral population with a reduced replicative capacity.


Many HIV-infected patients treated with protease inhibitors (PI) develop PI-resistant HIV-1 variants and rebounds in viremia, but their CD4 T-cell counts often do not fall. We hypothesized that in these patients, T-cell counts remain elevated because PI-resistant virus spares intrathymic T-cell production. To test this, we studied recombinant HIV-1 clones containing wild-type or PI-resistant protease domains, as well as uncloned isolates from patients, in activated peripheral blood mononuclear cells. However, the replication of PI-resistant but not wild-type HIV-1 isolates was highly impaired in thymocytes. In addition, patients who had PI-resistant HIV-1 had abundant thymus tissue as assessed by computed tomography. We propose that the inability of PI-resistant HIV-1 to replicate efficiently in thymus contributes to the preservation of CD4 T-cell counts in patients showing virologic rebound on PI therapy.


See articles 6 and 7 in General/HIV section above (authors: den Brinker and Sulkowski)


Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
6. *For more information on resistance and antiretroviral use, see www.HIVResistanceWeb.com*
C. People with Clotting Disorders

Background

A large proportion of HIV positive transplant patients also have hemophilia. Individuals with hemophilia are a very high risk of having HCV-HIV co-infection.

A recent survey of Hemophilia Treatment Centers found that over 40% of HCV infected adults also have HIV infection (Ewenstein, Survey, MASAC,NHF 1998). Historically, individuals with hemophilia are excluded from clinical trials (e.g. AIDS and hepatitis treatment trials) because of 1) bleeding risks and 2) management of co-morbidities, including hepatitis and potential for early and severe hepatotoxicity. However, when adequate factor replacement is given, the risk of bleeding with liver biopsy is no different from non-hemophilic subjects. Further, liver transplantation cures hemophilia. (It is important to note that there are some reports of bleeding in individuals with hemophilia treated with protease inhibitors, making it difficult to decisively determine the cause of bleeding in these individuals.)

Question #1

Should all sites be required to offer the study protocol to people with clotting disorders, or should this be a site-specific option?

If not, what is the fall back plan for each institution where the decision is not to include these patients, to assure they are not unfairly discriminated against.

Question #2

Should the protocol require sites to have a hematologist (with expertise in hemophilia and bleeding disorders) available to participate in the management of all patients?

Question #3

What is the acceptable minimum clinical requirement for management of individuals with bleeding disorders; and, if these minimum requirements are not available, what alternatives exist?

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
References: People with Clotting Disorders


Four patients with hemophilia A have undergone liver transplantation in our institution, three successfully. The first was a 21-year-old man with chronic active hepatitis (CAH) in whom the effects of previous abdominal operations prevented the satisfactory technical insertion of the new liver. He died intraoperatively. The second patient was a 15-year-old boy with CAH who began to synthesize factor VIII coagulant activity (F VIII:C) within 18 hours of successful liver transplantation and has continued to do so for almost 2 years (F VIII:C range 0.89 to 3.20 U/mL). The first 2 months of his postoperative course were complicated by infections, but since that time he has done well and has returned to school. The third patient was a 48-year-old man with portal fibrosis and severe ascites. He synthesized F VIII:C (range 0.96 to 1.50 U/mL) within six hours after reestablishment of circulation through the new liver. His postoperative course was complicated by numerous infections, and he died with sepsis and an acquired immunodeficiency-like syndrome 4 months after transplantation. The fourth patient was a 47-year-old mild hemophiliac with CAH who produced adequate factor VIII:C levels following transplantation (range 0.79 to 2.80 U/mL). These patients demonstrate that liver transplantation in hemophiliacs with end-stage liver disease may be lifesaving and results in correction of the F VIII:C deficiency and associated hemorrhagic tendency.


Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.

To evaluate the safety and efficacy of didanosine (ddl) monotherapy and three different combinations of zidovudine (ZDV) and ddl in asymptomatic human immunodeficiency virus-1 (HIV-1) infection, we conducted an open-label, phase I/II study in 126 asymptomatic HIV-1-infected hemophilic and nonhemophilic subjects with a CD4 count of 200 to 500/mm3 stratified for prior zidovudine treatment and baseline CD4 count. Study arms included arm A, low-dose combination (ZDV 150 mg and ddl 134 mg, daily); arm B, moderate-dose combination (ZDV 300 mg and ddl 334 mg, daily); arm C, high-dose combination (ZDV 600 mg and ddl 500 mg, daily), and arm D, ddl monotherapy (ddl 500 mg, daily). Earlier, more frequent hepatotoxicity was experienced by hemophilic subjects (P = .008), but there were no differences in toxicity between treatment arms (P = .51), nor were there any differences in the rate of development of clinical endpoints by treatment (P = .41). Smaller median CD4 increases occurred over the first 12 weeks for arms A and D, 44/mm3 and 42/mm3, than arms B and C, 105/mm3 and 114/mm3, respectively, (P = .015). Hemophilia status (P = .0004) and prior ZDV experience (P = .044) independently predicted weaker CD4 responses during the first 12 weeks of treatment. Using a regression model and adjusting for hemophilia status, prior ZDV treatment, and baseline CD4, there was a significant reduction in quantitative viral load from baseline by week 12 for all treatment arms combined (P = .0001), with significantly lower median percent reduction for arm A (56.3%) than arms B, C, and D (94.6%, 98.5%, and 91.9%, respectively, P = .015). Although greater hepatotoxicity and weaker CD4 responses occur in hemophilic subjects, didanosine monotherapy and combination therapy with zidovudine are safe and effective in asymptomatic HIV-1-infected patients.


Assessment of chronic hepatitis C virus infection requires a liver biopsy in most circumstances. There is a reluctance to perform liver biopsy in haemophiliacs because of a perceived risk of haemorrhage, although with adequate factor concentrate replacement in patients without factor concentrate inhibitors it should be safe. We report a 4-year experience of liver biopsy in patients with haemophilia infected with chronic hepatitis C virus. Of 55 patients seropositive for anti-HCV, 35 have undergone liver biopsy; the median age of this group was 33 years (range 13-68). Seven patients had a normal liver. 22 had portal tract inflammation, four with

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lymphoid aggregates. Mild piece-meal necrosis was observed in only two and no bile duct injury was found. 11 patients had mild mixed micro- and macro-vesicular fat. 19 patients had no evidence of fibrosis despite an estimated median duration of disease of 20 years (range 8-43). In the remaining 16 patients the maximum degree of fibrosis achieved was stage III. Patients with more significant fibrosis could not be identified on the basis of ALT or HCV RNA. There were no complications of liver biopsy in this series. Liver biopsy following a well-defined protocol in chronic hepatitis C virus haemophiliac carriers is safe in the absence of factor concentrate inhibitors. In this young group of patients without HIV infection there was no evidence of significant liver disease despite a considerable duration of disease. Performing liver biopsy allows accurate information to be given to the patient and avoids unnecessary therapy. The relative youth of this group may be important in the light of the benign histology.

