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Poster H-124: 5-year Survival of HCV-HIV Coinfected Liver Transplant Recipients (OLT): A Case-Control Study

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Background: Recurrent HCV after OLT is a major cause of graft loss and death. Preliminary studies performed in single centers with smaller numbers of patients suggest poorer survival in HCV-HIV coinfected than in monoinfected patients. This study determined 5-year survival in Spanish HCV-HIV coinfected and HCV monoinfected OLT recipients.
Methods: 81 consecutive HCV-HIV coinfected patients who underwent OLT between 2002-2006 and were followed until December 2007 were included in the study. Data were obtained from the FIPSE OLT-HIV-05-GESIDA 45-05 database. HIV-infected recipients were matched with 243 HCV-monoinfected patients (1:3 ratio) who underwent OLT during the same period in the 17 Spanish institutions that performed OLT in HIV-infected patients. Other matched criteria were age (12 years), gender, calendar year (1 year), same site, HBV coinfection, and presence of hepatocellular carcinoma. Data for HIV-negative recipients were obtained from the Spanish Liver Transplant Registry. Differences in continuous variables between the groups were analyzed using Wilcoxon's signed-rank test. Time to graft survival and death was estimated with the KaplanMeier method. The equality of the distributions of the times to an event among the groups was estimated using the generalized log-rank test.
Results: 29 (35.8%) HCV-HIV coinfected and 51 (20.9%) HCV monoinfected patients died during a median 2.6 (IRQ: 1.25-3.53) years of follow-up. Median age was 42 and 46 years, respectively. Male gender, HBV coinfection and HCC were present in 78%, 16%, and 8% in each group. Four (5%) and 12 (5%) patients needed retransplantation, respectively. Survival (95% confidence intervals) rates at 1, 2, 3, 4 and 5 years for HCV-HIV coinfected and HCV monoinfected patients were 87.5% (78-93) vs. 89.1% (84.4- 92.4), 70.8% (59-79.8) vs. 75.9% (75.8- 86.2), 61.8% (48.3-72.7) vs. 77.4% (71- 82.3), 58.3% (43.9-70.3) vs. 76.2% (70- 81.9), and 47.9% (30-63.7) vs. 75.1 % (67.8- 80.9), respectively ($p<0.01$). Graft survival rates at 1, 3, and 5 years for HCV-HIV coinfected and HCV monoinfected patients were 77% (66-85) vs. 85% (81- 90), 52% (36-66) vs. 76 % (70- 81), and 37% (20-55) vs. 67 % (58 - 75), respectively ($p<0.01$).
Conclusions: Short-term patient and graft survival in HCV-HIV OLT coinfected patients was similar to that of HCV monoinfected OLT recipients. However, mid-long-term survival was poorer in HCV-HIV coinfected patients.

BACKGROUND

Preliminary studies performed in single centers with small number of patients with OLT suggest poorer survival in HCV-HIV coinfected than in HCV monoinfected patients.

Prognostic factors of mortality are not well known.

OBJECTIVE

To study the 5-year survival in Spanish HCV-HIV coinfected and HCV monoinfected OLT recipients and to know the prognostic factors of mortality in HCV-HIV-coinfected OLT recipients.

PATIENTS & METHODS

- Prospective study of the first 84 HCV/HIV-1-infected patients who underwent OLT in Spain (2002-06).
- Variables analyzed:
  - Pre-OLT recipient variables: HIV (stage, CD4 cell count, plasma HIV-1 RNA viral load, cART regimens) & liver disease (MELD, Child, plasma HCV RNA viral load)
  - Donor and operative variables
  - Post-OLT variables: immunosuppression, rejection, infection, toxicity & the same HIV variables described above).
- HIV-infected recipients were administered the same immunosuppression & prophylaxis as HIV-negative patients.

