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ORIGINAL ARTICLE

Epidemiology and Outcome of Infections in Human Immunodeficiency Virus/Hepatitis C Virus–Coinfected Liver Transplant Recipients: A FIPSE/GESIDA Prospective Cohort Study

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Information about infections unrelated to acquired immunodeficiency syndrome (AIDS) in human immunodeficiency virus (HIV)–infected liver recipients is scarce. The aims of this study were to describe the prevalence, clinical characteristics, time of onset, and outcomes of bacterial, viral, and fungal infections in HIV/hepatitis C virus (HCV)–coinfected orthotopic liver transplant recipients and to identify risk factors for developing severe infections. We studied 84 consecutive HIV/HCV-coinfected patients who underwent liver transplantation at 17 sites in Spain between 2002 and 2006 and were followed until December 2009. The median age was 42 years, and 76% were men. The median follow-up was 2.6 years (interquartile range = 1.25-3.53 years), and 54 recipients (64%) developed at least 1 infection. Thirty-eight (45%) patients had bacterial infections, 21 (25%) had cytomegalovirus (CMV) infections (2 had CMV disease), 13 (15%) had herpes simplex virus infections, and 16 (19%) had fungal infections (7 cases were invasive). Nine patients (11%) developed 10 opportunistic infections with a 44% mortality rate. Forty-three of 119 infectious episodes (36%) occurred in the first month after transplantation, and 53 (45%) occurred after the sixth month. Thirty-six patients (43%) had severe infections. Overall, 36 patients (43%) died, and the deaths were related to severe infections in 7 cases (19%). Severe infections increased the mortality rate almost 3-fold [hazard ratio (HR) = 2.9, 95% confidence interval (CI) = 1.5-5.8]. Independent factors for severe infections included a pre-

Abbreviations: AIDS, acquired immunodeficiency syndrome; BDL, below detection level; cART, highly active combined antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; PCP, *Pneumocystis jiroveci* pneumonia.

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A list of the investigators is provided in the supporting information.

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transplant Model for End-Stage Liver Disease (MELD) score >15 (HR = 3.5, 95% CI = 1.70-7.1), a history of AIDS-defining events before transplantation (HR = 4.0, 95% CI = 1.9-8.6), and non–tacrolimus-based immunosuppression (HR = 2.5, 95% CI = 1.3-4.8). In conclusion, the rates of severe and opportunistic infections are high in HIV/HCV-coinfected liver recipients and especially in those with a history of AIDS, a high MELD score, or non–tacrolimus-based immunosuppression. *Liver Transpl 18:70-82, 2012.* © **2011 AASLD.**

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Orthotopic liver transplantation (OLT) is the best treatment option for human immunodeficiency virus 1 (HIV1)–infected patients with end-stage liver disease. Before the implementation of highly active combined antiretroviral therapy (cART), OLT in these patients was contraindicated because of the high mortality rate. With the availability of highly active antiretroviral therapy and the consequent reductions in opportunistic infections, which have extended the life expectancy of HIV1-infected patients, coinfections with hepatitis C virus (HCV) significantly affect survival. Nowadays, patients with controlled HIV infections who are receiving cART are considered candidates for OLT. Cohort studies in several countries have shown that the overall short-term survival rates of HIV1-infected patients who undergo OLT are similar to those of HIV-negative patients with no HCV coinfection.[1-11] The survival rate after transplantation for HIV/HCV-coinfected patients is lower than the rate for HCV-monoinfected patients, but it is satisfactory.[1-11] Moreover, HIV1-infected patients do not have an increased risk of postoperative complications or a higher incidence of opportunistic infections or tumors in comparison with HIV-negative patients.[4,12] Published analyses of HIV1-infected transplant recipients do not describe in detail posttransplant infectious events unrelated to acquired immunodeficiency syndrome (AIDS) but instead focus on survival, graft loss, and acute rejection episodes. Moreover, the incidence and risk factors of opportunistic infections in HIV1-infected patients during the posttransplant period remain unclear.

The aims of this study were to describe the prevalence, clinical characteristics, time of onset, and outcomes of bacterial, viral, and fungal infections in HIV/HCV-coinfected OLT recipients and to identify risk factors for developing severe infections.

PATIENTS AND METHODS

The study sample comprised 84 consecutive HIV/HCV-coinfected patients who underwent OLT at 17 centers in Spain between 2002 and 2006 and were followed until December 2009. Data were obtained from the Spanish Foundation for AIDS Research and Prevention (FIPSE OLT-HIV 05) and the Spanish Group (GESIDA 45-05) database. The institutional review boards of all the participating sites approved the study. All patients signed the informed consent form.

Transplant Criteria

The criteria for accepting HIV1-infected patients for transplantation were the same as those followed in Spain for HIV-negative patients.[13] According to their HIV infection status, patients also had to fulfill the following criteria[14]: no opportunistic infections [except for tuberculosis, esophageal candidiasis, or *Pneumocystis jiroveci* pneumonia (PCP)], a $CD4^+$ T cell count >100 cells/μL (>200 cells/μL if the patient had a previous opportunistic infection), and a plasma HIV RNA viral load that was undetectable or suppressible with cART. Former intravenous drug users needed to have abstained from heroin or cocaine use for more than 2 years. The minimum period of abstinence for alcohol was 6 months.