D. History of Opportunistic Complications

Background

Adhering to the proof of concept approach of selecting patients for transplant who we are the least likely to ham with immunosuppression (ie those most likely to do well), we have decided to exclude patients with a history of opportunistic complications, either infections or neoplasms (OI/ONs), during the first phase of this program. However, because increasing data sets suggest that protective immune reconstitution does occur in the context of HAART, we have decided to reevaluate this decision after the first 20 participants are followed for six months. This group will include all those individuals who are eligible for and agree to retrospective enrollment in the current Transitional Phase of the Multi-Site Study (12 anticipated kidney and 7 anticipated liver recipients). If one or fewer opportunistic complications occurs in this group, we would open the inclusion criteria to people who have not had an active OI/ON for a defined number of years.

Question #1

Are we still comfortable with this plan for reevaluating the inclusion criteria?

Question #2

Is there new research that should inform our thinking about OIs and eligibility?
References: History of Opportunistic Complications


BACKGROUND: Patients infected with HIV who experience increases in CD4(+) cell counts are at reduced risk for opportunistic infections. However, the safety of discontinuing prophylaxis against Mycobacterium avium complex has been uncertain. OBJECTIVE: To compare the rate of M. avium complex infection in patients with increased CD4(+) cell counts who receive azithromycin and those receiving placebo. DESIGN: Randomized, double-blind, placebo-controlled trial. SETTING: 29 university-based clinical centers in the United States. PARTICIPANTS: 643 HIV-1-infected patients with a previous CD4(+) cell count less than 0.05 x 10(9) cells/L and a sustained increase to greater than 0.10 x 10(9) cells/L during antiretroviral therapy. INTERVENTION: Azithromycin, 1200 mg once weekly (n = 321), or matching placebo (n = 322). MEASUREMENTS: Mycobacterium avium complex cultures, CD4(+) cell counts, and clinical evaluations for AIDS-defining illnesses and bacterial infections were done every 8 weeks. Plasma HIV-1 RNA levels were measured at 16-week intervals. RESULTS: During follow-up (median, 16 months), 2 cases of M. avium complex infection were reported among the 321 patients assigned to placebo (incidence rate, 0.5 event per 100 person-years [95% CI, 0.06 to 1.83 events per 100 person-years]) compared with no cases among the 322 patients assigned to azithromycin (CI, 0 to 0.92 events per 100 person-years), resulting in a treatment difference of 0.5 event per 100 person-years (CI, -0.20 to 1.21 events per 100 person-years) for placebo versus azithromycin. Both cases were atypical in that M. avium complex was localized to the vertebral spine. Patients receiving azithromycin were more likely than those receiving placebo to discontinue treatment with the study drug permanently because of adverse events (8% vs. 2%; hazard ratio, 0.24 [CI, 0.10 to 0.57]). CONCLUSIONS: Prophylaxis against Mycobacterium avium complex can safely be withdrawn or withheld in adults with HIV infection who

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
experience increases in CD4(+) cell count while receiving antiretroviral therapy.


BACKGROUND: Several agents are effective in preventing Mycobacterium avium complex disease in patients with advanced human immunodeficiency virus (HIV) infection. However, there is uncertainty about whether prophylaxis should be continued in patients whose CD4+ cell counts have increased substantially with antiviral therapy. METHODS: We conducted a multicenter, double-blind, randomized trial of treatment with azithromycin (1200 mg weekly) as compared with placebo in HIV-infected patients whose CD4+ cell counts had increased from less than 50 to more than 100 per cubic millimeter in response to antiretroviral therapy. The primary end point was M. avium complex disease or bacterial pneumonia. RESULTS: A total of 520 patients entered the study; the median CD4+ cell count at entry was 230 per cubic millimeter. In 48 percent of the patients, the HIV RNA value was below the level of quantification. The median prior nadir CD4+ cell count was 23 per cubic millimeter, and 65 percent of the patients had had an acquired immunodeficiency syndrome-defining illness. During follow-up over a median period of 12 months, there were no episodes of confirmed M. avium complex disease in either group (95 percent confidence interval for the rate of disease in each group, 0 to 1.5 episodes per 100 person-years). Three patients in the azithromycin group (1.2 percent) and five in the placebo group (1.9 percent) had bacterial pneumonia (relative risk in the azithromycin group, 0.60; 95 percent confidence interval, 0.14 to 2.50; P=0.48). Neither the rate of progression of HIV disease nor the mortality rate differed significantly between the two groups. Adverse effects led to discontinuation of the study drug in 19 patients assigned to receive azithromycin (7.4 percent) and in 3 assigned to receive placebo (1.1 percent; relative risk, 6.6; P=0.002). CONCLUSIONS: Azithromycin prophylaxis can safely be withheld in HIV-infected patients whose CD4+ cell counts have increased to more than 100 cells per cubic millimeter in response to antiretroviral therapy.


BACKGROUND: It is unclear whether primary prophylaxis against Pneumocystis carinii pneumonia can be discontinued in patients infected with the human immunodeficiency virus (HIV) who are successfully treated with combination antiretroviral therapy. We prospectively studied the safety of stopping prophylaxis among patients in the Swiss HIV Cohort Study. METHODS: Patients were eligible for our study if their CD4 counts had increased to at least 200 cells per cubic millimeter and 14 percent of total lymphocytes while they were receiving combination antiretroviral therapy, with these levels sustained for at least 12 weeks. Prophylaxis was stopped at study entry, and patients were examined every three months thereafter. The development of P. carinii pneumonia was the primary end point, and the development of toxoplasmic encephalitis the secondary end point. RESULTS: Of the 262 patients included in our analysis, 121 (46.2 percent) were positive for IgG antibodies to Toxoplasma gondii at base line. The median CD4 count at study entry was 325 per cubic millimeter (range, 210 to 806); the median nadir CD4 count was 110 per cubic millimeter (range, 0 to 240). During a median follow-up of 11.3 months (range, 3.0 to 18.8), prophylaxis was resumed in nine patients, and two patients died. There were no cases of P. carinii pneumonia or toxoplasmic encephalitis. The one-sided upper 99 percent confidence limit for the incidence of P. carinii pneumonia was 1.9 cases per 100 patient-years (based on 238 patient-years of follow-up). The corresponding figure for toxoplasmic encephalitis was 4.2 per 100 patient-years (based on 110 patient-years of follow-up). CONCLUSIONS: Stopping primary prophylaxis against P. carinii pneumonia appears to be safe in HIV-infected patients who are receiving combination antiretroviral treatment and who have had a sustained increase in their CD4 counts to at least 200 cells per cubic millimeter and to at least 14 percent of total lymphocytes.