ACCEPTANCE CRITERIA FOR OLT*

- **Liver criteria**: the same as for the non-HIV-infected population.
- **HIV criteria:**

  1) Clinical: no previous C events (CDC, 1993) except some OIs (TB, Can, PCP); and,

  2) Immunological: pre-OLT CD4 cell count >100 cells/mm3 for OLT; and,

  3) Virological: RNA HIV-1 viral load BDL on cART or, if detectable, post-SOT suppression predicted.
- **Drug abuse criteria**: A) No heroin or cocaine abuse for >2 years; B) No alcohol abuse for >6 months.

* Miró JM et al. Enferm Infecc Microbiol Clin. 2005; 23:353-362.

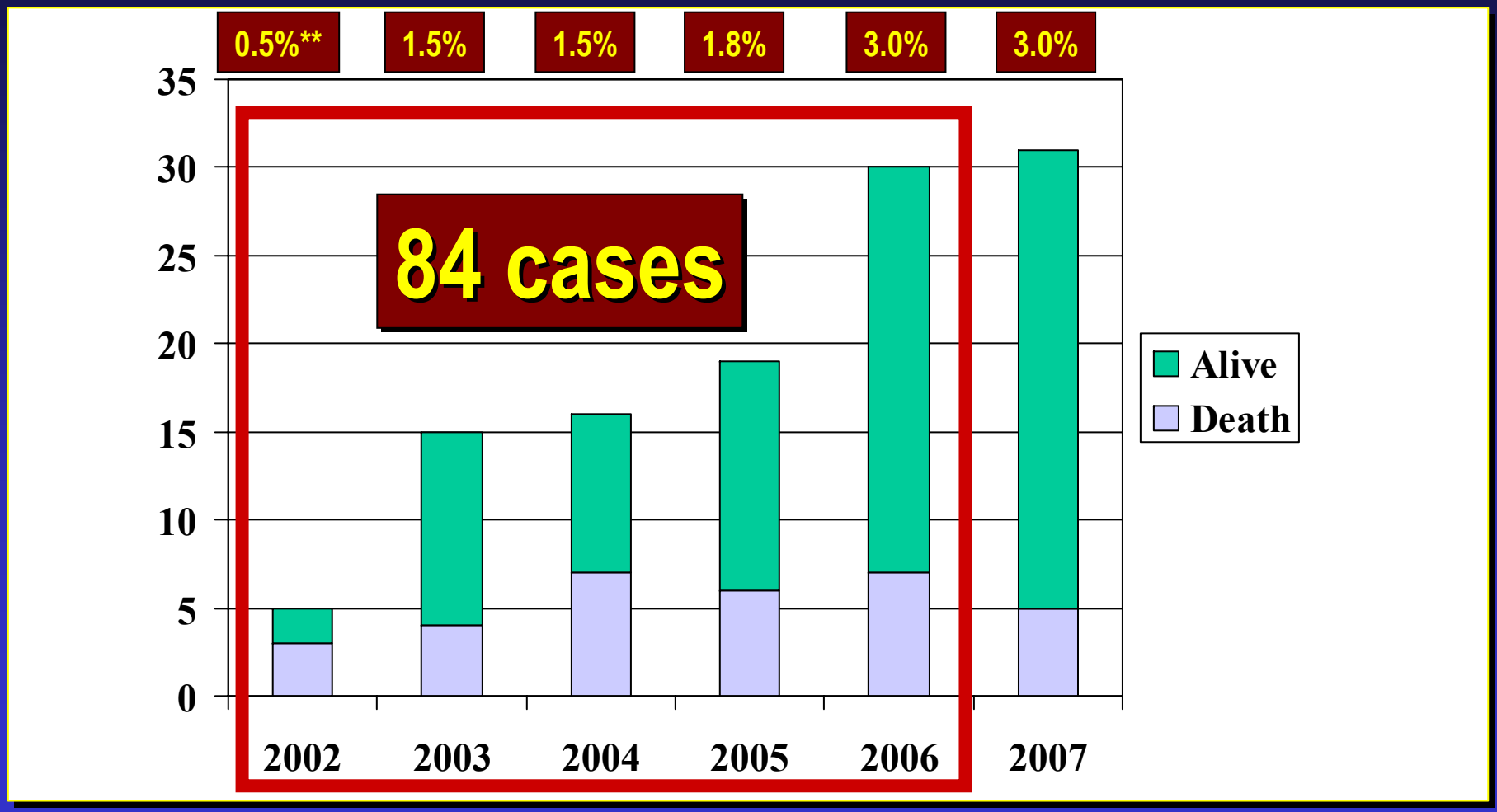
CASES & CONTROLS (1:3 ratio)