Data Collection, Entry, and Processing

The following variables were recorded for each patient:

1. Pre-OLT data, which included demographic data and data related to liver disease [hepatitis B virus (HBV) coinfections, Model for End-Stage Liver Disease (MELD) score, Child-Turcotte-Pugh class, and hepatocellular carcinoma], HCV infection (plasma RNA HCV viral loads, genotype, and anti-HCV treatment), and HIV infection [infection duration, risk factors for acquiring an HIV1 infection, previous AIDS events according to the 1993 AIDS criteria from the Centers for Disease Control and Prevention (CDC), plasma HIV1 RNA viral loads, $CD4^+$ T cell counts, and cART regimens].
2. Peri-OLT data, which included the year of OLT, the center, the donor characteristics, and the transfusion requirements for surgery. The donor risk index, a score that is derived from 8 donor variables (donor age, height, and race; cause of donor's brain death; donation after cardiac death status; partial/split liver status; place of donation; and cold ischemia time) and is used to estimate the influence of donor characteristics on patient and graft outcomes after transplantation, was calculated according to the criteria of Feng et al.[15]
3. Technical complications during surgery, infectious complications, immunosuppressive regimens, rejection episodes, graft function, HCV recurrence, and treatments and outcomes (AIDS events, plasma HIV1 RNA viral loads, $CD4^+$ T cell counts, and cART regimens).

The MELD score was calculated with the United Network for Organ Sharing modification.[16] For all patients, the Child-Turcotte-Pugh class and the

MELD score were determined at the time of registration on the waiting list and before OLT.

Antiretroviral therapy was administered until the day of surgery and was resumed once the patient was stable and oral intake had been reintroduced according to national guidelines.[17] HIV-infected recipients received the same immunosuppressive regimens as HIV-negative recipients according to local protocols. Post-OLT and anti-HIV antimicrobial prophylaxis were administered according to national guidelines.[18,19]

These variables were collected at each site with a standardized case report form. Information for each patient was first recorded at the time of registration on the OLT waiting list and was then prospectively collected for up to 10 years after OLT. Patient information was sent every 6 months to the coordinating center and was entered into the Spanish Foundation for the Investigation and Prevention of Acquired Immunodeficiency Syndrome OLT-HIV 05/Spanish Group for the Study of Acquired Immunodeficiency Syndrome 45-05 database.[20] There were 2 data entries per patient, and queries and reports on missing data were sent periodically to the local investigators for resolution. An audit was performed at all participating sites (information was checked for patients who were selected at random).

Definitions

The definitions of HIV1, HCV, and HBV infections, acute rejection, infectious episodes, and posttransplant complications were based on clinical guidelines and previous studies.[21,22]

The CDC guidelines were followed for the definition of nosocomial bacterial infections.[23]

Latent tuberculosis infection was defined as previous tuberculosis or a positive tuberculin skin test.[24,25]

Cytomegalovirus (CMV) infection and disease were defined according to the guidelines proposed by Ljungman et al.[26] CMV disease was either viral syndrome or end-organ disease.

Fungal infections were defined according to the criteria proposed by the European Organization on Research and Treatment in Cancer and the Mycoses Study Group.[27]

We defined pneumonia as a new episode of a pulmonary infiltrate accompanied by clinical symptoms (fever, cough, dyspnea, or pleuritic chest pain) requiring hospitalization or appearing during a hospital stay.[28] Hospital-acquired pneumonia was defined according to the CDC criteria[23]: new or increased production of purulent sputum and/or a fever $> 38^{\circ}C$ accompanied by chest signs compatible with lung consolidation and/or new or progressive radiographic evidence of chest infiltrates not attributable to heart failure or other noninfectious processes.[28] Intubated patients included those with a new pulmonary infiltrate (according to chest radiographs) accompanied by a fever $> 38^{\circ}C$, a white blood cell count $> 12 \times 10^9$/L, or purulent tracheal secretions.[28]

TABLE 1. Main Characteristics of the Cohort (n = 84)

Age (years)*	42 (39-45)
Male sex [n (%)]	64 (76)
Caucasian race [n (%)]	82 (98)
HIV risk factors [n (%)]	
Intravenous drug user	63 (75)
Hemophiliac	4 (5)
Heterosexual	10 (12)
Others	7 (8)
HBV coinfection [n (%)]	13 (15)
HCV genotype [n (%)]	
1/4	58 (69)
2/3	19 (23)
Nontypable	7 (8)
Plasma HCV RNA viral load (U/mL)*	466,000 (146,000-1,590,000)
Liver cancer: hepatocellular carcinoma [n (%)]	14 (17)
Child-Turcotte-Pugh class [n (%)]	
A	10 (12)
B	38 (45)
C	35 (42)
Not applicable	1 (1)
MELD score*	15 (11-18)
Previous CDC category C events [n (%)]	18 (21)
Pretransplant cART [n (%)]	
Nucleoside reverse transcriptase inhibitor–based	11 (13)
Protease inhibitor–based	20 (24)
Efavirenz-based	37 (44)
Other combinations	16 (19)
$CD4^+$ T cells*	
Absolute number (cells/μL)	296 (200-420)
%	26 (19-33)
Plasma HIV RNA viral load <200 copies/mL [n (%)]	80 (95)
Time on the OLT waiting list (months)*	4 (2-7)
Type of donor [n (%)]	
Cadaveric	83 (99)
Living donor	1 (1)
Donor risk index*	1.4 (1.17-1.77)
Immunosuppressive therapy at hospital discharge/ 1 month [n (%)]	
Cyclosporine-based	26 (31)
Tacrolimus-based	54 (64)
Other regimens	4 (5)
Therapy for acute rejection episodes [n (%)]	32 (38)
Steroid boluses	13 (41)
Increased baseline immunosuppression	19 (59)
Follow-up	
Time (months)*	24 (15.7-37.9)
Infections [n (%)]	54 (64)
Crude mortality [n (%)]	36 (43)

*The data are presented as medians and interquartile ranges.

