HIV e trapianto di fegato

G. Verucchi

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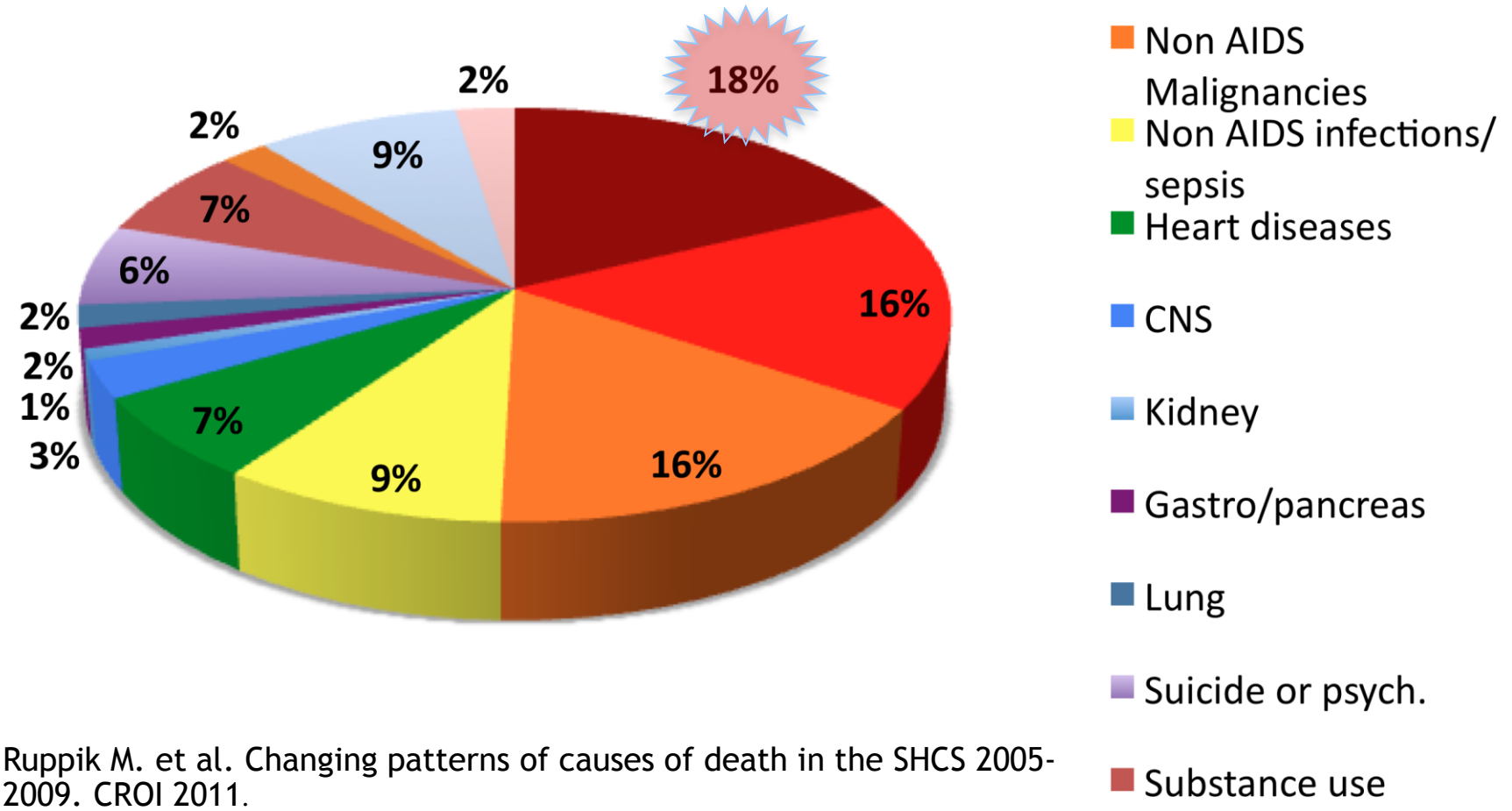
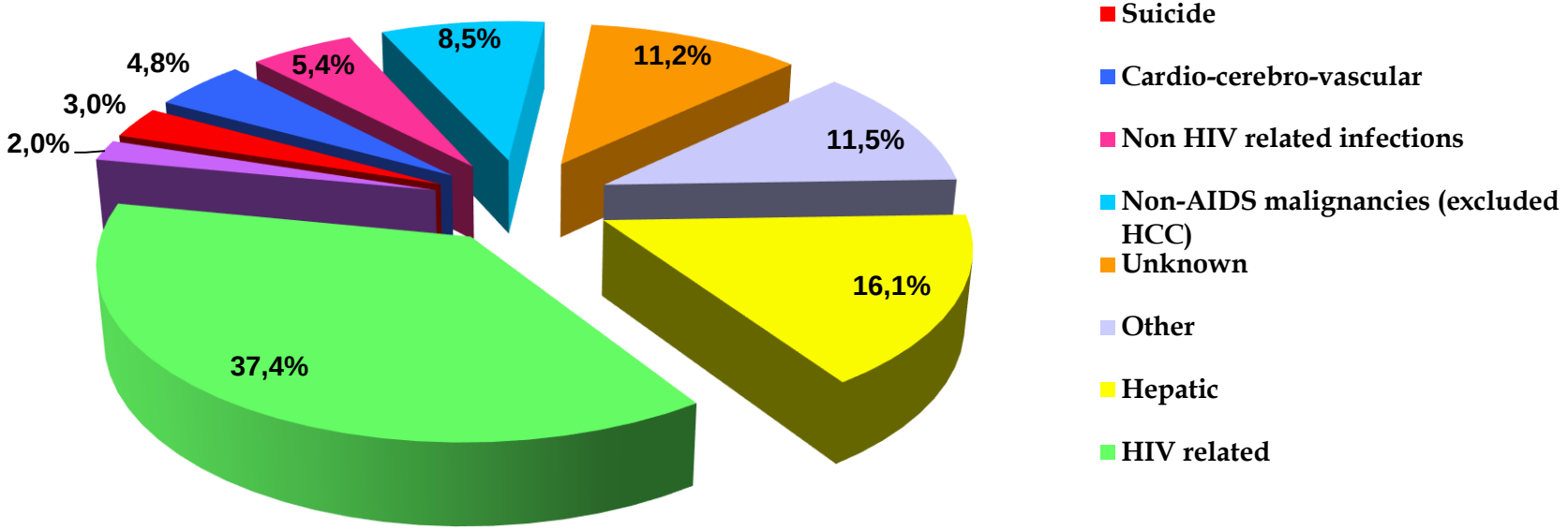
Causes of death in the Swiss HIV Cohort study 459 deaths between 2005 and 2009



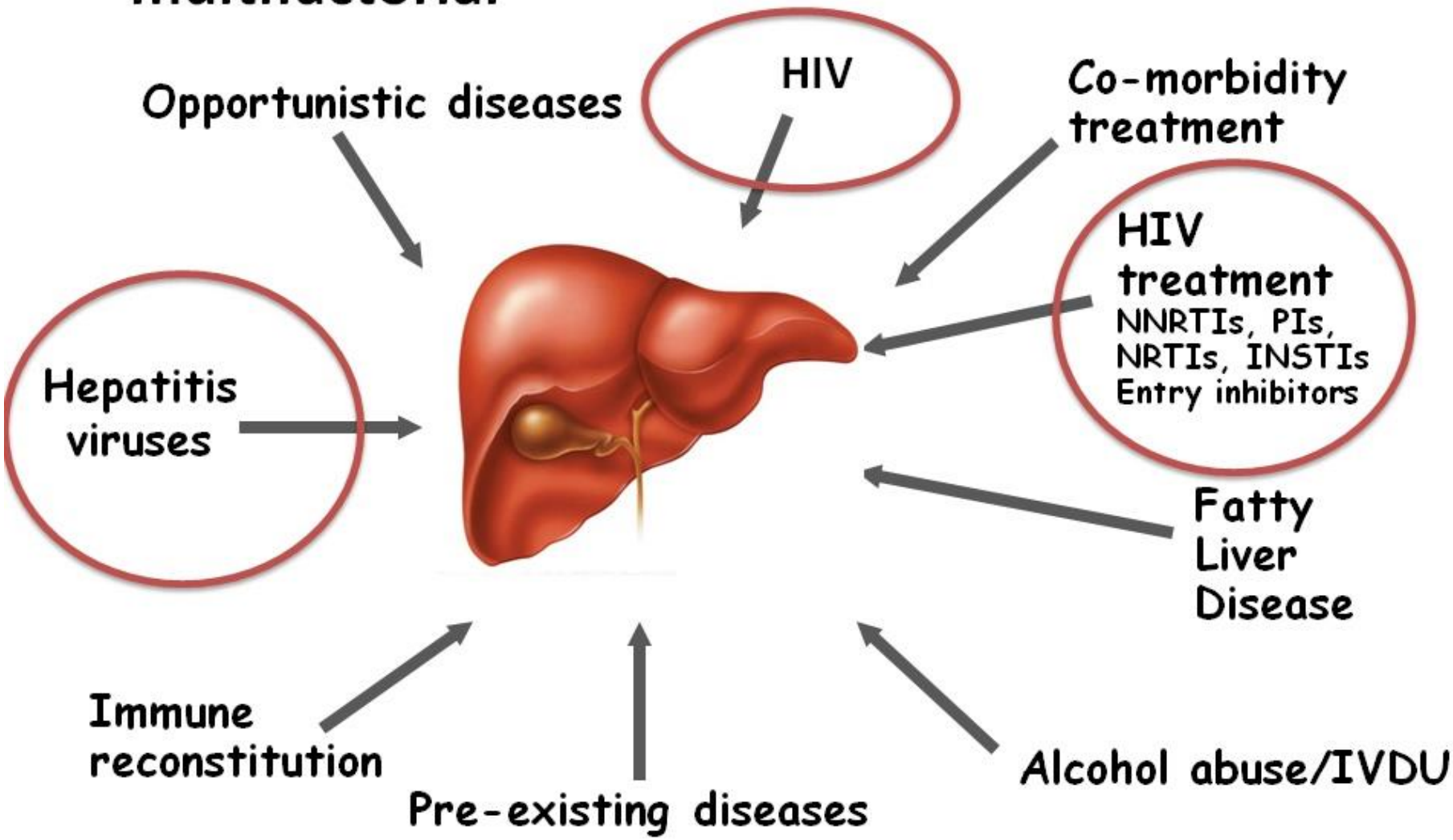
Ruppik M. et al. Changing patterns of causes of death in the SHCS 2005-2009. CROI 2011.