- **Cases (HCV+HIV coinfected patients)**
  - **84 consecutive HCV-HIV coinfected** patients with OLT between 2002-2006 and followed until 2007.
  - Data were obtained from the FIPSE OLT-HIV-05-GESIDA 45-05 database.
- **Controls (HCV monoinfected patients)**
  - HIV-infected recipients were matched with **252 HCV-monoinfected** patients who underwent OLT.
  - Matched criteria: same site, age (±12 years), gender, calendar year (±1 year), HBV coinfection and presence of hepatocellular carcinoma.
  - Data for HIV-negative recipients were obtained from the SETH database.

STATISTICAL ANALYSIS

- Continuous variables were assessed using the *t* test for normally distributed data or the Mann-Whitney U test otherwise, and the Fisher exact test for categorical data.
- The Cox model was used to analyze the time to death, and all covariates with a $P<0.10$ on univariate analysis were used to identify independent predictors of mortality.
- Patient survival analysis was performed using the Kaplan-Meier method and groups were compared using the log-rank test and Cox regression analysis.
- The analysis was performed using SAS version 9.1.3 software (SAS Institute, Cary, NC, USA) and the level of significance was established at 0.05 (two-sided).

OLT in Spanish HIV-infected patients in the HAART era (2002-07) (N=116*)



*4 patients had retransplantation; ** OLT in HIV-infected recipients/OLT in general population ratio.

Main Characteristics & Outcome

	HIV+HCV N=84	HCV N=252
Male gender	78%	78%
Age (years)*	42	46
HBV coinfection	16%	16%
HCC**	8%	8%
Follow-up (yrs)*	2.6	1.9
Retransplantation	**4 (5%)**	**12 (5%)**
Death	**30 (36%)**	**50 (20%)**

* Median; ** Hepatocellular carcinoma.

Causes of Death in HIV+ and HIV- recipients

	HIV+HCV N=30	HCV N=50
Infections	6* (20%)	9 (18%)
HCV recurrence	14* (47%)	21 (42%)
Cancer	2 (7%)	2 (4%)
Technical complications	0 (-)	4 (8%)
Others	10 (33%)	14 (28%)

* Two patients had a HCV recurrence and an infection as cause of death.