TABLE 2. Immunosuppressive Drugs Given Over Time

Time	Steroids	Cyclosporine A	Tacrolimus	Mammalian Target of Rapamycin Inhibitors	Mycophenolate Mofetil
Hospital discharge/ 1 month [n (%)]	84 (100)	30 (36)	54 (64)	0 (0)	29 (35)
3 months [n (%)]	84 (100)	24 (29)	60 (71)	3 (3)	35 (42)
6 months [n (%)]	81 (96)	21 (25)	60 (72)	3 (3)	36 (43)
12 months [n (%)]	64 (76)	18 (21)	62 (74)	4 (5)	43 (51)

NOTE: Thirteen patients (15%) received induction therapy with basiliximab; no patients received daclizumab, antilymphocyte globulins, or alemtuzumab.

TABLE 3. Infection Frequencies, Related Mortality Rates, and Infectious Events in HIV/HCV-Coinfected Liver Transplant Recipients (n = 84)

	Analysis by Patients		
	Patients [n (%)]	Related Mortality [n/N (%)]	Analysis by Episodes (n)
Any infection	54 (64)	7/54 (13)	119
Severe infection	36 (43)	7/36 (19)	62
Bacterial infection	38 (45)	1/38 (3)	73
Bacteremia	8 (9.5)	—	13
Peritonitis	7 (8)	—	9
Sepsis	5 (6)	1/5 (20)	5
Pneumonia	9 (11)	1/9 (11)	15
Fungal infection			
All fungal infections	16 (19)	—	19
Invasive fungal infections	7 (8)	2/7 (29)	7
CMV			
CMV infection	21 (25)	—	21
CMV disease	2 (2)	1/2 (50)	2
Other viral infections			
Uncomplicated herpes simplex infection	13 (15)	—	20
Varicella zoster	1 (1)	—	1
Influenza	2 (2)	—	2
Tuberculosis	2 (2)	1/2 (50)	2

Acute cholangitis was defined according to the criteria proposed by Wada et al.[29] (suggestive clinical symptoms, an inflammatory response, and altered liver function parameters according to blood tests and morphological criteria in radiological examinations).

Systemic inflammatory response syndrome was defined as the presence of 2 of the following: a temperature >38 or <36°C, a heart rate >90 bpm, tachypnea (>20 breaths per minute, hyperventilation, or a partial pressure of carbon dioxide <32 mm Hg), and an altered white cell count (>12,000 or <4000 leukocytes/mm^3 or >10 nonsegmented neutrophils in the differential count). Sepsis was defined as systemic inflammatory response syndrome with an infectious origin. Severe sepsis was defined as infectious systemic inflammatory response syndrome with signs of dysfunction in at least 1 organ. Septic shock was defined as severe sepsis requiring hemodynamic support (fluids and vasoactive drugs).[30,31]

Severe infections were defined as any bacterial infections with the criteria of severe sepsis or septic shock, bloodstream infections, invasive fungal infections,[32] CMV disease,[26] invasive viral infections,[33] and mycobacterial disease.[34]

Posttransplant Prophylaxis

The principal investigator at each site selected the surgical and antifungal prophylaxis according to the protocol. No prophylaxis for herpes simplex virus was administered per protocol after transplantation. In all centers, valganciclovir at a dose of 900 mg/day was used as prophylaxis for 100 days in high-risk liver recipients (donor-positive/recipient-negative). For recipient-positive patients, all centers performed CMV monitoring, and valganciclovir was administered as preemptive therapy at a dose of 900 mg/12 hours if

CMV replication was observed. All patients received prophylaxis with double-strength cotrimoxazole (800/160 mg) 3 times per week during the first year after transplantation. This prophylaxis was stopped after 1 year in patients with a $CD4^+$ T cell count >200 cells/mm^3 for more than 3 months and an undetectable plasma HIV RNA viral load while they were on antiretroviral therapy.[19] The prophylaxis was resumed if the patients did not meet the previous criteria or developed acute rejection.

TABLE 4. Microorganisms Responsible for Posttransplant Bacterial Infections in HIV/HCV-Coinfected Patients (n = 52)

Microorganism	Patients [n (%)]
Gram-positive	
Staphylococcus aureus	6 (12)
Clostridium difficile	5 (10)
Enterococcus faecalis	4 (8)
Coagulase-negative staphylococci	2 (4)
Corynebacterium species	1 (2)
Streptococcus viridans	1 (2)
Streptococcus pneumoniae	1 (2)
Enterococcus faecium	1 (2)
Rothia dentocariosa	1 (2)
Gram-negative	
Escherichia coli	10 (19)
Pseudomonas aeruginosa	7 (13)
Campylobacter jejuni	5 (10)
Acinetobacter baumannii	3 (6)
Stenotrophomonas maltophilia	2 (4)
Proteus mirabilis	1 (2)
Citrobacter freundii	1 (2)
Salmonella species	1 (2)

NOTE: The 52 isolates corresponded to 50 episodes of infection because 3 episodes were polymicrobial (2 isolates).