Cause of death, n=868



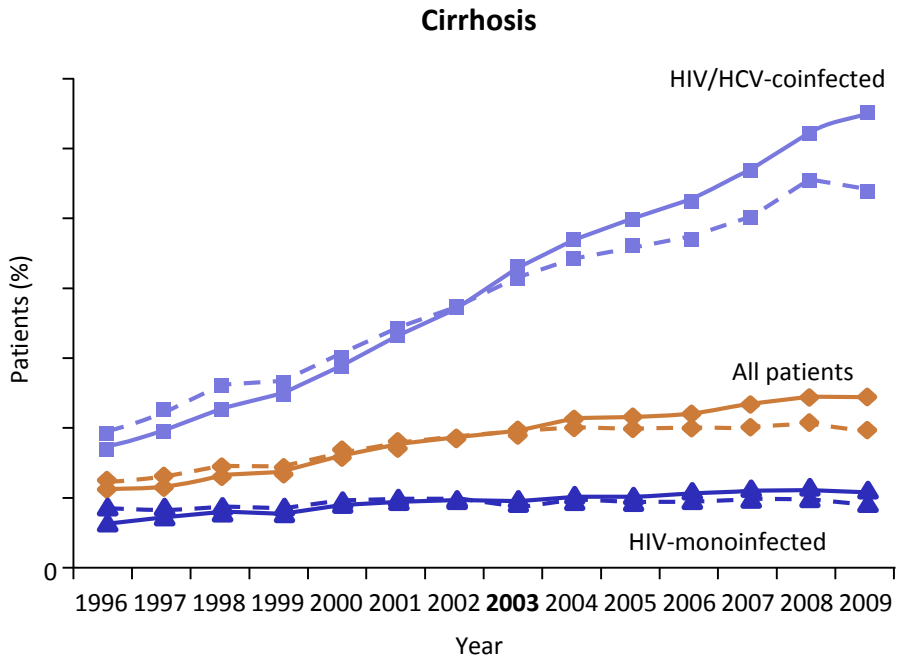
June 2017 Report

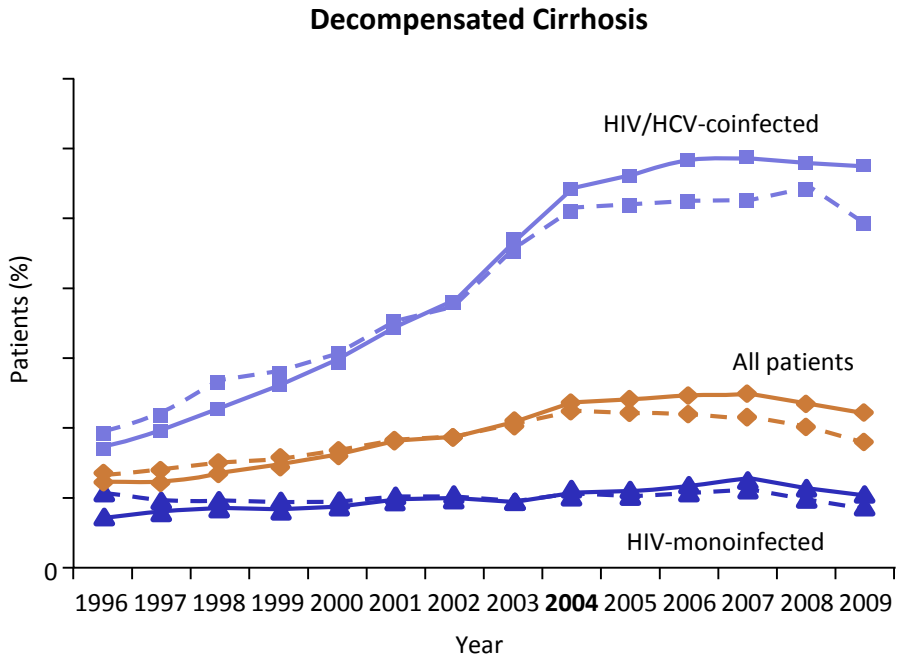
Liver Disease in HIV-infected Patients - multifactorial



Sulkowski M. *et al.* Ann Intern Med. 2003;138:197-207 Guaraldi G *et al* Clin Infect Dis 2008 47(2): 250-257
Greub G *et al.* Lancet 2000;356:1800-1805

Increasing prevalence of cirrhosis and decompensated cirrhosis in HIV/HCV-coinfected veterans

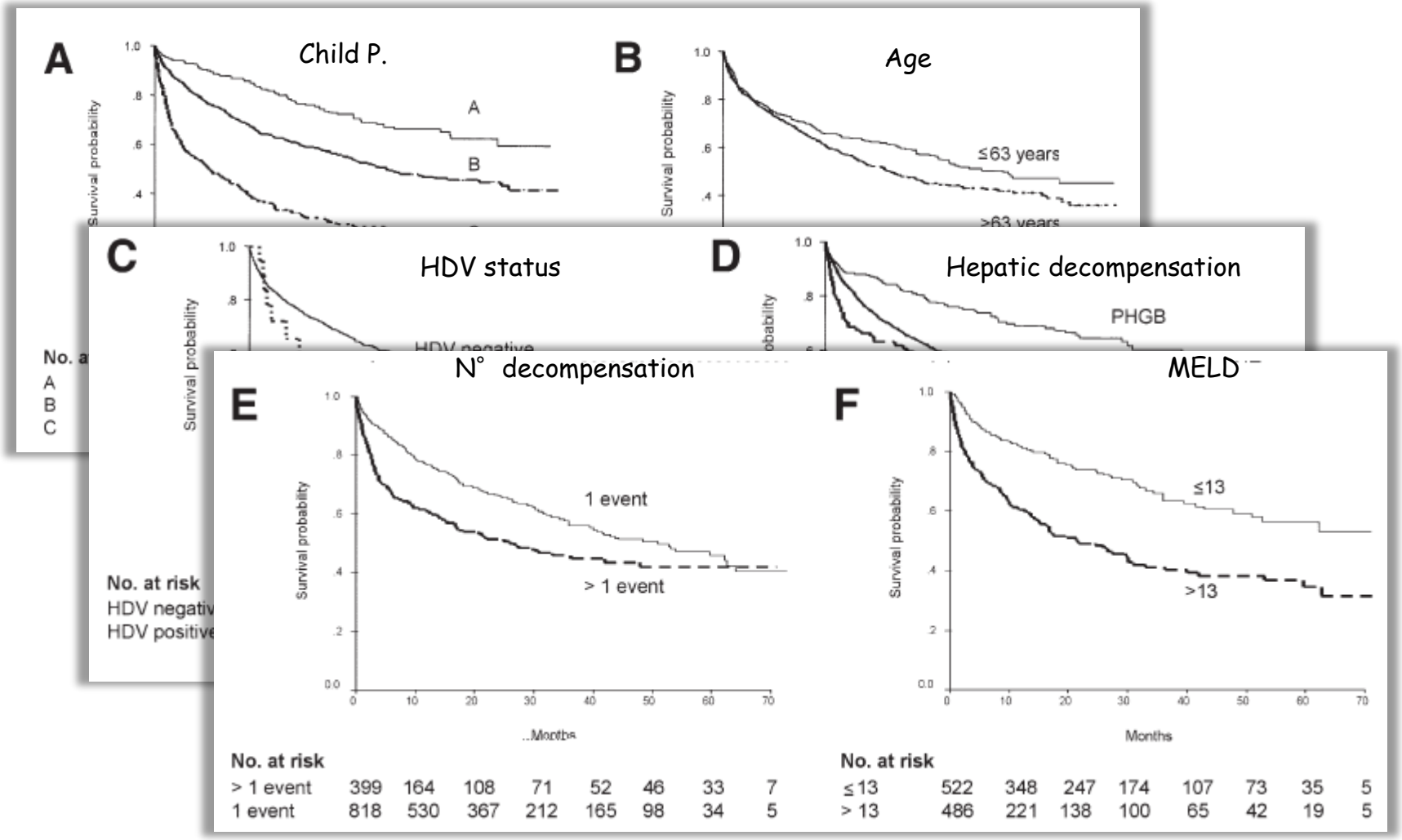




- US Veterans Affairs study analyzed prevalence of cirrhosis and decompensated cirrhosis among HIV patients in the registry (N = 24,040)
- Substantial increases in the prevalence of cirrhosis and decompensated cirrhosis in HIV/HCV-coinfected patients vs HIV-monoinfected patients between 1996 and 2006
  - Cirrhosis: 3.5%-13.2% (HIV/HCV-coinfected) vs 1.7%-2.2% (HIV-monoinfected)
  - Decompensated cirrhosis: 1.9%-5.8% (HIV/HCV-coinfected) vs 1.1%-1.2% (HIV-monoinfected)

HCV, hepatitis C virus; HIV, human immunodeficiency virus.
Ioannou et al. Hepatology. 2013;57:249.