Causes of death in HIV+ recipients

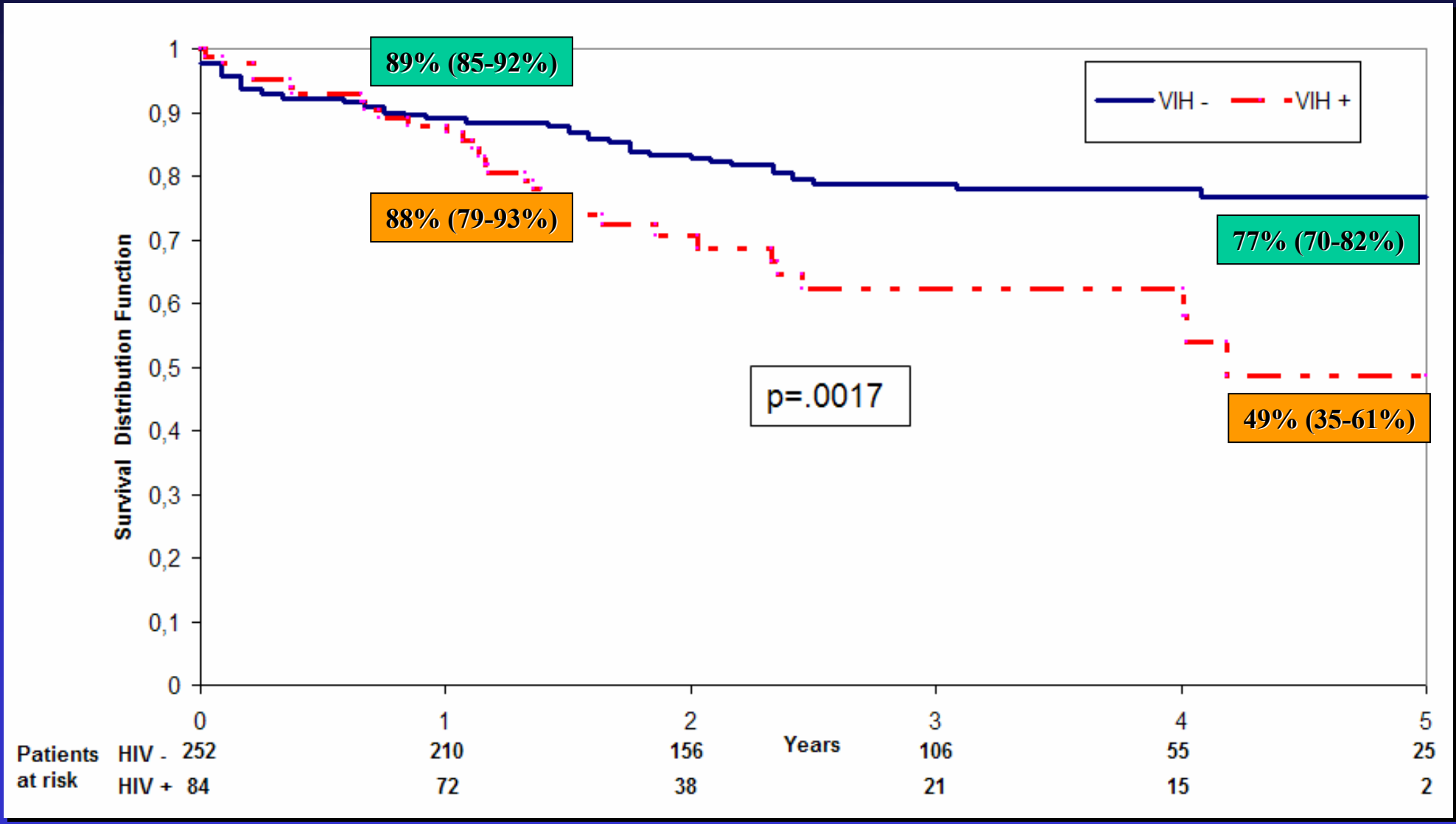
Early mortality (<12 mo.)	**10 (33%)**
- Post-op. complications*	4
- Severe cholestatic HCV hepatitis	4
- Other**	2
Late mortality (>12 mo.)	**20 (67%)**
- Graft ELSD – HCV reinfection	11
- Chronic rejection	2
- Other***	9

* MOF (1) Hepatic artery thrombosis (1), Pneumonia (1), Chronic rejection (1); ** Massive variceal bleeding and lactic acidosis 1 case each; *** Infections (3), Cancer (2), Hepatic artery thrombosis (2), MOF (1), Colangitis (1).