Statistical Analysis

Categorical variables were expressed as percentages and were compared with the chi-square test or Fisher's exact test if necessary. Continuous variables were expressed as means and standard deviations or as medians and interquartile ranges; this depended on whether their distribution was normal or nonnormal. A Kaplan-Meier survival analysis was used to estimate the effect of any infection or severe infection on mortality. A Cox regression analysis was performed with stepwise backward analysis to find independent variables associated with severe infections. All statistics were considered significant when the 2-tailed *P* value was less than 0.05.

RESULTS

During the study period, we enrolled 84 HIV/HCV-coinfected patients. Table 1 summarizes the main characteristics of the cohort. Most patients had a controlled HIV infection. Eighteen patients (21%) had a history of AIDS-defining events [24 episodes: tuberculosis (11), PCP (5), esophageal candidiasis (5), cerebral toxoplasmosis (2), and grade III intracervical neoplasia (1)]. Eight patients had a latent tuberculosis infection (ie, a positive tuberculin skin test) that was diagnosed any time before or during the pretransplant evaluation. Five patients received treatment with isoniazid, and 1 received treatment with rifampin. Two patients were not treated, and 1 developed pulmonary tuberculosis.

Almost 90% of the patients were classified as Child-Turcotte-Pugh class B or C. HVC genotypes 1 and 4 predominated (69%). The most frequently used cART regimens were based on efavirenz. The median age of the patients was 42 years, 76% were men, and 75% were former drug users. The median follow-up was 24 months (interquartile range 15.7-37.9), and 54 recipients (64%) developed at least 1 infection. The crude mortality was 43% (36 patients died).

TABLE 5. Sources of 73 Episodes of Bacterial Infections in HIV/HCV-Coinfected Liver Transplant Recipients

Source	Early Infections: ≤30 Days (n)	Infections Between Days 31 and 180 (n)	Late Infections: >180 Days (n)	Overall [n (%)]
Respiratory tract	12	1	5	18 (25)
Biliary	2	1	9	12 (16)
Gastritis/enteritis/colitis	2	3	6	11 (15)
Urinary tract infection	1	3	5	9 (12)
Peritonitis	1	1	5	7 (10)
Bacteremia of unknown origin	2	1	2	5 (7)
Catheter-related bacteremia	2	0	1	3 (4)
Surgical wound infection	3	0	0	3 (4)
Intra-abdominal infection	2	0	0	2 (3)
Sinusitis	0	0	2	2 (3)
Perianal abscess	0	0	1	1 (1)

NOTE: The results include microbiologically and clinically diagnosed infections.

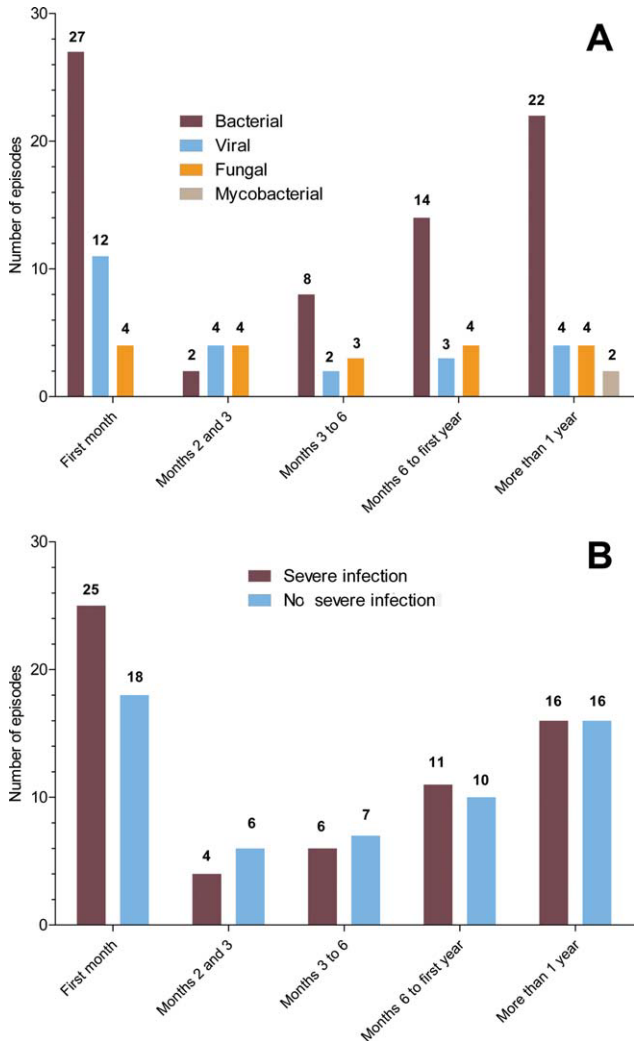

Figure 1. Distribution of infectious episodes during the posttransplant period by (A) the etiology of the infections and (B) the severity of the episodes. Asymptomatic episodes of CMV infections were not included in this analysis.