BACKGROUND: The incidence of nearly all AIDS-defining opportunistic infections (OIs) decreased significantly in the United States during 1992-1998; decreases in the most common OIs Pneumocystis carinii pneumonia (PCP), esophageal candidiasis, and disseminated Mycobacterium avium complex (MAC disease) were more pronounced in 1996-1998, during which time highly active antiretroviral therapy (HAART) was introduced into medical care. Those OIs that continue to occur do so at

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
low CD4+ T lymphocyte counts, and persons whose CD4+ counts have increased in response to HAART are at low risk for OIs, a circumstance that suggests a high degree of immune reconstitution associated with HAART. PCP, the most common serious OI, continues to occur primarily in persons not previously receiving medical care. The most profound effect on survival of patients with AIDS is conferred by HAART, but specific OI prevention measures (prophylaxis against PCP and MAC and vaccination against Streptococcus pneumoniae) are associated with a survival benefit, even when they coincide with the administration of HAART. Continued monitoring of incidence trends and detection of new syndromes associated with HAART are important priorities in the HAART era.


CONTEXT: Acquired immunodeficiency syndrome-related opportunistic illnesses (OIs) continue to occur after initiation of potent antiretroviral therapy in patients with human immunodeficiency virus (HIV) infection. Risk factors for clinical progression to OIs during potent therapy are not well defined. OBJECTIVE: To examine the incidence of and risk factors for OIs among patients treated with potent antiretroviral therapy in a population-based study. DESIGN: The Swiss HIV Cohort Study, a prospective cohort study of adult HIV-infected persons. SETTING: Seven study centers throughout Switzerland. PATIENTS: A total of 2410 cohort study participants with a potential follow-up of at least 15 months after starting potent therapy between September 1995 and December 1997. MAIN OUTCOME MEASURES: Disease-specific incidence of OIs during the 6 months preceding potent antiretroviral therapy and at 3 intervals after initiating therapy; risk factors for development of OIs during therapy. RESULTS: Of the 2410 participants, 143 developed 186 OIs after initiation of potent antiretroviral therapy. Incidence of any OI decreased from 15.1 per 100 person-years in the 6 months before therapy to 7.7 in the first 3 months after starting treatment, 2.6 in the following 6 months, and 2.2 per 100 person-years between 9 and 15 months. Reductions in incidence ranged from 38% per month for Kaposi sarcoma (P<.001) to 5% per month for non-Hodgkin lymphoma (P = .31). Baseline CD4 cell count continued to predict the risk of disease progression after initiating potent therapy. Compared with CD4 cell counts above 200 x 10(6)/L, the hazard ratio for developing OIs was 2.5 (95% confidence interval [CI], 1.4-4.5) for counts between 51 and 200 x 10(6)/L and 5.8 (95% CI, 3.2-10.5) for counts below 51 x 10(6)/L at baseline. Independent of baseline CD4 cell

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
count, a rise in CD4 cell count by 50 x 10(6)/L or more and undetectable 
HIV-1 RNA in plasma (<400 copies/mL) by 6 months reduced risk of 
subsequent events, with hazard ratios of 0.32 (95% CI, 0.20-0.52) and 
0.39 (0.24-0.65), respectively. CONCLUSIONS: Our data indicate that the 
risk of developing an OI for a person receiving potent antiretroviral therapy 
is highest during the initial months of therapy. Baseline CD4 cell count and 
immunologic and virologic response to treatment were strong predictors of 
disease progression in patients receiving potent therapy. Individuals with 
CD4 cell counts of 50 x 10(6)/L or below may need close clinical 
surveillance after initiation of potent therapy.

8. Masur, H., Kaplan, J., “Does Pneumocystis carinii prophylaxis still need to 

Monforte, A., De Luca, A., Mongiardo, N., Cerri, M. C., Chiodo, F., Concia, 
E., Bonazzi, L., Moroni, M., Ortona, L., Esposito, R., Cossarizza, A., De 
Rienzo, B., “Discontinuation of primary prophylaxis for Pneumocystis 
carinii pneumonia and toxoplasmic encephalitis in human 
immunodeficiency virus type 1-infected patients: the changes in 
opportunistic prophylaxis study,” JID 2000, Volume: 184, Issue 5, Pages: 
1635-42.

BACKGROUND: A multicenter open, randomized, controlled trial was 
conducted to determine whether primary prophylaxis for Pneumocystis 
carinii pneumonia and toxoplasmic encephalitis can be discontinued in 
patients infected with human immunodeficiency virus type 1 (HIV-1) 
whose CD4+ T cell counts have increased to >200 cells/mm3 (and who 
have remained at this level for at least 3 months) as a result of highly 
active antiretroviral therapy (HAART). Patients were randomized to either 
the discontinuation arm (i.e., those who discontinued prophylaxis; n=355) 
or to the continuation arm (n=353); the 2 arms of the study were similar in 
terms of demographic, clinical, and immunovirologic characteristics. 
During the median follow-ups of 6.4 months (discontinuation arm) and 6.1 
months (continuation arm) and with a total of 419 patient-years, no patient 
developed P. carinii pneumonia or toxoplasmic encephalitis. The results of 
this study strongly indicate that primary prophylaxis for P. carinii 
pneumonia and toxoplasmic encephalitis can be safely discontinued 
inpatients whose CD4+ T cell counts increase to >200 cells/mm3 during 
HAART.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
4. POLICY AND ETHICS – DONORS

Background

Organs are in high demand and availability is scarce even for populations traditionally eligible for transplant. Expanding the definition of the populations eligible for transplant may be perceived as threatening to those who are currently advocating for the interests of potential transplant recipients. Careful examination of risks and benefits of the various organ donor pools (cadaveric, living, high risk), in the context of this study, must be undertaken.
Reference: Policy and Ethics – Donors

A. Cadaveric versus Living Donors

Background

Some believe that cadaveric organs should not be utilized in an experimental context until the safety and efficacy of the procedure are demonstrated. Some believe that living kidney and/or liver donation should be restricted only to circumstances with proven benefit to the recipient because it is unethical to subject the donor to risk in an experimental setting.

Question #1

Is it ethical to use organs from cadaveric donors in a Phase I experimental study, considering that these organs are in very short supply?

Question #2

Should potential donors or their families be able to restrict donation so that organs would not be available for our study subjects? And, how much privacy should the potential recipient have when the donor has a real morbidity and mortality in the act of donating (above and beyond the durability of the gift because of the underlying disease)?

Question #3

In the absence of data on the safety and efficacy of transplants in HIV+ individuals, is it ethical to allow living donors to assume the risks of donation?

Question #4

What are the informed consent issues related to living donation? Should the potential recipient be required to reveal his or her HIV status to potential donors?

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
References: Cadaveric versus Living Donors


Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
B. High Risk Organs

Background

A donor who is considered to be at “high risk” of having an infection is one where the infection is in the early stages and cannot yet be detected with the tests that are used to screen the donors of organs. These include: HIV, hepatitis B, hepatitis C and other infections that are spread through sexual activity or drug use but have not yet been identified. People are considered to be at high risk if they are known to have recently used injection drugs, are men who have sex with other men, are commercial sex workers, or have been recently incarcerated. Accepting the possibility of being offered an organ from a high risk donor does not guarantee that such an organ will be available. However, in the context of this study, it is likely that a high risk organ could be available before a normal risk organ.

Question #1

Should the use of high risk organs be allowed per site discretion?

Question #2

Should study sites be allowed to restrict access exclusively to high risk organs?