Probability of survval according to predictors of death other than HIV infection



Pineda et al Hepatol 2005

Requisiti dei Centri Trapianto autorizzati ad eseguire trapianti di fegato in soggetti con infezione da HIV

1. Esistenza nella stessa unità ospedaliera e/o collaborazione con una Divisione di Malatti Infettive in ambito metropolitano dotata di reparto di degenza ordinaria e di Day Hospital, formalizzata mediante atti dei Legali Rappresentanti.

2. La Clinica/Divisione di Malattie Infettive dovrà certificare di sottoporre, al momento della rilevazione, a terapia antiretrovirale un numero non inferiore a 400 pazienti/anno in follow-up attivo. Tale requisito garantisce la necessaria esperienza di management clinico dei pazienti.

3. Esistenza di collaborazione, formalizzata mediante atti dei Legali Rappresentanti, con un servizio di Microbiologia e Virologia che, unitamente alle indagine batteriologiche, virologiche, micologiche e parassitologiche, indispensabili per una corretta gestione dei pazienti immunocompromessi, assicuri l'esecuzione di:

   Test per la determinazione della Viremia plasmatica di HIV
   - Test genotipico delle mutazioni di resistenza di HIV
   - Viremia quantitativa di HCV e HBV
   - Ricerca di resistenza per i farmaci anti HBV

(G.U. Serie Generale , n. 113 del 17 maggio 2011)

Requisiti dei Centri Trapianto autorizzati ad eseguire trapianti di fegato in soggetti con infezione da HIV

Il Centro trapianti deve inoltre provvedere all'addestramento del personale sulla scrupolosa adozione delle precauzioni universali, sulla possibilita' di introdurre in uso presidi di sicurezza nonche' garantire la disponibilita' dei farmaci necessari alla corretta applicazione della profilassi post-esposizione (PPE) per gli operatori sanitari secondo i protocolli nazionali attualmente vigenti.

(G.U. Serie Generale , n. 113 del 17 maggio 2011)

F) Criteri aggiuntivi di inclusione

1. Infezione da HIV documentata
2. Capacita' di fornire/acquisire il Consenso informato
3. Pazienti mai trattati con terapia antiretrovirale con conta di linfociti CD4-, circolanti, stabilmente ≥ 100/mmc.
4. Pazienti in terapia antiretrovirale, senza precedenti infezioni opportunistiche –"AIDS defining" con conta dei linfociti CD4+ ≥ 100/mmc, stabile da almeno 6 mesi. HIV-1- RNA undetectable al momento dell'inclusione in lista; e' ammessa la presenza di attiva replicazione virale di HIV in pazienti con malattia epatica scompensata e, per tale motivo, intolleranti alla terapia antiretrovirale purche' presentino una documentata risposta alla terapia antiretrovirale nell'ultimo ciclo terapeutico.
5. Pazienti con storia di una o piu' patologie opportunistiche "AIDS defining" devono avere conta dei linfociti CD4 ≥ 200/mmc, stabile da almeno 6 mesi e HIV-RNA undetectable, se in trattamento, o documentata risposta alla terapia antiretrovirale nell'ultimo ciclo terapeutico
6. Compliance al trattamento immunosoppressivo e antiretrovirale ed alla profilassi delle infezioni opportunistiche, se indicata.

I pazienti verranno monitorati, a cura del centro che ha in carico il paziente, per CD4 e HIV-RNA con cadenza trimestrale durante la permanenza in lista d'attesa.

La perdita di uno o piu' criteri di inclusione determina uscita temporanea dalla lista fino al recupero di validita' di tutti i criteri di inclusione.

G) Criteri di esclusione

1. Mancanza dei criteri immunologici e virologici di inclusione
2. Storia di patologie opportunistiche per le quali non esistono al momento attuale opzioni terapeutiche efficaci (Criptosporidiosi, Leucoencefalopatia Multifocale Progressiva, Infezioni da Mycohacterium abscessus. etc.)
3. Diagnosi di Sarcoma di Kaposi viscerale
4. Storia di neoplasia (eccezion fatta per carcinoma baso-cellulare ed il carcinoma in situ della cervice con disease-free documentata superiore ai 5 anni; la guarigione dalla patologia neoplastica dovra' essere certificala da uno specialista oncologo)

(G.U. Serie Generale , n. 113 del 17 maggio 2011)

Centri Trapianto autorizzati

(G.U. Serie Generale , n. 113 del 17 maggio 2011)

HIV criteria for liver transplantation in IHV infected patients in Europe and the USA

	Spain	France	Italy	UK	US
Previous AIDS-defining events					
Opportunistic infections (OIs)	Some*	Some*	None in the previous year	None after HAART-induced immune reconstitution	Most**
Neoplasms	No	Not defined	No		No**
CD4 cell count/mm^3					
No previous OIs	>100	>100***	>200 or >100 if decompensated cirrhosis	>200 or >100 if portal hypertension	>100
Previous OIs	>200	>100***			>200
Plasma HIV-1 RNA viral load <50 copies/ml on HAART**	Yes		Yes	Yes	Yes

*In Spain and France, patients with previous tuberculosis, *Pneumocystis jiroveci* pneumonia, or esophageal candidiasis can be evaluated for LT.
**In the USA, only progressive multifocal leukoencephalopathy, cryptosporidiosis, multidrug systemic fungal infections, lymphoma, and visceral Kaposi's sarcoma are exclusion criteria.
***Patients under 100 CD4 cells/mm^3 were not excluded in France (case by case evaluation).
****If HIV plasma viral load was detectable, post-LT suppression with HAART should be predicted in all patients.

Miro JM et al J.Hepatol 2015

Severity of Disease and death on the waitlist

58 HIV+ (1997-2002)

1359 HIV-

	HIV+	HIV-
OLTx	15 (25,9%)	860(63,3%)
Non OLTx	43	499
Died	21(36,2%)	211 (15,5%)

The cumulative survival 880 days vs 1427

Ragni MV et al Liver transpl 2005

Severity of Disease and death on the waitlist

	HIV+	HIV-
MELD	16±1,4	15±0,3
Bilirubin	6,6±1,2	5,7±0,2
creatinine	1,3±0,1	1,3±0,0
INR	1,5±0,1	1,5±0,0

12/21 (57.1%) dying from infection

Ragni MV et al Liver transpl 2005

MELD Score Is an Important Predictor of Pretransplantation Mortality in HIV-Infected Liver Transplant Candidates

ARUNA SUBRAMANIAN,* MARK SULKOWSKI,* BURC BARIN,‡ DONALD STABLEIN,‡ MICHAEL CURRY,§ NICHOLAS NISSEN,‖ LORNA DOVE,¶ MICHELLE ROLAND,# SANDER FLORMAN,** EMILY BLUMBERG,‡‡ VALENTINA STOSOR,§§ D. T. JAYAWEERA,‖‖ SHIRISH HUPRIKAR,¶¶ JOHN FUNG,## TIMOTHY PRUETT,*** PETER STOCK,‡‡‡ and MARGARET RAGNI§§§

Characteristics of Liver Transplant Candidates by Transplant Status

	Transplant	No Transplant	Died	*P* value[a]
No. enrolled, n (%)				
HIVTR	58 (35)	85 (51)	24 (14)	N/A
UNOS	377 (48)	327 (41)	88 (11)	N/A
Median (IQR), age, y				
HIVTR	47 (42–52)	47 (43–51)	50 (41–55)	.85
UNOS	48 (43–52)	50 (44–54)	49 (43–54)	.09
Race (white), n (%)				
HIVTR	41 (71)	68 (80)	16 (67)	.34
UNOS	275 (73)	239 (73)	69 (78)	.8
Male sex, n (%)				
HIVTR	44 (76)	71 (84)	21 (88)	.39
UNOS	309 (82)	254 (78)	75 (85)	.19
Median (IQR), baseline CD4				
HIVTR	315 (229-437)	264 (189-399)	237 (146-348)	.03
UNOS	—		—	—
No. (%) Detectable HIV RNA				
HIVTR	9 (16)	6 (7)	5 (21)	.09
UNOS	—		—	—
No. (%) HCV infection				
HIVTR	47 (81)	60 (71)	18 (75)	.37
UNOS	277 (73)	253 (77)	62 (70)	.3

[a]For tests comparing transplant, no transplant, and died groups within cohort.