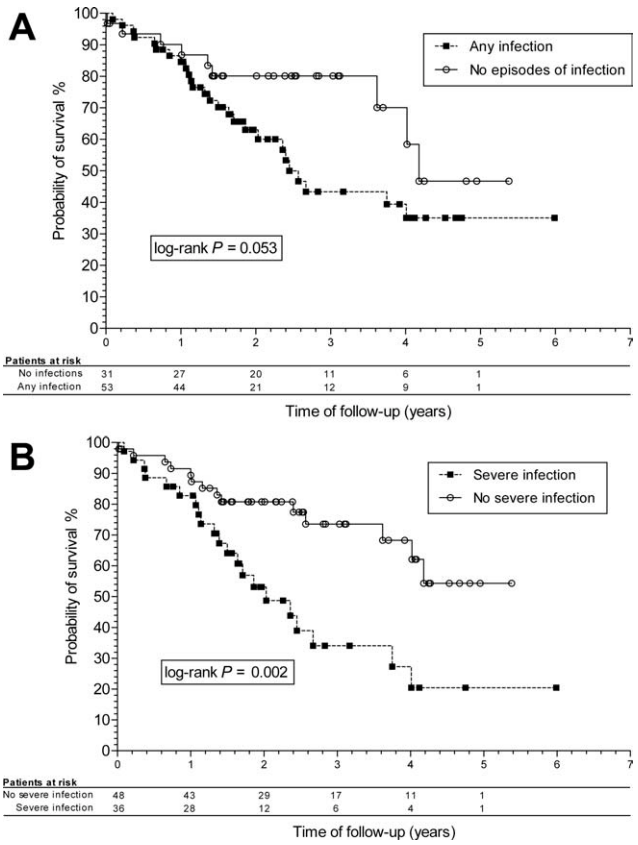

Figure 2. Kaplan-Meier survival analysis of HIV/HCV-coinfected liver transplant recipients according to the occurrence of (A) any infectious episodes and (B) severe infectious episodes.

Variations in the immunosuppression regimens during the posttransplant period are shown in Table 2.

The frequencies and numbers of infectious episodes and the related mortality rates are summarized in Table 3. We recorded 73 episodes of bacterial infections in 38 patients (incidence of bacterial infections = 45%). Fifty of these 73 episodes (68%) had a confirmed microbiological diagnosis of infection (3 were polymicrobial), and 23 had a clinical diagnosis without a bacterial isolate (mainly bacterial pneumonia and cholangitis; Table 4). The sources of the bacterial infections are listed in Table 5.

As for viral infections, 21 patients (25%) had a CMV infection, and 2 developed CMV disease; in 1 of these cases, the infection was disseminated, and the patient died. Most other viral infections were uncomplicated herpes simplex infections (20 episodes in 13 patients), varicella zoster (1 patient), or influenza [2 cases (1 with influenza A and 1 with influenza B)].

There were 19 fungal infections in 16 patients (19%), and 7 were invasive [2 episodes of zygomycosis (1 involved the surgical wound, and 1 was rhinocerebral), 1 episode of invasive pulmonary aspergillosis, 2 episodes of candidemia, 1 episode of *Candida* cholangitis, and 1 episode of PCP]. Two patients died from fungal infections.

Two patients had tuberculosis 1 year after transplantation. One of the patients beyond had tuberculosis disease several years before transplantation, and another had a positive tuberculin skin test but did not receive treatment for his latent tuberculosis infection. One of these patients died of disseminated disease.

Thirty-six patients (43%) had severe infections, and 7 (19%) died.

Thirty patients (36%) had at least 1 infection within the first month after OLT, 14 patients (17%) had an infection between the first and sixth months, and 10 patients (12%) had an infection after the sixth month (ie, a late infection). Figure 1 shows the distribution of infections after transplantation according to the etiology of the infections and the severity or lack of severity of the episodes. Asymptomatic CMV infectious episodes were not included in the analysis.

Thirty-six patients (43%) died, and the deaths were infection-related in 7 cases (19%). There was a trend

TABLE 6. Cox Regression Analysis of Factors Associated With Severe Infections in HIV/HCV-Coinfected Liver Recipients in the Posttransplant Period

	No Severe Infections (n = 48)	Severe Infections (n = 36)	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Patient age (years)*	42.3 ± 5.4	42.9 ± 5.6	1.01 (0.95-1.07)	0.46	—	—
Donor age (years)*	54.8 ± 21.4	54.0 ± 19.9	1.00 (0.98-1.01)	0.85	—	—
Donor risk index*	1.4 ± 0.3	1.5 ± 0.33	1.94 (0.65-5.82)	0.20	—	—
Recipient sex: male [n (%)]	34 (71)	30 (83)	1.7 (0.5-5.5)	0.31	—	—
Pretransplant MELD score > 15 [n (%)]	15 (31)	19 (53)	2.4 (1.2-4.6)	0.047	3.5 (1.7-7.1)	0.001
Nadir $CD4^+$ T cell count (cells/μL)*	201 ± 137	244 ± 217	1.00 (0.99-1.01)	0.36	—	—
Baseline detectable HIV viral load [n (%)]	4 (8)	7 (19)	2.66 (0.8-9.1)	0.25	—	—
Baseline $CD4^+$ T cell count < 300 cells/mm^3 [n (%)]	21 (44)	18 (50)	1.2 (0.6-2.2)	0.52	—	—
History of category C AIDS-defining events [n (%)]	5 (10)	13 (36)	3.0 (1.5-6.1)	0.005	4.0 (1.9-8.6)	<0.001
Packs of blood or derivatives transfused during surgery*	12.5 ± 9.3	13.2 ± 12.3	1.00 (0.98-1.04)	0.41	—	—
Induction therapy [n (%)]†	7 (15)	6 (17)	0.97 (0.4-2.3)	0.79	—	—
Non–tacrolimus-based immunosuppression [n (%)]	12 (25)	18 (50)	2.0 (1.06-4.00)	0.03	2.5 (1.3-4.8)	0.006
Mycophenolate mofetil [n (%)]‡	23 (48)	21 (58)	1.3 (0.7-2.5)	0.48	—	—
Posttransplant surgical complications [n (%)]	17 (35)	16 (44)	1.4 (0.7-2.7)	0.34	—	—
Acute rejection [n (%)]	17 (35)	15 (42)	0.8 (0.11-6.1)	0.29	—	—
Steroid boluses for acute rejection [n (%)]	6 (13)	7 (19)	1.8 (0.2-14.9)	0.38	—	—