Question #3

Should any other definitions of “high risk” be considered in the context of this study, e.g. age, co-morbidities, etc?

Question #4

Can or should high risk organ availability be enhanced, and if so how?
References: High Risk Organs


The transmission of infection by a cadaver donor organ can result not only in loss of the allograft but also in death of the immunosuppressed recipient. Despite the shortage of cadaver organ donors, every donor must be evaluated thoroughly for the potential transmission of infectious disease, because the consequences of the organ donor events can have a profound effect on the transplant outcome. This review summarizes current knowledge about serological screening of organ donors to determine the suitability of organs from cadaver donors for transplantation.
5. THE ROLE OF COMMUNITY ADVISORY BOARDS IN RESOLVING ETHICAL ISSUES

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
6. REIMBURSEMENT POLICIES

Background

Payment by third party payers for procedures that are considered experimental is not assured. What are the challenges in dealing with both government and private insurance?

This is a brainstorming session that will also discuss the experiences of transplant centers in dealing with reimbursement for study-related health care services.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
Reference: Reimbursement Policies


How can health plans make fair determinations about when "experimental" (and costly) treatments such as high dose chemotherapy with autologous bone marrow transplantation should be covered despite lack of clear clinical consensus about their benefits? Different models for managing "last chance" therapies evolving in some health plans offer promising examples of how issues of fairness and legitimacy in decision-making can be addressed.
7. PROTECTING SUBJECTS TO MINIMIZE RISKS AND MAXIMIZE BENEFITS OF PARTICIPATION IN THE CLINICAL TRIAL

Background

Two multi-site meetings have been held over the last two years where many research and clinical any issues were discussed. As our experience evolves, however, we must continue to reevaluate these issues.

A. Should there be an Off-study Protocol?

Background

A decision was made in the past that data collection should be maximized on all patients, and that we did not support the formation of an off-study registry. However, some centers participating in the study may be willing to transplant patients not meeting study criteria, and some centers not participating in the study may still transplant people with HIV infection.

Question #1

Should we as a group support these transplants be done without any formal data collection?

Question #2

Should we create a minimal data collection procedure for off-study transplants?

Question #3

Is it acceptable for a single center to do transplants both on and off protocol?

Question #4

If a participating center decides to perform transplants off protocol, should we as a group reconsider the specific criteria that excluded the patient from the protocol (e.g. history of opportunistic complications or others)?

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
B. OUTREACH AND ADVERTISING – HOW MUCH?

Background

This study represents hope for people with HIV who are in need of a transplant. It is incumbent on us that we both provide information and access to the public and deliver a balanced message about the unknowns and risks associated with this experimental intervention. At the same time, we must control outreach and referrals so individual centers are not overwhelmed.

Question #1

How do we both provide information and access to the public and deliver a balanced message about the unknowns and risks associated with this experimental intervention?

Is it the study sites’ role to inform the community and public and raise their awareness about the potential benefits and risks of organ transplants in HIV and to educate and inform about issues related to HCV/HIV co-infection treatment and kidney and HIV health issues?

Question #2

How do we control outreach and referrals so individual centers are not overwhelmed?

Is it appropriate to exercise control over how many people hear about the program so the sites don’t get overwhelmed? How should the sites handle requests for information? Can local community organizations near a site make themselves available to public inquiries? Should each site establish a local CAB if the local community is interested?
8. REVIEW OF SATURDAY’S PRESENTATIONS

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
9. RESOURCE ISSUES

Background

Organs are in high demand and availability is scarce even for populations traditionally eligible for transplant. Expanding the definition of the populations eligible for transplant may be perceived as threatening to those who are advocating for traditional (HIV negative) transplant recipients.
References: Resource Issues


Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
A. Should HIV+ Subjects be Given a Rare Resource?

Question #1

Should scarce organ resources be used to evaluate whether or not transplant on the HIV positive population is safe and effective? If not, why not?
References: Should HIV+ Subjects be Given a Rare Resource?

Prognosis in HIV


   BACKGROUND: We used data from Europe, North America, and Australia to assess the effect of exposure category on the AIDS incubation period and HIV-1 survival and whether the effect of age at seroconversion varies with exposure category and with time since seroconversion. METHODS: 38 studies of HIV-1-infected individuals whose dates of seroconversion could be reliably estimated were included in the analysis. Individual data on 13030 HIV-1-infected individuals from 15 countries were collated, checked, and analysed centrally. We calculated estimates of mortality and AIDS incidence rates and estimated the proportions of individuals surviving and developing AIDS at each year after seroconversion from the numbers of observed deaths or cases of AIDS and the corresponding person-years at risk. Analyses were adjusted for age at seroconversion, time since seroconversion, and other factors as appropriate. FINDINGS: Mortality and AIDS incidence increased strongly with time since seroconversion and age at seroconversion. Median survival varied from 12.5 years (95% CI 12.1-12.9) for those aged 15-24 years at seroconversion to 7.9 years (7.4-8.5) for those aged 45-54 years at seroconversion, whereas for development of AIDS the corresponding values were 11.0 years (10.7-11.7) and 7.7 years (7.1-8.6). There was no appreciable effect of exposure category on survival. For AIDS incidence, the exposure category effect that we noted was explained by the high incidence of Kaposi’s sarcoma in those infected through sex between men. We estimated that among people aged 25-29 years at seroconversion 90% (89-91) and 60% (57-62) survived to 5 years and 10 years, respectively, after seroconversion, whereas 13% (12-15) and 46% (44-49), respectively, developed AIDS (excluding Kaposi’s sarcoma). INTERPRETATION: Before widespread use of highly-active antiretroviral therapy (before 1996), time since seroconversion and age at seroconversion were the major determinants of survival and development of AIDS in Europe, North America, and Australia.


Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
BACKGROUND: Hepatitis C virus (HCV) infection is highly prevalent among HIV-1-infected individuals, but its contribution to the morbidity and mortality of coinfected patients who receive potent antiretroviral therapy is controversial. We used data from the ongoing Swiss HIV Cohort Study to analyze clinical progression of HIV-1, and the virological and immunological response to potent antiretroviral therapy in HIV-1-infected patients with or without concurrent HCV infection. METHODS: We analyzed prospective data on survival, clinical disease progression, suppression of HIV-1 replication, CD4-cell recovery, and frequency of changes in antiretroviral therapy according to HCV status in 3111 patients starting potent antiretroviral therapy. RESULTS: 1157 patients (37.2%) were coinfected with HCV, 1015 of whom (87.7%) had a history of intravenous drug use. In multivariate Cox's regression, the probability of progression to a new AIDS-defining clinical event or to death was independently associated with HCV seropositivity (hazard ratio 1.7 [95% CI 1.26-2.30]), and with active intravenous drug use (1.38 [1.02-1.88]). Virological response to antiretroviral therapy and the probability of treatment change were not associated with HCV serostatus. In contrast, HCV seropositivity was associated with a smaller CD4-cell recovery (hazard ratio for a CD4-cell count increase of at least 50 cells/μL=0.79 [0.72-0.87]). INTERPRETATION: HCV and active intravenous drug use could be important factors in the morbidity and mortality among HIV-1-infected patients, possibly through impaired CD4-cell recovery in HCV seropositive patients receiving potent antiretroviral therapy. These findings are relevant for decisions about optimum timing for HCV treatment in the setting of HIV infection.