GASTROENTEROLOGY 2010;138:159–164

MELD Score Is an Important Predictor of Pretransplantation Mortality in HIV-Infected Liver Transplant Candidates

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Risk Factors for Pretransplantation Mortality in HIV (+) Transplant Candidates

Univariate analysis	HR for death	*P* value	HR, MELD score ≥25	*P* value
Univariate analysis				
Risk factor at enrollment				
MELD score ≥25	15.0	<.0001	—	
HCV coinfection	1.0	.97	0.8	.52
Protease inhibitor regimen	1.5	.37	1.2	.59
CD4 count <200/μL	1.1	.74	1	.94
Detectable HIV RNA	3.2	.02	2.79	.005
Multivariate analysis				
Risk factor at enrollment				
MELD score 15–19	5.7	.005		
MELD score 20–24	21.4	<.0001		
MELD score ≥25	101.1	<.0001		
CD4 count <200/μL	2.4	.07		
Detectable HIV RNA	1.0	.98		

GASTROENTEROLOGY 2010;138:159–164

Liver transplantation in HIV-infected patients: main series of cases in the later ART era (2002-2008).

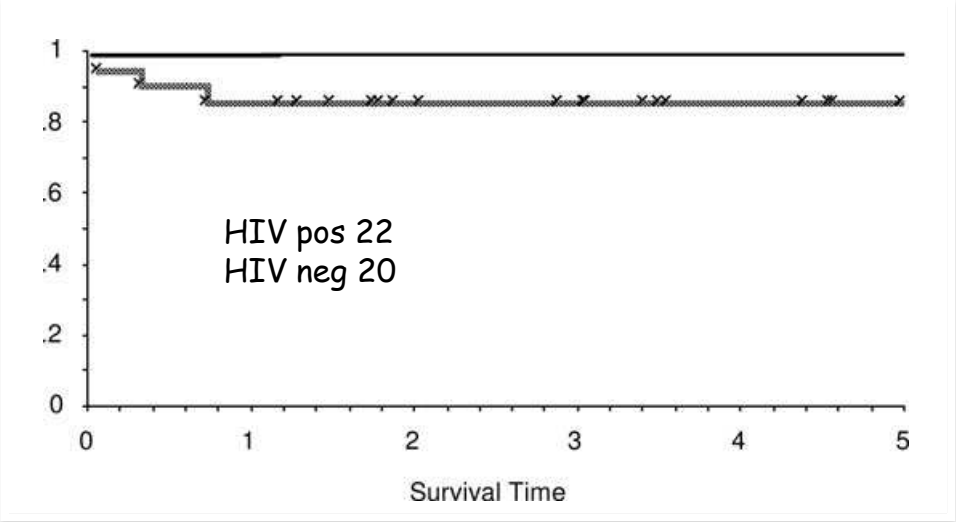
	N°	Survival rate% 1 years 2	
Ragni (2003)	24	87	75
Neff (2003)	16	100	80
Norris (2004)	14	79	70
deVera (2006)	27	-	48
Schereibman (2007)	15	73	67
Coffin (2007)	16	85	85
Spanish study (2008)	127	80	74
Grossi (2008)	60	58.3	-

Post LT Survival of HIV positive patients coinfected with HBV

Author	n	Survival (%)	
		1yr	3yrs
Fung 2004	3	100	-
Norris 2004	4	100	-
Duclos-Vallee 2006	5	100	-
Schreibman 2007	8	75	-
Roland 2007	5	100	-
Tateo 2009	13		100

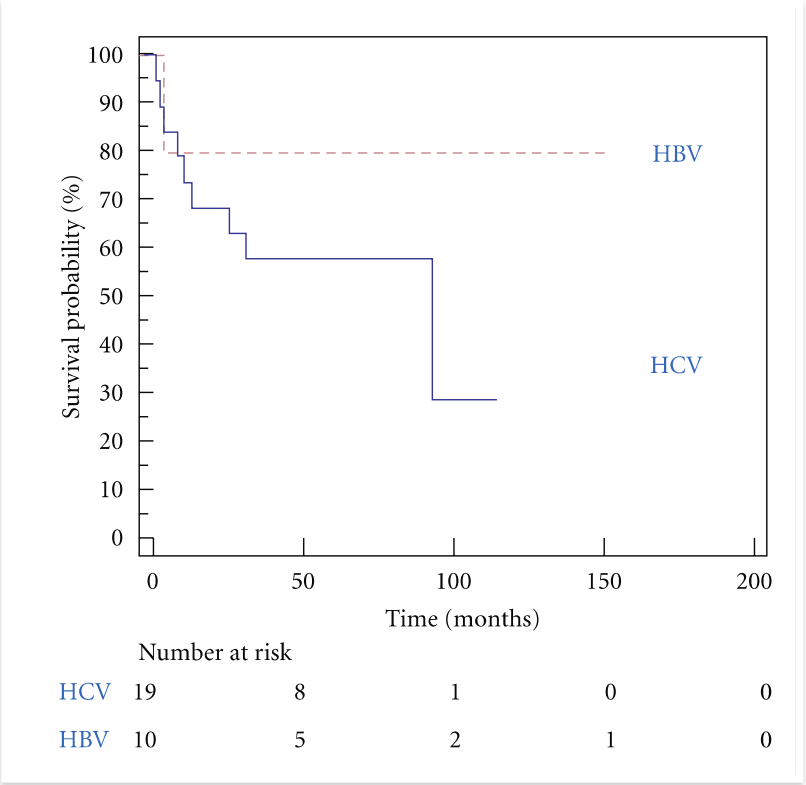
Fung et al Liver Transplant 2004, Norris et al Liver Transplant 2004,
Duclos-Vallee et al J Hepatol 2006, Schreibman et al Transplantation 2007,
Roland et al Am J Transplant 2007, Tateo et al AIDS 2009

Post LT Survival of HIV positive patients coinfected with HBV

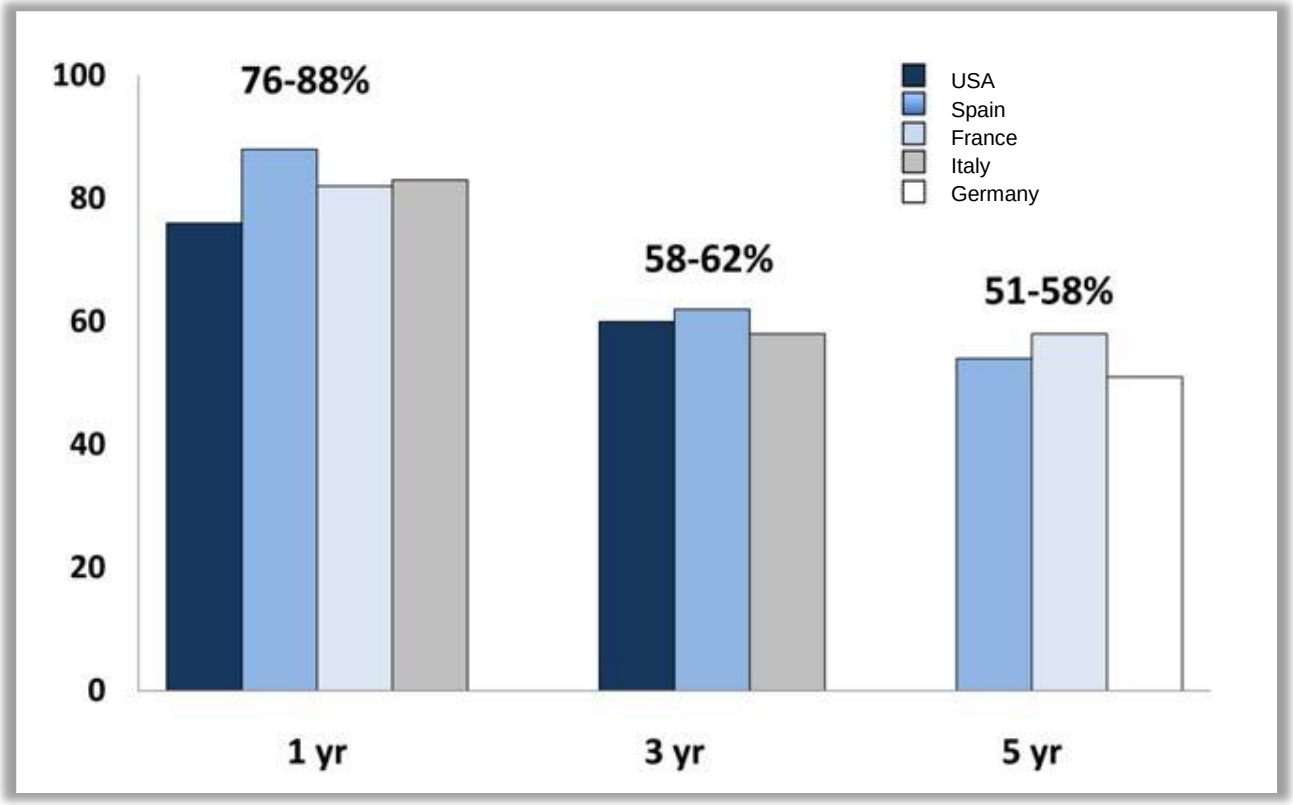


Coffin CS et al Am, J Transpl. 2010

Anadol E et al AIDS Research and Treatment 2012



Cumulative patient survival in HIV/HCV-coinfected LT recipients in USA, Spain, France, Italy, Germany



Stock PG et al Hepatology 2015

Patient survival after transplantation in HIV/HCV-coinfected and HCV monoinfected liver recipients in France, Spain and USA