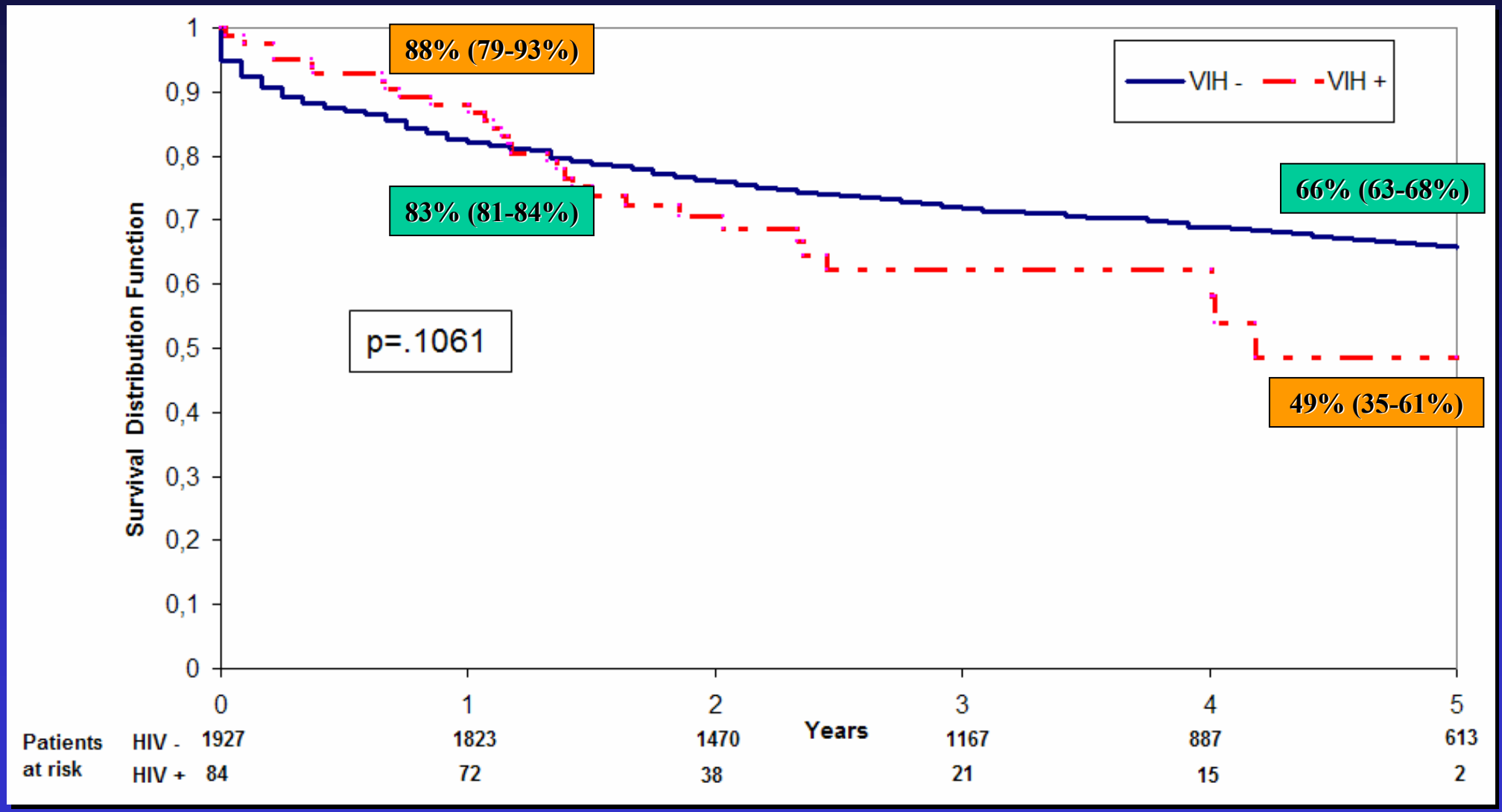
Five-year patient survival of OLT in HCV/HIV-coinfected recipients was lower than of HCV-monoinfected matched patients

Survival at:	HIV + Recipients N=84	HIV - Recipients N=252	p
1 year	88%	89%	NS
3 years	62%	78%	<0.01
5 years	49%	77%	<0.01