HIV and Transplantation


A 46-year-old Hispanic male with a history of intravenous drug abuse and sexual promiscuity received a cadaveric renal transplant in January 1984. He tested positive for HIV-1 in February 1986. Infectious complications began 19 months after transplantation and were managed successfully until his death from sepsis 109 months posttransplant. Other HIV-infected long-term solid organ transplant survivors are reviewed from the literature. The effects of prednisone and cyclosporine on HIV-1 expression are discussed briefly.
Programs in HIV


CONTEXT: Time to development of acquired immunodeficiency syndrome (AIDS) and time to death have been extended with the increased use of combination therapy and protease inhibitors. Cohort studies following up persons with human immunodeficiency virus (HIV) infection in periods characterized by different therapies offer the opportunity to estimate therapy effectiveness at the population level. OBJECTIVE: To assess the effectiveness of self-reported, long-term potent antiretroviral therapy in a cohort of 536 men whose duration of HIV infection was known (seroconverters). DESIGN: Cohort study. The cohort was compared for time to development of AIDS and time to death in 1984 to 1990, 1990 to 1993, 1993 to July 1995, and July 1995 to July 1997 when the major treatments were no therapy, monotherapy, combined therapy, and potent antiretroviral therapy, respectively. Survival analysis methods with time zero set as the date of seroconversion and incorporating staggered entries into each period were used. Mean CD4 cell change, stratified by infection duration, was determined for each period using a random effects model. SETTING: The Multicenter AIDS Cohort Study (MACS) in 4 urban areas (Baltimore, Md; Chicago, Ill; Los Angeles, Calif; and Pittsburgh, Pa). PARTICIPANTS: A total of 5622 men who were 18 years or older were enrolled into MACS. Of the 5622, there were 2191 HIV-positive individuals at enrollment. Of the 3431 men who were HIV-negative, 536 were observed to seroconvert and were followed up for up to 13 years. The group of 536 who seroconverted constituted the study population. MAIN OUTCOME MEASURES: Time from seroconversion to development of AIDS and to death and change in CD4 cell count. RESULTS: A total of 231 seroconverters developed AIDS, and 200 men died. Using 1990 to 1993 as the reference period, the relative hazard of AIDS was 1.04 (95% confidence interval [CI], 0.73-1.48) during 1993 to July 1995 and 0.35 (95% CI, 0.20-0.61) during July 1995 to July 1997. Relative hazards of death were 0.87 (95% CI, 0.58-1.31) and 0.62 (95% CI, 0.38-1.01) for the same periods. The relative time (the factor by which times are contracted or expanded) to development of AIDS was 0.97 (95% CI, 0.86-1.09) for 1993 to July 1995 and 1.63 (95% CI, 1.40-1.89) for July 1995 to July 1997. Relative survival time for 1993 to July 1995 was 1.01 (95% CI,0.91-1.12) and for July 1995 to July 1997 was 1.21 (95% CI, 1.07-1.36) relative to 1990 to 1993. The rate of CD4 cell count decline in July 1995 to July 1997 was significantly lower (P.05) compared with the previous 2 periods. CONCLUSIONS: In the calendar period when potent antiretroviral therapy was introduced, the time to development of AIDS

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and time to death were extended, and rate of CD4 cell count decline was arrested.


CONTEXT: Declines in the number of acquired immunodeficiency syndrome (AIDS) deaths were first observed in 1996, attributed to improvements in antiretroviral therapy and an increase in the proportion of persons receiving therapy. OBJECTIVE: To examine national trends in survival time among persons diagnosed as having AIDS in 1984-1997. DESIGN, SETTING, AND SUBJECTS: Retrospective cohort study using data from a population-based registry of AIDS cases and deaths reported in the United States. MAIN OUTCOME MEASURE: Months of survival after AIDS diagnosis through December 31, 1998, compared by year of diagnosis. RESULTS: Among 394705 persons with an AIDS-defining opportunistic illness (OI) diagnosed in 1984-1997, median survival time improved from 11 months for 1984 diagnoses to 46 months for 1995 diagnoses. Among persons with an OI diagnosed in 1996 and 1997, 67% were alive at least 36 months after diagnosis and 77% were alive at least 24 months after diagnosis, respectively. Among 296621 AIDS cases diagnosed during 1993-1997, 65% were based on immunologic criteria and 35% on OI criteria; 80% were among men; and 42% were among non-Hispanic blacks, 40% among non-Hispanic whites, 17% among Hispanics, 1% among Asians/Pacific islanders, and less than 1% among American Indians/Alaska natives. The probability of surviving at least 24 months increased from 67% for those with immunologic diagnoses in 1993 to 90% in 1997 and from 49% for those with OI diagnoses in 1993 to 80% in 1997. Survival time increased with each year of diagnosis from 1984 to 1997 for blacks, whites, and Hispanics. The greatest annual survival gains occurred among persons receiving an AIDS diagnosis in 1995 and 1996. CONCLUSIONS: Survival time after AIDS diagnosis improved from 1984 to 1997. While AIDS incidence is declining, improved survival times present a growing public health challenge as the number of persons living with chronic human immunodeficiency virus disease/AIDS increases.


OBJECTIVE: Despite advances in antiretroviral treatment, a large number of HIV-infected patients still require hospitalization. This study describes the characteristics of HIV patients requiring hospitalization before and after the advent of potent antiretroviral therapies. METHODS: Information was collected on all HIV-positive patients admitted to the New York
Hospital-Cornell Medical Center in New York City. Data was collected from 1 January through 30 June 1995, and during the same 6-month interval in 1997. RESULTS: In each time period over 1500 outpatients were receiving treatment for HIV infection. There was a significant decrease in the incidence of admission [60.4 per 100 patient-years (PY) in 1995, 28.8 per 100 PY in 1997], and length of stay (10 versus 8 days). The median CD4 cell count of all HIV-infected patients admitted to the hospital doubled: 37 x 10(6)/l in 1995 versus 80 x 10(6)/l in 1997. However, there was no significant change in the median CD4 cell count of patients diagnosed with opportunistic infections. The incidence of the most common diagnosis (bacterial pneumonia, 8.0 per 100 PY in 1995 versus 3.6 per 100 PY in 1997) and the most common opportunistic infection (Pneumocystis carinii pneumonia 7.6 per 100 PY in 1995 versus 2.4 per 100 PY in 1997) decreased significantly. CONCLUSIONS: Since the introduction of potent antiretroviral therapy, a significant decrease in the incidence of hospital admission and opportunistic infections has occurred. There has been a doubling of the median CD4 cell count of inpatients. There has been no significant change in the median CD4 cell count at which patients present with opportunistic infections.