Country	1 year	2 years	3 years	4 years	5 years	*p* value
France						
HCV/HIV coinfection (N = 44)	-	73%	-	-	51%	0.004
HCV monoinfection (N = 35)	-	91%	-	-	81%	
Spain						
HCV/HIV coinfection (N = 84)	88%	71%	62%	60%	54%	0.008
HCV monoinfection (N = 252)	90%	81%	76%	73%	71%	
United States						
HCV/HIV coinfection (N = 89)	76%	-	60%	-	-	<0.001
HCV monoinfection (N = 235)	92%	-	79%	-	-	

Miro JM et al J.Hepatol 2015

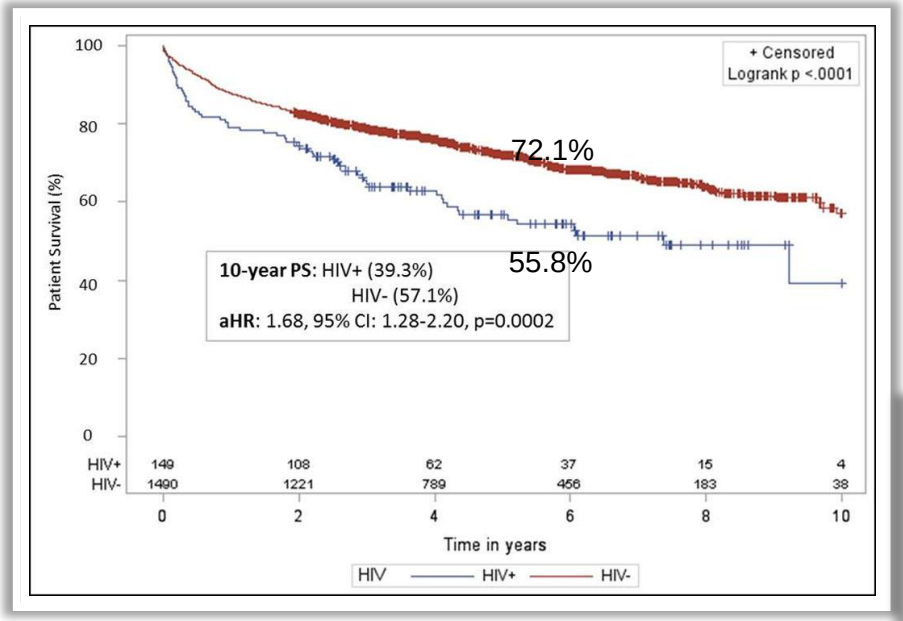
Predictive factors of mortality in HIV/HCV coinfected liver recipients in the French,Spanish, and US cohorts

	HCV/HIV and HCV liver recipients	Including only the HCV/HIV cohort
French cohort		n.p.
HIV-1 infection	1.91 (0.7-5.18)*	
MELD score (1-unit increase)	1.08 (1.01-1.15)	
Donor age	1.04 (1.00-1.07)	
Spanish cohort		
HIV-1 infection	2.20 (1.42-3.41)	n.a.
HCV genotype 1	2.14 (1.24-3.41)	2.98 (1.32-6.76)
Donor risk index	3.03 (1.57-5.83)	9.48 (2.75-32.73)
Negative plasma HCV RNA viral load**	0.23 (0.10-0.49)	0.14 (0.03-0.62)
US cohort		
HIV-1 infection	2.3 (1.3-3.8)	n.a.
BMI at listing <21		3.2 (1.3-7.7)
Combined kidney-liver transplant		3.8 (1.6-9.1)
Anti-HCV positive donor		2.5 (1.1-5.6)
Donor age (by decade)		1.3 (1.0-1.6)

n.p., analysis not performed; n.a., not applicable; BMI, body mass index.
*Hazard ratio (95% confidence interval).
**RNA HCV clearance with/out anti-HCV therapy before or after liver transplantation.

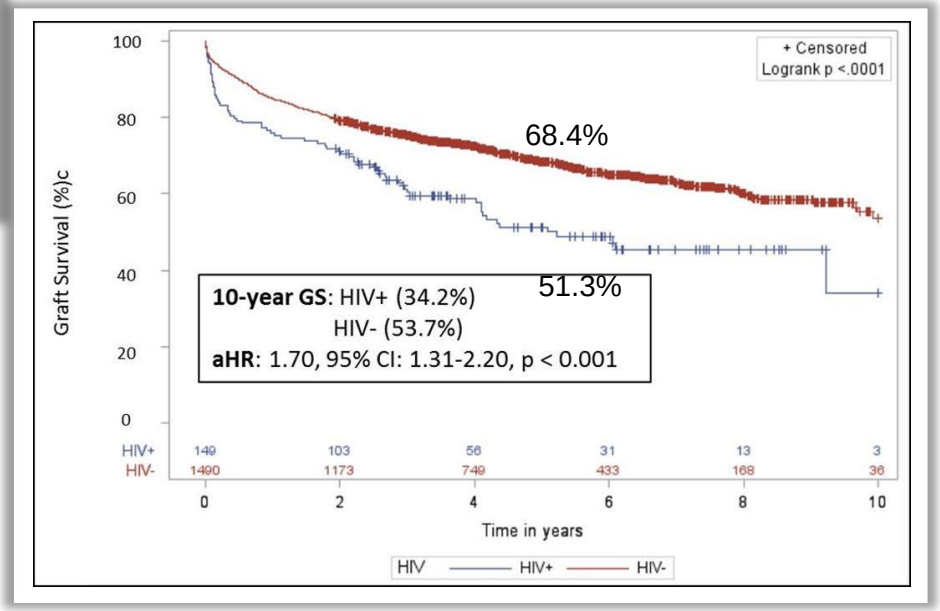
Miro JM et al J.Hepatol 2015

Patient and graft survival HIV+ vs HIV-



Patient survval

Graft survival



Locke JE et al Transplantation 2016

Patient survival by Transplant Era and HCV Status

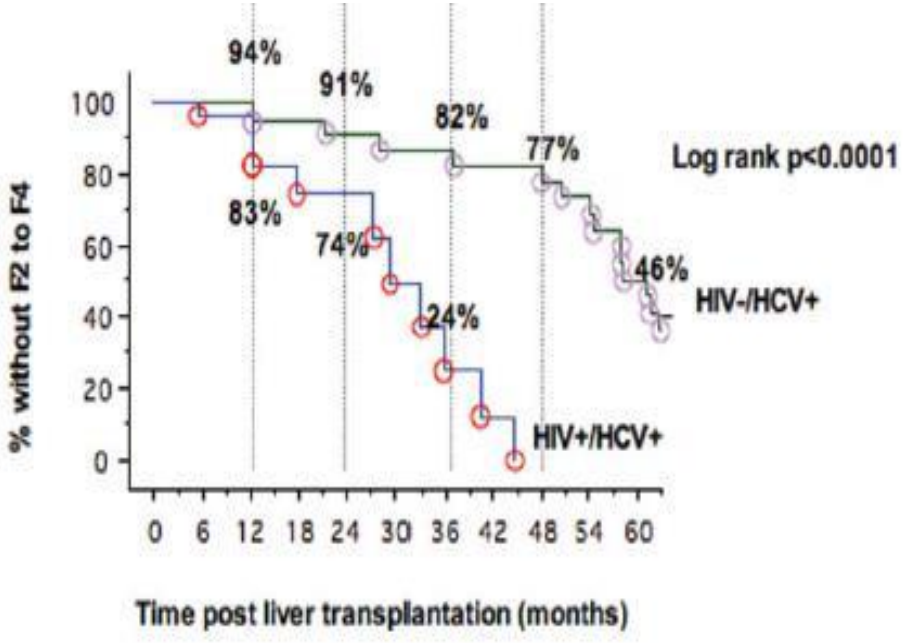
	Early (2002-2007), HR (95% CI)	Modern (2008-2011), HR (95% CI)
Graft loss		
All HIV+	1.86 (1.23-2.70)	1.58 (1.06-2.34)
All HIV–	ref	ref
Monoinfected (HIV+/HCV–)	3.26 (1.61-6.67)	0.89 (0.42-1.88)
No infection (HIV–/HCV–)	ref	ref
Coinfected (HIV+/HCV+)	1.56 (1.02-2.39)	2.07 (1.33-3.22)
HCV alone (HIV–/HCV+)	Ref	ref
Death		
All HIV+	1.66 (1.11-2.50)	1.88 (1.26-2.82)
All HIV–	ref	ref
Monoinfected (HIV+/HCV–)	3.58 (1.62-7.91)	1.11 (0.52-2.35)
No infection (HIV–/HCV–)	ref	Ref
Coinfected (HIV+/HCV+)	1.37 (0.86-2.19)	2.24 (1.43-3.53)
HCV alone (HIV–/HCV+)	ref	ref

Risk for graft loss and patient death for monoinfected patients have improved over time. However, outcomes among coinfected patients remain poor even in the modern transplant era.