*The data are presented as means and standard deviations.
†With polyclonal anti-lymphocyte antibodies or anti-CD25 antibodies.
‡During the first 3 months after transplantation.

toward higher mortality in patients who had at least 1 infectious episode (Fig. 2A). The occurrence of a severe infection increased the mortality rate almost 3-fold [hazard ratio (HR) = 2.9, 95% confidence interval (CI) = 1.5-5.8, $P = 0.002$; Fig. 2B].

A Cox regression analysis of predictive factors associated with the development of severe infections showed that a pretransplant MELD score >15 (HR = 3.50, 95% CI = 1.70-7.10), a history of AIDS-defining events before transplantation (HR = 2.5, 95% CI = 1.5-5.1), and non–tacrolimus-based immunosuppression (HR = 2.5, 95% CI = 1.3-4.8) were independent predictors of severe infections (Table 6). The effects of the MELD score, a history of AIDS-defining events, and the type of immunosuppression at the time of severe infections are shown in Figure 3.

Table 7 summarizes the characteristics of the patients who developed opportunistic infections after transplantation (10 episodes in 9 patients; incidence = 11%). The opportunistic infections included 2 episodes of zygomycosis, 1 episode of invasive aspergillosis, 2 episodes of CMV disease, 2 episodes of esophageal candidiasis (both in the same patient), 2 episodes of tuberculosis, and 1 episode of PCP (with the onset 6 days after transplantation). A $CD4^+$ T cell count less than 200 cells/μL was recorded for 33% of the patients (3/9). Five patients (56%) developed late opportunistic infections (6 months after transplantation). The incidence rate of tuberculosis in our cohort was 3140 cases per 100,000 patients per year. Opportunistic infections led to death for 44% of our patients (4 deaths in 9 patients), and the mortality rate was higher for those opportunistic infections occurring in the late post-transplant period (more than 6 months after transplantation, 3 deaths out of 5 episodes of late opportunistic infection [60%] versus 1 death out of 5 episodes of early opportunistic infection [20%]).

DISCUSSION

Our data show that posttransplant infections are a major cause of morbidity after transplantation in HIV1-infected liver recipients and that the incidence and etiologies in the early posttransplant period are