HIV and Treatment


   We report the clinical and biological course of infection with human immunodeficiency virus HIV type 1 in 11 liver transplant recipients who acquired this infection between 1985 and 1987. Eight patients were infected by blood or blood products from graft-related transfusions and one by the graft itself; the remaining two patients were infected after transplantation and had independent risk factors. All patients received a triple-drug immunosuppressive regimen including cyclosporine. The mean duration of follow-up after liver transplantation was 52 months standard error, +/- 32 months. Chronic graft rejection was documented in four cases. The cumulative incidences of HIV-related complications and HIV-related deaths were 82% and 27%, respectively. Three patients died rapidly of HIV disease. The survival rate 7 years after transplantation was 36% among the 11 HIV-infected patients, whereas it was approximately 70% among HIV-negative liver transplant recipients during the same
period. The course of HIV infection in the four survivors did not appear to differ from that in other patients infected by blood transfusion.


Five recipients of solid-organ transplants who were infected with human immunodeficiency virus HIV were studied at the University of Minnesota, and our data were compared with data from 83 reported cases of HIV-infected recipients of solid organs from other centers. Sixty-six of the 88 patients were seronegative for HIV before transplantation and received organs or transfusions of blood from individuals who were seropositive for HIV. Seven patients four recipients of kidney transplants and three recipients of liver transplants received transplants after routine screening for HIV. Twenty-five 28% of the 88 patients developed AIDS, and 20 80% of these 25 patients died of AIDS-related complications a mean of 37 months after transplantation. Another nine patients 10% had other HIV-related diseases. The mean time of progression to AIDS was 27.5 months among all patients with AIDS. For patients who were seronegative for HIV at the time of transplantation, the mean time of progression to AIDS was 32 months, whereas patients seropositive before transplantation developed AIDS within 17 months. Shortly after transplantation, eleven 17% of the patients who were initially seronegative experienced a febrile syndrome attributed to HIV. Ten patients, including eight recipients of kidney transplants and two recipients of liver transplants, maintained normal allograft function despite low-dose immunosuppressive therapy.


Twenty-five whole-organ recipients treated from 1981 through September 1988 were HIV carriers. Eleven were infected before transplantation, although this was not known until later in 8 recipients. The other 14 were infected perioperatively. Ten of the 25 recipients were infants or children. The organs transplanted were the liver n 15 , and the heart or kidney n 5, each . After a mean follow-up of 2.75 years range, 0.7-6.6 years , 13 recipients are alive. Survival is 7/15, 2/5, and 4/5 of the liver, heart, and kidney recipients, respectively. The best results were in the pediatric group 70% survival in which only 1 of 10 patients died of AIDS. In contrast, AIDS caused the death of 5 of 15 adult recipients and was the leading cause of death. Transplantation plus immunosuppression

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
appeared to shorten the AIDS-free time in HIV+ patients as compared to nontransplant hemophiliac and transfusion control groups. Accrual of HIV+ transplant recipients has slowed markedly since the systematic screening of donors, recipients, and blood products was begun in 1985.

**Allocation Policy**


The role of patient psychosocial and lifestyle characteristics in decisions about the allocation of scarce health care resources has not been examined. In this national survey using the Criteria for Selection of Transplant Recipient (CSTR) Scale, organ transplant coordinators (N = 559) identified the psychosocial and lifestyle criteria they believe should be considered in patient selection/rejection for organ transplant. Using factor analysis to reduce the data, six factors were identified: current lifestyle/psychiatric problems, family/socioeconomic issues, habits, controlled lifestyle/psychiatric issues, cost, and stigmatized conditions. Patients who were in prison for a serious crime, used cocaine, had AIDS, or were HIV positive (criteria making up the Stigma factor), were more likely to be labeled for exclusion from transplant than those with other psychosocial/lifestyle characteristics. When transplant coordinators perceived that patients’ psychosocial and lifestyle problems were under control or corrected, they were more likely to consider them for a transplant. For all but the cost factor, criteria were most stringent for heart transplants. Although over 90% of the coordinators assessed patients and participated in patient selection for transplant, master's prepared nurses were more likely than nurses with other educational preparation to be involved in organ recipient selection. These findings can serve as a prototype for how decisions are made for allocating other scarce health care resources.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
B. History of UNOS Criteria Relative to HIV and How May the MELD Criteria Impact Allocation of Organs to People with HIV

UNOS Policy

June 1992

4.0 Acquired Immune Deficiency Syndrome (AIDS) and Human Pituitary Derived Growth Hormone (HPDGH) and Human T-Lymphotropic Virus Type (HTLV-I)

These policies apply to the pretransplant consideration of potential organ donors and/or potential organ recipients, with regard to AIDS, HPDGH, and HTLV-1.

4.1 Screening Potential Organ Donors for Anti-HIV Antibody.
All potential donors are to be tested by use of a screening test licensed by the U.S. Food and Drug Administration (FDA) for Anti-Human Immune Deficiency Virus (HIV) Antibody (Ab). If the potential donor's pre-transfusion test for the antibody is negative and blood for subsequent transfusions has been tested and found to be negative for HIV-Ab, retesting the potential donor for HIV-Ab is not necessary. If no pre-transfusion sample of the potential donor's blood is available, the Host OPO (as defined in Policy 2.1) must provide, to the recipient transplant center the screening test results and a complete history of all transfusions received by the donor during the ten (10) day period immediately prior to removal of the organ. Organs from donors with a positive screening test are not suitable for transplantation unless subsequent confirmation testing indicates that the original tests' results were falsely positive for HIV-Ab. If additional tests related to HIV are performed, the results of all tests must be communicated immediately to the UNOS Organ Center and all institutions receiving organs from the donor. Exceptions for cases in which the testing cannot be completed prior to transplant are provided in paragraph 4.1.3 below.

4.1.1 Donor History.
The Host OPO will obtain a history on each potential donor in an attempt to determine whether the potential donor is in a "high risk" group, as defined by the Centers for Disease Control. The Host OPO must communicate the donor history to all institutions receiving organs from the donor.

4.1.2 Organ Sharing.
UNOS members shall not knowingly participate in the transplantation or sharing of organs from donors who are confirmed reactive for HIV-Ab by an FDA licensed screening test unless subsequent confirmation testing unequivocally indicates that the original test's results were falsely positive for HIV-Ab.

4.1.3 Exceptions.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
Exceptions to the guidelines set forth above may be made in cases involving non-renal organs, when, in the medical judgment of the staff of the Host OPO and recipient institution, an extreme medical emergency warrants the transplantation of an organ, the donor of which has not been tested for HIV antibody. The transplant surgeon is obligated to obtain informed consent from the recipient or next of kin in such cases.

4.1.4 Donor Consent Forms.
UNOS member institutions are encouraged to include in each donor consent form a notice that all potential donors will be screened for medical acceptability for organ donation and that results of such tests may be the basis for not using the organ in transplantation.

4.2 Screening Potential Transplant Recipients for HIV Antibody.
Testing for HIV-Ab shall be a condition of candidacy for organ transplantation, except in cases where such testing would violate applicable state or federal laws or regulations. Patients whose test results are confirmed positive should undergo appropriate counseling.