Locke JE et al Transplantation 2016

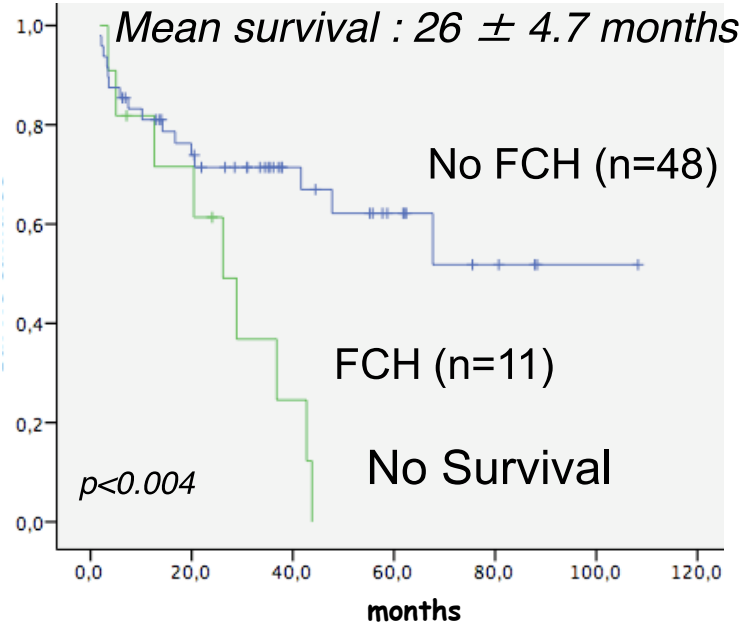
Higher rate and more severe recurrence of HCV after LT in HIV+

Progression to Fibrosis after LT for HCV with or without HIV infection



Duclos-Vallèè et al Hepatology 2008

Very severe HCV recurrence Fibrosis Cholestatic Hepatitis 20% FCS in HIV+ vs 5% in HIV-



Antonini et al Am.J.Transpl 2011

Treatment of HCV re-infection in OLT with pegylated interferon plus ribavirin

Efficacy of HCV Therapy in HIV/HCV LT Recipients

Author	*N* treated genotypes	Peg and RBV doses	Duration (wks)	Biochemical response *N* (%)	SVR *N* (%)	Histology stable or improved *N* (%)	Other findings
Wojcik, 2007, German [48]	4, G1 ($n=2$), G2/3 ($n=2$)	Peg-IFN 180 ug/wk RBV 11/mg/kg	24–48	4/4 (100%)	4/4 (100%)	4/4 (100%)	2/4 with cholestatic hepatitis
Castells, 2006, Spain [50]	5, all G1	Peg-IFN 1.5 ug/kg RBV 800–1000 mg/d	24–48	5/5 (100%)	1/5 (20%)	N/A	Rx started at first sign histologic disease, median 12 wks
DeVera, 2006, US [30]	15, majority G1	IFN and peg-IFN, RBV 800 mg daily	54–131	10/15 (66%)	4/15 (27%)	1/9 (11%)	6 deaths during treatment No responses in those with cholestatic hepatitis
Duclos-Vallee, 2007, France [27]	19, G1 ($n=12$)	IFN and peg-IFN and RBV 400–800 mg daily	Variable, 44–52 most frequent	10/19 (53%)	3/19 (16%) 2/3 G3	3/19 (16%)	3 with severe cholestatic disease; 2/3 treated, 1 death and 1 clinical response, no SVRs
Vennarecci, 2006, Italy [49]	9	Peg-IFN and RBV (doses not provided)	N/A	N/A	1/9 (11%)	N/A	3 with severe cholestatic hepatitis

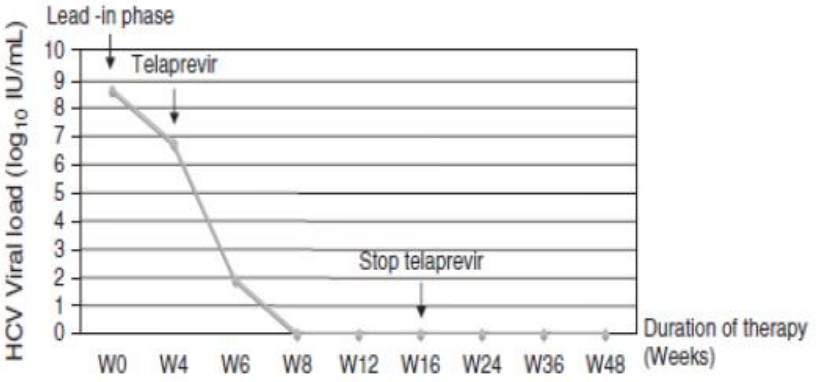
Peg-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response; G, genotype; N/A, not available in manuscript; Rx, treatment.

Successful anti-hepatitis C virus therapy with telaprevir in an HIV/hepatitis C virus co-infected patient with a severe recurrence of hepatitis C virus infection on the liver graft

Teresa M. Antonini[a,b,c,k], Valerie Furlan[d,k], Elina Teicher[a,e,k], Stephanie Haim-Boukobza[b,c,f,k], Mylene Sebagh[b,c,g,k], Audrey Coilly[a,b,c,k], Laurence Bonhomme-Faivre[h,k], Gilles Peytavin[i,j], Anne-Marie Roque-Afonso[b,c,f,k], Daniel Vittecoq[e,k], Didier Samuel[a,b,c,k], Anne-Marie Taburet[d,k] and Jean-Charles Duclos-Vallée[a,b,c,k]

AIDS 2013, **27**:2655–2659

(a)



From W4 to W48, the HCV viral load was undetectable, and liver test parameters normalized. A sustained virological response (SVR) was obtained 24 weeks after stopping therapy (Fig. 1). The 2-year liver biopsy showed a portal fibrosis with some porto-portal bridging without necro-inflammatory activity (Metavir A0F2).

A0F2).

LIVER TRANSPLANTATION

The effect of new HCV drugs on liver transplantation outcomes

Didier Samuel and Jean-Charles Duclos-Vallée

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY
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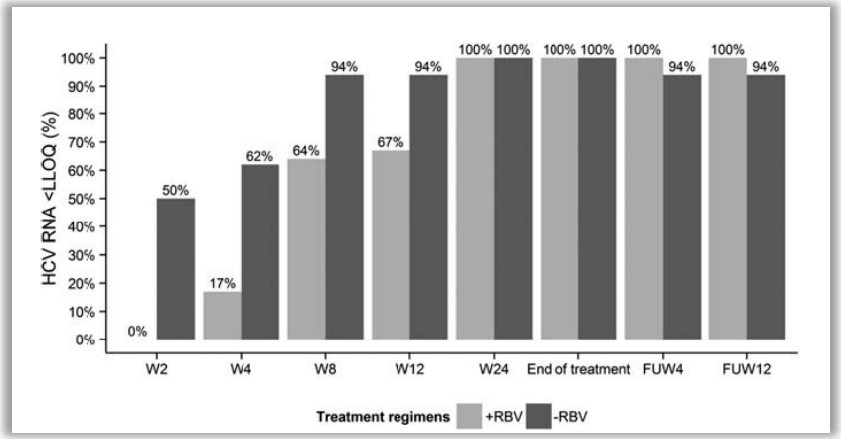
Sofosbuvir and Daclatasvir in Mono and HIV infected with recurrent Hepatitis C after Liver Transplant

	Overall (n = 22)	HCV-monoinfected (n = 16)	HCV/HIC-coinfected (n = 6)
HCV-RNA decline (log), median (IQR)			
Week 1	3.3 (2.5-4.1)	3.15 (2.35-3.55)	4.15 (3.5-4.26)
Week 2	1.1 (0.7-1.3)	1.1 (0.7-1.3)	0.9 (0.3-1.3)
Week 3	0.7 (0.6-1.3)	0.9 (0.6-1.3)	0.6 (0.5-1.3)
Week 4	0.2 (0-0.7)	0.2 (0-0.5)	0. (0-0.7)
Week 4			
HCV-RNA < LOQ	11 (50)	6 (37)	5 (83)
Week 8			
HCV-RNA < LOD	21 (95)	15 (94)	6 (100)
Week 12			
HCV-RNA < LOD	22 (100)	16 (100)	6 (100)
Week 24			
HCV-RNA < LOD	22 (100)	16 (100)	6 (100)
At week 4 (SVR4)	22 (100)	16 (100)	6 (100)
At week 12 (SVR12)	22 (100)	16 (100)	6 (100)

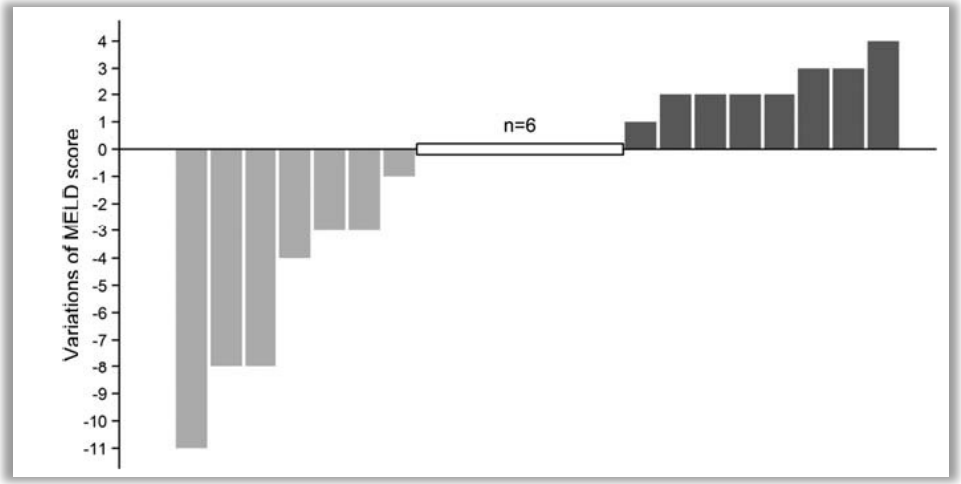
Castells L et al Ann.Hepatol. 2017

Sofosbuvir-Based Regimens in HIV/HCV Coinfected Patients After Liver Transplantation: Results From the ANRS CO23 CUPILT Study