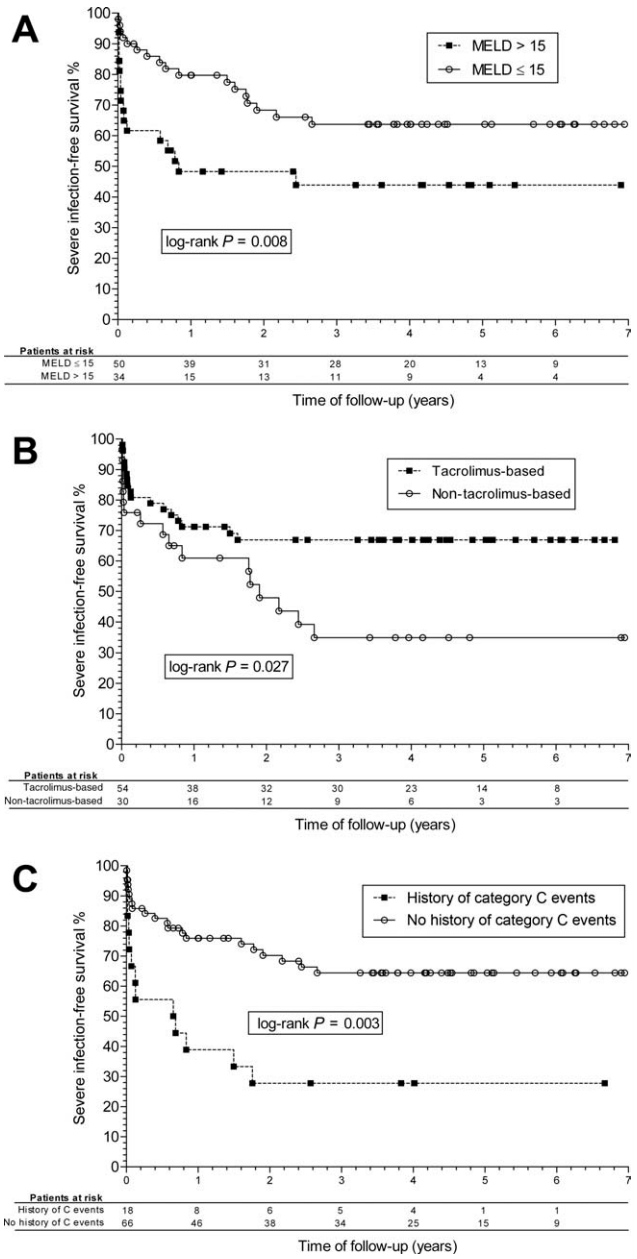

Figure 3. Kaplan-Meier survival analysis of the incidence of severe infections according to (A) the preoperative MELD score, (B) tacrolimus-based immunosuppression, and (C) a history of AIDS-defining events before transplantation.

similar to those reported for HIV-negative liver recipients.[8]

Bacteria were the principal etiological agents of the posttransplant infections. Forty-five percent of the patients developed a bacterial infection during follow-up, and 9.5% had bacteremia. These rates are similar to those published for HIV-negative liver recipients in Spain (incidence of bloodstream infections = 10.4%).[35] Notably, the incidence of bacterial infections decreases during the posttransplant period for HIV-negative recipients, whereas in our cohort of HIV-infected recipients, the rate of bacterial infections increased progressively 3 months after transplantation. In our study, the incidence of incisional surgical site infections was 2.3%, which is similar to the rate observed in the HIV-negative population. In a multicenter study of 1222 liver recipients in Spain, the risk of incisional surgical site infections was 4.3%.[36] However, the incidence of intra-abdominal infections (2%) was slightly lower than that in HIV-negative recipients (8%). Most cases of early bacterial infections were secondary to surgery (surgical wound infections or secondary peritonitis) or invasive procedures (central venous catheter insertion) or were urinary tract infections. Biliary bacterial infections were more prevalent in the late period, probably because of late biliary strictures due to ischemic cholangiopathy. Most infections that occurred more than 180 days after transplantation were community-acquired.

Most viral infections in this cohort were uncomplicated non-CMV herpes simplex infections. Although evidence of herpes simplex reactivation in HIV-negative recipients is scarce, up to 42% of the patients in a small study showed evidence of oral reactivation after transplantation.[37] Nonetheless, the reactivation of herpes simplex infections in HIV1-infected liver recipients did not produce severe manifestations, and the patients' recovery was uneventful. Interestingly, 2 patients developed influenza some time after transplantation. An annual influenza vaccination should be a goal for liver transplant recipients in general and for HIV1-infected liver transplant recipients in particular because it is the best way of protecting them against influenza.[38]

With CMV disease, disseminated herpes simplex infections, invasive fungal infections, and tuberculosis considered to be opportunistic events, approximately 11% of the HIV-infected liver recipients developed an opportunistic infection, and 50% of these infections were late (occurring more than 6 months after transplantation). Four patients with opportunistic infections had a $CD4^+$ T cell count below 200 cells/μL, and in all 4 patients, the plasma HIV1 RNA viral load was undetectable at the time of infection; this leads us to believe that the opportunistic infections occurred not because of uncontrolled HIV infections but rather because of complications during the transplant process. A large study of HIV-negative solid organ recipients in Spain revealed a 6% incidence of opportunistic infections.[39] In addition, organ transplant recipients receiving alemtuzumab, a humanized monoclonal anti-CD52 antibody that induces profound and sustained lymphocyte depletion, have been reported to develop opportunistic infections at a rate of 10%.[40,41]

One of the most important concerns about liver transplantation in the HIV-infected population is the possibility of the development of opportunistic infections as a result of either uncontrolled HIV infections after transplantation or therapy with immunosuppressive agents. Approximately 11% of our patients developed an opportunistic infection; this percentage is similar to that reported for solid organ recipients treated with alemtuzumab.[41] Thus, HIV-infected patients undergoing liver transplantation should be

TABLE 7. Characteristics of Episodes of Opportunistic Infections in HIV/HCV-Coinfected Liver Transplant Recipients

Patient Number	Opportunistic Disease	Age (Years)/ Sex	$CD4^+$ T Cells [cells/μL (%)]/Viral Load		History of Category C AIDS-Defining Events	Posttransplant Time	Location	Active Prophylaxis	Outcome	Comments
			Before Transplantation	At the Time of Infection						
502	CMV disease	49/male	118 (26)/BDL	182 (28)/BDL	Tuberculosis and esophageal candidiasis	18 months	Disseminated	Acyclovir	Death	CMV^+ before transplantation
708	CMV disease	48/male	60 (7)/BDL	36 (unknown)/BDL	Tuberculosis	46 days	Liver	None	Cured	CMV^+ before transplantation
601	*P. jiroveci*	47/male	240 (13)/BDL	240 (13)/BDL	Tuberculosis	6 days	Pulmonary	None	Cured	
1309	*Aspergillus* species	39/male	1152 (21)/BDL	777 (26)/BDL	No	4 months	Pulmonary	Fluconazole	Death	Lactic acidosis and bacterial coinfections*
301	Candidiasis	39/male	290 (40)/BDL	138 (23)/BDL	No	4 months	Esophagus	None	Cured	
301	Candidiasis	39/male	290 (40)/BDL	72 (24)/BDL		8 months	Esophagus	None	Cured	
705	Zygomycosis	48/male	216 (unknown)/BDL	216 (unknown)/BDL	Tuberculosis, esophageal candidiasis, and PCP	14 days	Surgical wound	None	Cured	
1202	Zygomycosis	39/male	360 (29)/BDL	288 (34)/BDL	No	18 months	Rhinocerebral	None	Death	
501	Tuberculosis	42/male	363 (36)/BDL	206 (40)/BDL	Tuberculosis	21 months	Miliary	None	Death	
1605	Tuberculosis	45/male	351 (27)/BDL	235 (39)/BDL	No	23 months	Pulmonary	None	Cured	Pretransplant tuberculin skin test and no prophylaxis