Case (N=84) - Control (N=252) study: Patient survival after OLT in HCV-infected patients according to HIV status



HIV+ (N=84) *vs.* HIV- (N=1,927) patient survival after OLT in HCV-infected patients according to HIV status



Five-year graft survival of OLT in HCV/HIV-coinfected recipients was lower than of HCV-monoinfected patients

Survival at:	HIV + Recipients N=84	HIV - Recipients N=252	p
1 year	77%	86%	NS
3 years	52%	76%	<0.01
5 years	37%	67%	<0.01

Univariate Analysis of Mortality: Pre-OLT variables (p<0.10)

Variable	HR (95%CI)	*P* value
HCV Genotype		
- 2, 3 or 4	1	
- 1	2.44 (1.09; 5.47)	.03
Plasma HCV RNA viral load		
- Below median (< 400.000)	1	
- Above median (≥ 400.000)	1.98 (0.95; 4.15)	.07
HBV coinfection		
- No	1	
- Yes	0.16 (0.02;1.15)	.07
MELD score		
- WL (1 unit increase)	1.08 (1.02;1.15)	.01
- Pre-OLT (same)	1.07 (1.02;1.13)	.001

Univariate Analysis of Mortality
Donor and operative variables (p<0.10)

Variable	HR (95%CI)	*P* value
Donor age		
- < 60 years	1	
- ≥ 60 years	1.94 (0.94;3.98)	.07
Cause of donor brain death:		
- Cranial traumatism	1	
- Other	4.17 (1.22;14.3)	.02
RBC transfusion		
- ≤ 3 Units	1	
- > 3 Units	3.51 (1.60;7.69)	.001

Univariate Analysis of Mortality
Post-OLT variables (p<0.10)

Variable	HR (95%CI)	*P* value
Negative HCV RNA VL*		
- No	1	
- Yes	0.16 (0.02;1.16)	.07
Peak HCV RNA after OLT**		
- 1 $\log_{10}$ VL increase	1.57 (0.97;2.55)	.07
Chronic rejection		
- No	1	
- Yes	3.44 (0.80;15)	.09
Invasive Fungal infection		
- No	1	
- Yes	4.24 (1.43;12)	.009

* SVR pre-OLT or post-OLT; ** During the first 6 months after OLT.

Multivariate Analysis of Mortality (model I) Only Pre-OLT variables

Variable	HR (95%CI)	*P* value
MELD		
- WL (1 unit increase)	1.08 (1.02;1.15)	.012

Pre-OLT variables ($p<0.10$)

Multivariate Analysis of Mortality (model II) All variables

Variable	HR (95%CI)	*P* value
HCV Genotype		
- 2, 3 or 4	1	
- 1	2.53 (1.12; 5.70)	.025
Cause of donor brain death		
- Craneal traumatism	1	
- Other	3.51 (1.05; 11.8)	.041
RBC Transfusion		
- ≤ 3 units	1	
- > 3 units	3.25 (1.47;7.19)	.004
Invasive fungal Infection		
- No	1	
- Yes	5.60 (1.83;17.1)	.002

Pre-OLT + Donor and perioperative + Post-OLT variables ($p<0.10$)

CONCLUSIONS

- OLT is a safe and effective short-term (1 year) procedure in HCV-HIV-coinfected recipients. However, graft and patient survival at 5 years was lower than the matched HCV monoinfected patients.

- When a multivariate analysis was performed taking into account pre-OLT, donor, operative and post-OLT variables, factors associated with mortality risk were: HCV Genotype 1, non-traumatic cause of donor brain death, operative high blood transfusion requirements and invasive fungal infection.

CONCLUSIONS (II)

- When a multivariate analysis was performed taking into account only pre-OLT variables, a high MELD score at the time of listing for OLT was the only variable associated with death.

- A better recipient and donor selection and effective anti-HCV therapies could improve the long term outcome of HCV OLT in HIV-infected recipients.

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Our patients.