Teresa Maria Antonini, MD,[1,2,3,4] Audrey Coilly,[1,2,3,4] Emilie Rossignol,[5,6] Claire Fougerou-Leurent,[5,6] Jérôme Dumortier,[7,8] Vincent Leroy,[9,10] Aurélie Veislinger,[5,6] Sylvie Radenne,[11] Danielle Botta-Fridlund,[12] François Durand,[13] Pauline Houssel-Debry,[14] Nassim Kamar,[15,16,17] Valérie Canva,[18] Philippe Perré,[19] Victor De Ledinghen,[20] Alexandra Rohel,[21] Alpha Diallo,[21] Anne-Marie Taburet,[4,22,23] Didier Samuel,[1,2,3,4] Georges-Philippe Pageaux,[24,25] and Jean-Charles Duclos-Vallée[1,2,3,4] for the ANRS C023 CUPILT study group



October 2013-Dicember 2015
29pts
Median delay LT-tx 37.5m IQR 14.4-99.2



37.9% developed infections
Cirrhosis and FCH first month

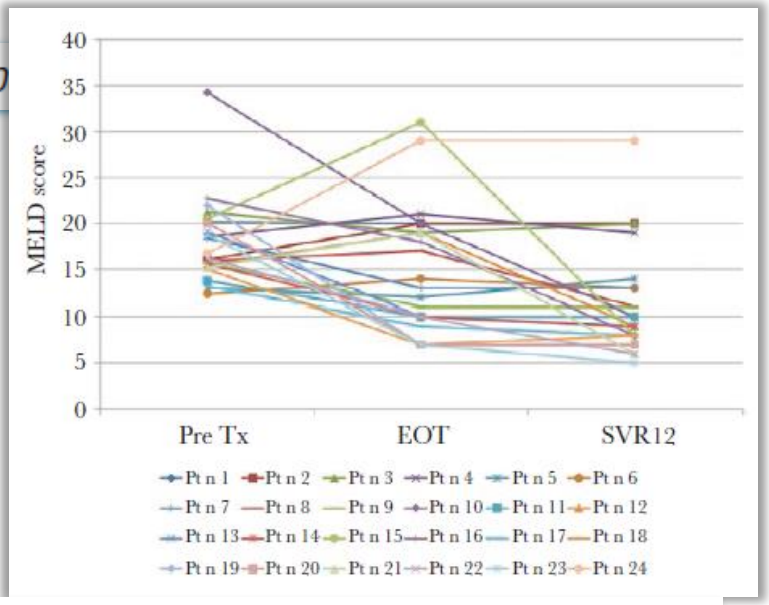
Transplantation 2018

Successful Pre- and Posttransplant Sofosbuvir-Based Anti-Hepatitis C Virus Treatment in Persons Living With Human Immunodeficiency Virus Infection

Giovanni Guaraldi,[1] Roberto Rossotti,[2] Gabriella Verucchi,[3] Marcello Tavio,[4] Luisa Pasulo,[5] Barbara Beghetto,[1] Giovanni Dolci,[1] Giulia Nardini,[1] Lorenzo Badia,[3] Anna Magliano,[4] Maria Cristina Moioli,[2] and Massimo Puoti[2]; HIV/HCV Italian Liver Transplant Group

[1]Infectious Diseases Departments of University of Modena, Italy; [2]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [3]University of Bologna, Italy; [4]Azienda Ospedaliera Universitaria Ospedali Riuniti, Ancona, Italy; and [5]Gastroenterology Department ASST Papa Giovanni XXIII, Bergamo, Italy

Op



All Patients		24					
Treatment		SOF ± RBV 24 Weeks		SOF + DCV ± R 12–24 Weeks		SOF + LDV ± RBV 12–24 Weeks	
Number of patients		10		12		2	
Treatment response		SVR 24: 7	NR: 3	SVR24: 11	D/O: 1[a]	SVR 24: 1	D/O: 1[b]
Patients status on January 31, 2017 (median follow up after treatment withdrawal up 18 months, IQR 14–20 months)	Death						1[b]
	Transplant without HCV recurrence	7		5		1	1[b]
	Transplant with HCV recurrence		1				
	SVR24 and delisted alive with MELD <10			6			
	NR and delisted		1[c]		1[a]		
	NR and on the waiting list with MELD >15		1				

Abbreviations: DCV, daclatasvir; D/O, drop out; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; LDV, ledipasvir; MELD, model for end-stage liver disease; NR, nonresponder; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR24, sustained virologic response 24 weeks posttreatment withdrawal.

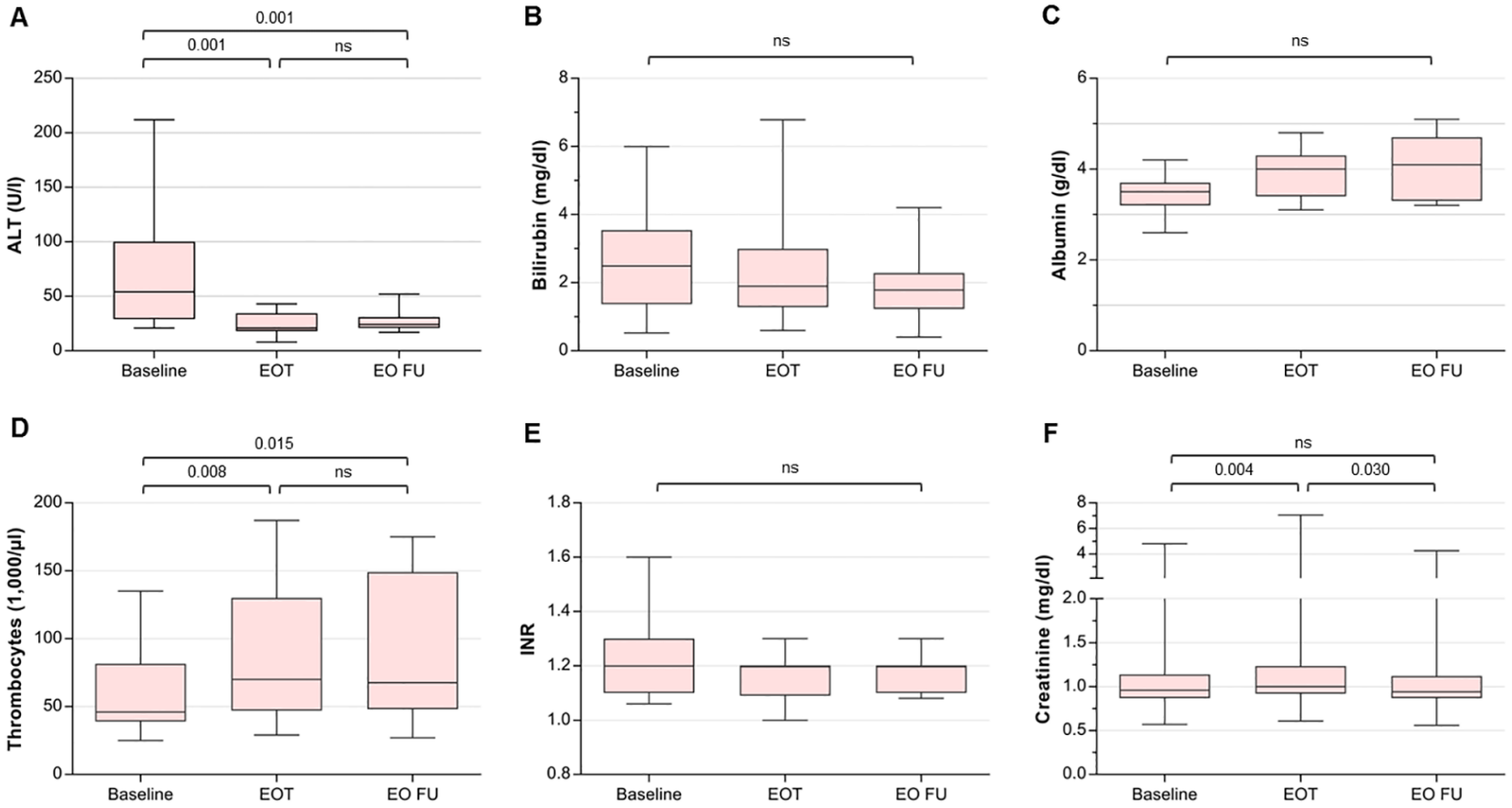
[a]Withdrawn from treatment and liver transplant list 12 weeks after treatment initiation for progression of hepatocellular carcinoma relapser after anti-HCV treatment (HCV genotype 3); treated with sorafenib on January 31, 2017, 17 months after treatment withdrawal, alive without progression of hepatocellular carcinoma with detectable HCV-RNA.

[b]Treated with SOF and LDV for 12 weeks before and after transplant; died for cerebral hemorrhage 1 month after liver transplant while on SOF + LDV with on treatment response.

[c]Withdrawn from liver transplant list for "de novo" hepatocellular carcinoma outside of Milan criteria; nonresponder to SOF and RBV for 24 weeks; on January 31, 2017, 19 months after treatment withdrawal, alive and on sorafenib with progession of hepatiocellular carcinoma and liver decompensation MELD 24.