4.2.1 HIV-Ab Sero-positive Transplant Candidates.
A potential candidate for organ transplantation whose test for HIV-Ab is positive but who is in an asymptomatic state should not necessarily be excluded from candidacy for organ transplantation, but should be advised that he or she may be at increased risk of morbidity and mortality because of immunosuppressive therapy.

4.2.2 Informing Personnel.
Health care personnel caring for patients who test positive for AIDS antibody should be so informed.

4.2.3 Patient Treatment.
Administering treatment to patients who test positive for the HIV antibody should not be optional or discretionary for health care personnel.

4.3 Disclosure of Information About HIV Antibody Status.
UNOS member institutions are urged to comply with state and federal statutes and regulations applicable to the disclosure of personalized data on actual or potential organ donors or recipients.

4.4 General Recommendations.
All UNOS member institutions are requested to adopt an overall health care policy addressing special HIV-related problems with regard to transplant candidates and recipients. It is recommended that each institution’s HIV-related health care policies incorporate the specific UNOS policies 4.1, 4.2, and 4.3 set forth above. It is also recommended that member institutions make their policies available upon request to the press and the public.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
4.5 Human Pituitary Derived Growth Hormone.
People who have received Human Pituitary Derived Growth Hormone (HPDG) shall be deferred as organ donors. An exception to this policy may be made in cases involving non-renal organs, when, in the medical judgment of the staff of the Host OPO and recipient institution, an extreme medical emergency warrants the transplantation of an organ, the donor of which has received HPGD. The transplant surgeon is obligated to obtain informed consent from the recipient or next of kin in such cases.

4.6 Screening Potential Organ Donors for HTLV-I [sic] Antibody.
All potential donors are to be tested by a screening test licensed by the FDA for Human T-Lymphotropic Virus Type I (HTLV-I) Antibody (Ab). If the potential donor's pre-transfusion test for the HTLV-I antibody is negative and blood for subsequent transfusions has been tested and found to be negative for HTLV-I Ab, retesting the potential donor for HTLV-I Ab is not necessary. If no pre-transfusion sample of the donor's blood is available, the Host OPO must provide to each recipient transplant program the screening test results and a complete history of all transfusions received by the donor during the ten (10) day period immediately prior to removal of the organ. Organs from donors with a positive screening test are not suitable for transplantation unless subsequent confirmation testing indicates that the original tests' results were falsely positive for HTLV-I-Ab. If additional tests related to HTLV-I Ab are performed, the results of all tests must be communicated immediately to the UNOS Organ Center and all recipient institutions. Exceptions for cases in which the testing cannot be completed prior to transplant are provided in paragraph 4.6.3 below.

4.6.1 Donor History.
The Host OPO will obtain a history on each potential donor in an attempt to determine whether the potential donor is in a "high risk" group, as defined by the Centers for Disease Control. The Host OPO must communicate the donor history to all recipient institutions.

4.6.2 Organ Sharing.
UNOS members shall not knowingly participate in the transplantation or sharing of organs from donors who are confirmed positive for HTLV-I-Ab by an FDA licensed screening test unless subsequent confirmation testing unequivocally indicates that the original test's results were falsely positive for HTLV-I-Ab.

4.6.3 Exceptions.
Exceptions to the guidelines set forth above may be made in cases involving non-renal organs, when, in the medical judgment of the staff of the Host OPO and recipient institution, an extreme medical emergency warrants the transplantation of an organ, the donor of which has not been tested for HTLV-I-Ab.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
Ab. The transplant surgeon is obligated to obtain informed consent from the recipient or next of kin in such cases.

4.6.4 Donor Consent Forms.
UNOS member institutions are encouraged to include in each donor consent form a notice that all potential donors will be screened for medical acceptability for organ donation and that results of such tests may be the basis for not using the organ in transplantation.

4.7 Post Transplant HIV Reporting.
When a transplant program director is informed that an organ recipient at that program is confirmed positive by Western Blot for HIV, or has died from HIV-related causes, the director shall notify as soon as practicable, the medical director or executive director of the procuring OPO and the UNOS Organ Center director by telecopying and mailing a completed UNOS Transplant HIV/Hepatitis B Form. The medical director or executive director of the procuring OPO shall be responsible for:

i. notification of the positive HIV test results as soon as practicable to any tissue bank and the director of any other transplant program that received tissue or an organ from the donor who is the subject of the investigation;

ii. management of the investigation to determine whether the organ donor was infected with HIV; and

iii. submission of a final written report to UNOS with 45 days which specifies the organizations and individuals who were notified, when the notifications occurred, and results of the investigation including final HIV serology status of the organ recipients who are the subjects of the investigation.

Upon receipt of a completed UNOS Transplant HIV/Hepatitis B Form that reports a confirmed positive Western Blot HIV test result, UNOS shall assist the procuring OPO in identifying all organ transplant programs and recipients who received an organ from the donor who is the subject of the investigation. UNOS will monitor the notification process to verify that the procuring OPO and all recipient organ transplant programs have been notified of the positive HIV test results and will request that any additional HIV test results be submitted to the procuring OPO with a copy to UNOS. UNOS will forward a copy of the OPO’s final report to the recipient transplant centers and the Division of Organ Transplantation of the Health Resources and Services Administration. Note: The identities of the donor and any organ recipient who are the subjects of the investigation shall remain confidential and under no circumstances should a transplant program or OPO disclose this information in a manner that is contrary to applicable law.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
UNOS POLICY NOTICE MEMO
To: Liver transplant candidates and their families
From: Deborah Surlas, RN, Chair, OPTN/UNOS Patient Affairs Committee
Subject: OPTN/UNOS Endorsement of MELD System
Date: July 16, 2001

OPTN/UNOS Board Endorses Further Development of Liver Urgency Scale

UNOS continuously develops new policies and refines other policies to keep up with the medical advances in transplantation and drug therapy. At its June 28-29 meeting, the OPTN/UNOS Board of Directors endorsed further development of the Model for End Stage Liver Disease (MELD) for possible implementation after the Board meeting next November. The organization has been developing the MELD/PELD (Pediatric End Stage Liver Disease) system for over a year. The new policy is expected to save lives on the liver transplant waiting list by prioritizing (ranking) patients by their short-term risk of death without a transplant.

What is the OPTN/UNOS?
The Organ Procurement and Transplantation Network (OPTN) was established by Congress to link all U.S. transplant hospitals and organ procurement organizations and ensure efficient, equitable distribution of donated organs. The U.S. Department of Health and Human Services (HHS) provides oversight of the OPTN through federal regulation and contract with the United Network for Organ Sharing (UNOS).

UNOS is a non-profit medical, scientific, and educational organization of volunteers and staff. Under the OPTN contract, UNOS maintains the nation’s organ transplant waiting list. It brings together medical professionals, transplant recipients and donor families to develop organ transplantation and allocation (distribution) policies. There are patient representatives on the Board of Directors and the various committees of the OPTN/UNOS, including the Patient Affairs Committee.