NOTE: Episodes of candidemia were not included because they were considered not opportunistic fungal infections but rather nosocomial complications of the transplant procedure. BDL viral loads were less than 200 copies/mL.
*Bloodstream infection by multidrug-resistant *A. baumannii* and spontaneous bacterial peritonitis by *E. coli*.

carefully evaluated for adequate prophylaxis and closely monitored, especially when other risk factors appear in the posttransplant period.

Fungal infections occurred in 17% of the patients, and 7 of the infections were invasive. Previously published results for the incidence of fungal infections in HIV-infected liver transplant recipients are controversial, mainly because of the small sample sizes. Although a small study by Norris et al.[5] did not reveal any invasive fungal infections in a cohort of 14 HIV-infected liver recipients (7 were HIV/HCV-coinfected), Ragni et al.[3] found an 8% incidence of invasive fungal infections in the late period among 24 HIV1-infected liver recipients. In a large multicenter study in the United States (4468 subjects), the 12-month cumulative incidence of invasive fungal infections in HIV-negative liver transplant recipients was 4.7%.[42] However, in one series including HIV-negative patients who were treated with etanercept because of corticosteroid-resistant acute graft-versus-host disease, the rate of invasive aspergillosis was 19%.[43] Although comparative studies of HIV-infected and HIV-negative liver transplant recipients are necessary, the incidence of invasive fungal infections in this population represents a threat, and these infections should be carefully prevented.

In Spain, the incidence and incidence rate of tuberculosis after liver transplantation in HIV-negative patients have been reported to be 0.53% and 541 cases per 100,000 transplants per year.[44] In this study, the incidence and incidence rate of tuberculosis were 2.4% and 3140 cases per 100,000 transplants per year, respectively (more than 4- and 5-fold higher than those for HIV-negative patients). In Spain, the incidence rate of tuberculosis in the general population is 18.9 cases per 100,000 persons per year.[44] Thus, the incidence rate of tuberculosis in HIV/HCV-coinfected liver transplant recipients is 166-fold higher than that reported in the general population. Other cohort studies of HIV/HCV-coinfected liver transplant recipients have not recorded any cases of tuberculosis.[5] This may be due to the small sample size analyzed on the one hand and to the lower prevalence of tuberculosis in the United Kingdom and elsewhere on the other hand. Hence, it is important to follow current recommendations for the diagnosis (the most sensitive interferon-γ release assays) and prevention of latent tuberculosis infections in solid organ recipients,[24] especially in areas such as Spain with a medium or high incidence of tuberculosis.

Severe infections, which are frequent in HIV/HCV-coinfected patients after liver transplantation (36 of 84 patients with an incidence of 43%), increased the risk of death almost 3-fold. De Vera et al.[9] showed that 22% of HIV-infected liver recipients died because of severe infections after transplantation. For HCV-monoinfected liver transplant recipients, the rate of mortality by sepsis was 15%, whereas it was 6.5% for HIV-negative recipients.[45] In our cohort, we investigated potential predictors of severe infections after transplantation and found that the highest risk belonged to patients with a higher MELD score or CDC category C events before transplantation. The latter finding is important because it identifies a subset of patients with a high risk of dying from severe infections. An opportunistic infection before transplantation is not an exclusion criterion if the infection can be prevented or treated.[14] In addition, an effective antiretroviral treatment has a protective effect. However, if this finding is confirmed in larger studies, an AIDS-defining opportunistic infection before transplantation could become an exclusion criterion. On the other hand, $CD4^+$ T cell counts and plasma HIV1 RNA viral loads in the pretransplant period were not associated with a higher risk of severe infections after transplantation. As for the MELD score, patients with more than 15 points at the time of transplantation had a 3.5-fold greater risk of severe infections. This is concordant with findings in non–HIV-infected individuals.[46,47] Finally, we do not have a clear explanation for the lower risk of infection in patients treated with tacrolimus-based immunosuppression, although some studies in HIV-negative liver recipients have shown that tacrolimus-based immunosuppression is associated with a lower risk of posttransplant infections than cyclosporine-based regimens.[48]

Our study has 2 main limitations. First, although it is one of the largest series of HIV/HCV-coinfected liver recipients, the number of patients does not allow us to generalize the results. Second, the lack of a control group of HIV-negative patients stops us from comparing the rates of infections between the 2 populations.

In conclusion, HIV/HCV-coinfected liver recipients have a high rate of severe and opportunistic infections. These patients should be closely monitored and receive adequate prophylaxis, especially if they have AIDS-defining opportunistic infections before transplantation and/or a high MELD score. Comparative studies with the HIV-negative population are warranted.

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APPENDIX

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