Organ sharing policies constantly change to improve transplantation. Policies are made to benefit every patient equally (justice) and make the best use of limited donor organs (utility). Patients on the waiting list are treated equally regardless of ethnicity, gender, religion, socio-economic status, or history of personal behavior.

What is the current liver allocation (distribution) policy?
There are 4 categories of patients, Status 1, 2A, 2B and 3. A patient's status category is determined by a point system, using objective and subjective factors. Status 1 patients are the most critical. They have fulminant (sudden) liver failure, or their newly transplanted liver did not function. They have a life expectancy of less than 7 days without a liver transplant. This category will remain in place and not be affected by the new system.

Status 2A patients are those who typically have chronic liver disease and are in the hospital's critical care unit with a life expectancy of less than 7 days without a liver transplant, as determined by objective and subjective medical criteria. Status 2B patients typically have chronic liver disease and are becoming more urgently in need of a transplant, but do not meet the criteria for Status 2A.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
Status 3 patients also have chronic liver disease and are under continuous medical care, but are not in the hospital, except for possible short stays. These patients do not meet the criteria for Status 2B.

What is the MELD scoring system?
It is a means of giving adult liver candidates a ‘score’ (number) based on how urgently they need a liver transplant within the next 3 months. The number is calculated by a formula using routine lab test results that are standardized at all hospitals. This is a much more precise method of ranking patients so that those most in need will be given the highest priority for donated livers, rather than simply allocating them to patients who have waited longer but who may be much more stable. The MELD policy will replace Status 2A, 2B and 3 with a continuous scale.

How will the MELD policy improve on the current policy?
The MELD system, which is based on numerous studies of medical data, is expected to save lives on the waiting list by more accurately determining who is in greatest need of a liver transplant within the next 3 months and giving those patients the highest priority. The MELD system is also based on objective (non-biased) medical criteria.

Who reviewed and approved the MELD system?
Proposals detailing the MELD system have twice been sent out to the general public for their comments. More than a dozen public meetings have been held at which panels of experts debated and refined the system. The various committees of the OPTN/UNOS, including the Patients Affairs and Minority Affairs Committees have given their input and endorsement. The Board of Directors of the OPTN/UNOS, which includes patients, donors, and their families, gives the final approval, subject to oversight by the Department of Health and Human Services.

How will the MELD scoring system help me?
Studies of systems that rank patients by priority, such as the MELD scoring system have suggested that a change to the MELD system will most likely reduce deaths on the liver waiting list. Instead of the current system that ‘lumps’ patients together in one of only 3 groups (Status 2A, 2B or 3), the MELD system will give you your own individual urgency status. By going to a more continuous scale, the system will more accurately indicate which patients are most in need. As you become in greater need of a transplant, your MELD score will increase, and you will move up in the ranking, thus receiving greater priority for organ offers.

What will my MELD score be?
Your individual MELD scores will be calculated by inserting your individual lab test results into a formula. As your lab results change, so will your MELD score. Your MELD score can go up and down as you wait for a transplant. As your MELD score increases, these lab tests will be done more frequently. The MELD score can range from 10 (less ill) to 40 (gravely ill).

How will waiting time affect the MELD system?
The MELD system puts emphasis on your need of a liver transplant in the next 3 months. Waiting time will be used as a tiebreaker if two patients with the same MELD score are offered an organ. Under the current system, waiting time is a principal factor in determining who is offered a donated liver. The Institute of Medicine has reported that waiting time is a poor indicator of how urgently a patient needs a liver transplant.
What if I am already on the waiting list?
You will be ‘grand fathered’ into the MELD system. You will be given credit for the time you have already been on the list. You will then continue to be ranked according to the severity of your illness, your MELD score.

What about pediatric patients?
Candidates under the age of 18 will be ranked according to the Pediatric End Stage Liver Disease (PELD) scoring system. This system is similar to the MELD, but recognizes the specific needs of children. Pediatric Status 1 will remain in place. Status 2B and 3 will be replaced with the PELD policy. (There is no Status 2A for pediatric patients.)

When will the MELD system go into effect?
The system and computer programming are still being refined. The new system is expected to take effect after final approval at the November 2001 OPTN/UNOS Board of Directors meeting.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
References: MELD Criteria


Abstract: A recent mandate emphasizes severity of liver disease to determine priorities in allocating organs for liver transplantation and necessitates a disease severity index based on generalizable, verifiable, and easily obtained variables. The aim of the study was to examine the generalizability of a model previously created to estimate survival of patients undergoing the transjugular intrahepatic portosystemic shunt (TIPS) procedure in patient groups with a broader range of disease severity and etiology. The Model for End-Stage Liver Disease (MELD) consists of serum bilirubin and creatinine levels, International Normalized Ratio (INR) for prothrombin time, and etiology of liver disease. The model's validity was tested in 4 independent data sets, including (1) patients hospitalized for hepatic decompensation (referred to as "hospitalized" patients), (2) ambulatory patients with noncholestatic cirrhosis, (3) patients with primary biliary cirrhosis (PBC), and (4) unselected patients from the 1980s with cirrhosis (referred to as "historical" patients). In these patients, the model's ability to classify patients according to their risk of death was examined using the concordance (c)-statistic. The MELD scale performed well in predicting death within 3 months with a c-statistic of (1) 0.87 for hospitalized patients, (2) 0.80 for noncholestatic ambulatory patients, (3) 0.87 for PBC patients, and (4) 0.78 for historical cirrhotic patients. Individual complications of portal hypertension had minimal impact on the model's prediction (range of improvement in c-statistic: <.01 for spontaneous bacterial peritonitis and variceal hemorrhage to ascites: 0.01-0.03). The MELD scale is a reliable measure of mortality risk in patients with end-stage liver disease and suitable for use as a disease severity index to determine organ allocation priorities.

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
C. Will the Public Accept Allocation of Limited Resources to People with HIV Infection?

Question #1

Given the current status of organ donation (poor community participation) and the risk that publicity about the study could impact donation levels, is it appropriate to draw from the pool of cadaveric donors for this study?

Question #2

What are the potential risks?

Question #3

Who are the important stakeholders?
10. CLINICAL MANAGEMENT ISSUES: HOW TO BALANCE THE NEEDS OF SUBJECTS AND THE HEALTHCARE TEAM?

Background

The management of people with HIV in the pre- and post-transplant setting is extraordinarily complicated. Signs and symptoms must be evaluated from both an HIV and transplant perspective. Drug interactions are multiple and complex.

Question #1

Given the complex clinical nature of this undertaking and the busy schedules of all involved, what are the minimum components of an appropriate transplant team for the study?

Question #2

Must every team contain a transplant surgeon, HIV physician, hepatologist and/or nephrologist and a pharmacologist, and/or clinical pharmacist?

Question #3

Is it acceptable to limit access to transplants due to geographic proximity to the transplant center because of the complex nature of treatment involved?

Note: The full text of citations marked with a double asterisk (**) can be found in the Conference Reader.
11. WORKING LUNCH

A) Writing Committee
B) Cost Effectiveness Study
C) Policy Impact: Where Do We Go From Here?
12. CONFERENCE CLOSE