Successful DAAs treatment of HCV/HIV-coinfected patients before and after liver transplantation

Patients on the liver transplant waiting list SVR 79,2%



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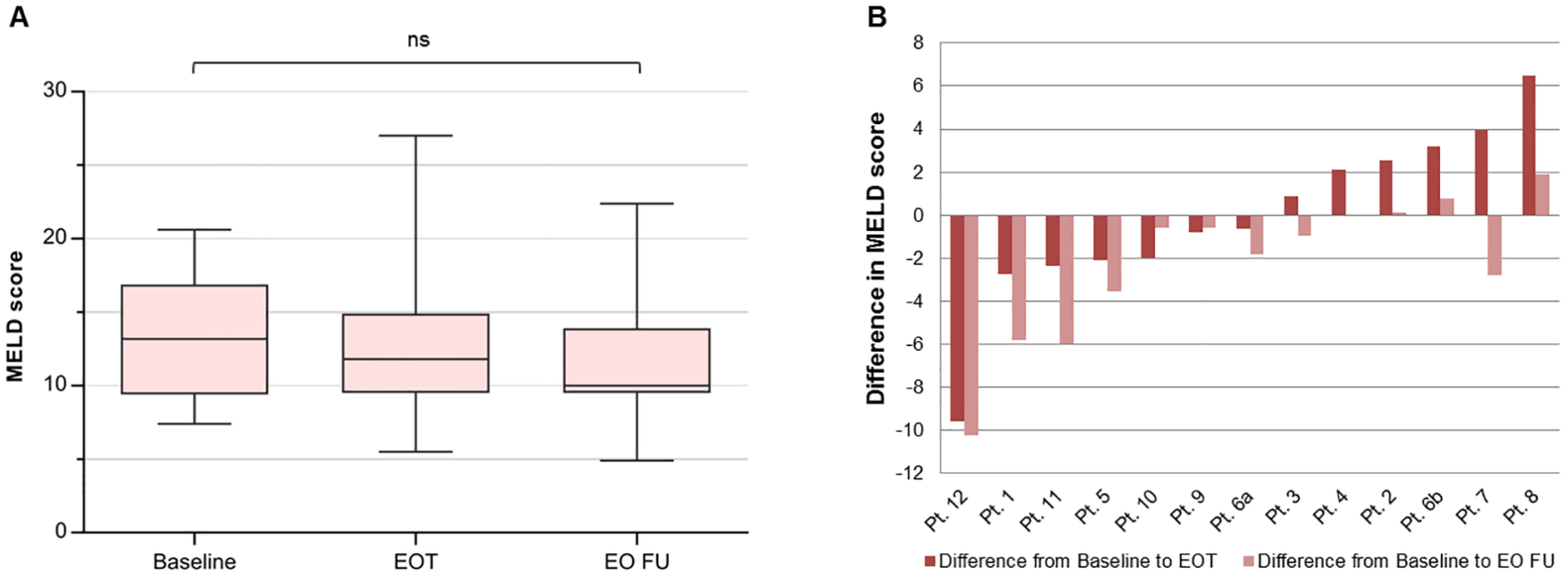
Successful DAAs treatment of HCV/HIV-coinfected patients before and after liver transplantation

Patients on the liver transplant waiting list SVR 79,2%



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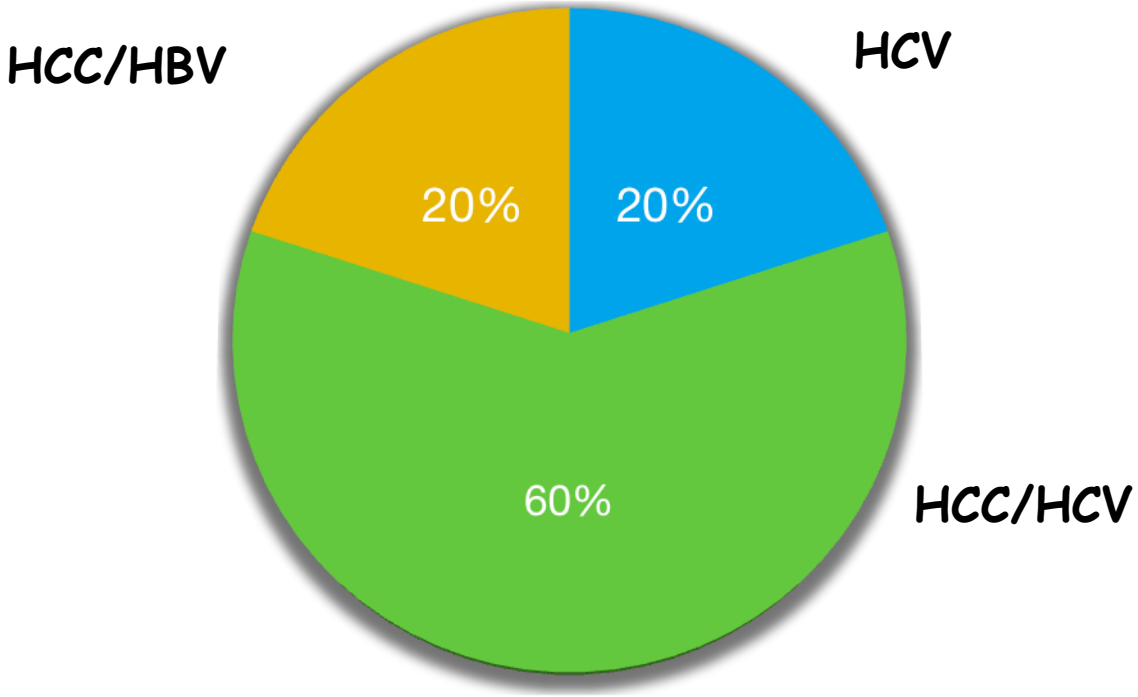
HCC e trapianto di fegato in HIV+



5 pazienti HIV in lista

- 1 per cirrosi HCV (eradicata con DAA)
- 3 per HCC su cirrosi HCV (2 eradicati con DAA, 1 eradicato con PEG-IFN + RBV)
- 1 per HCC su cirrosi HBV

Casistica S.Orsola

Liver Transplantation for Hepatocellular Carcinoma: The Impact of Human Immunodeficiency Virus Infection

Eric Vibert,[1,2,4] Jean-Charles Duclos-Vallée,[1,2,4] Maria-Rosa Ghigna,[2,4,6] Emir Hoti,[1] Chady Salloum,[1] Catherine Guettier,[2,4,6] Denis Castaing,[1,2,4] Didier Samuel,[1,2,4] and René Adam[1,3,5]

2003-2008: 147 listed for HCC in France: 65 (75%) HIV- and 21 (24%) HIV+

Table 1. Characteristics of HIV+ and HIV− Patients Listed for LT

Characteristic	HIV+ Patients	HIV− Patients	*P*
Patients, n	21	65	
Men, n (%)	18 (85)	52 (80)	0.68
Age, years	48 (41-63)	57 (37-72)	<0.001
HBV infection, n (%)	2 (9)	13 (20)	0.23
HCV infection, n (%)	17 (80)	47 (64)	0.23
HCV genotype 1, n/N (%)	6/14 (42)	22/43 (51)	0.75
HBV/HCV coinfection, n (%)	2 (9)	5 (7)	0.77
Child C, n (%)	5 (23)	15 (23)	0.62
MELD score	14 (8-31)	12 (7-37)	0.52
Nodules, n	1 (1-4)	1 (1-10)	0.18
Maximum diameter, mm	26 (14-45)	25 (5-55)	0.87
AFP level, μg/L	16 (3-7154)	13 (1-552)	0.04
Outside Milan criteria, n (%)	4 (19)	17 (26)	0.50
Outside UCSF criteria, n (%)	2 (9)	10 (15)	0.42

Quantitative variables are expressed as medians and ranges.

Table 3. Characteristics of HIV+ and HIV− Transplant Patients

Characteristic	HIV+ Patients	HIV− Patients	*P*
Patients, n	16	58	
Men, n (%)	13 (86)	46 (80)	0.96
Age, years	50 (43-63)	58 (37-72)	<0.002
Waiting time, months	6.4 ± 8.2	4.1 ± 4.8	0.18
HBV infection, n (%)	3 (20)	18 (31)	0.31
HCV infection, n (%)	15 (93)	45 (77)	0.13
HCV genotype 1, n/N (%)	5/12 (41)	20/37 (54)	0.55
HBV/HCV coinfection, n (%)	2 (13)	5 (9)	0.77
Child C, n (%)	4 (25)	14 (24)	0.97
MELD score	15 (8-31)	12 (7-37)	0.88
Nodules, n	1 (1-4)	1 (1-10)	0.35
Maximum diameter, mm	25 (14-45)	25 (5-55)	0.94
AFP level, μg/L	11 (3-934)	13 (1-552)	0.73
AFP progression, n/N (%)	3/16 (18)	12 (21)	0.92
Outside Milan criteria, n (%)	3 (18)	15 (25)	0.62
Outside UCSF criteria, n (%)	1 (13)	9 (15)	0.32

Quantitative variables are expressed as medians and ranges.

Significant higher rate of Drop-out on waiting-list in HIV+ patients

Table 2. Characteristics of Patients Who Dropped off the Transplant Waiting List

Sex/Age (Years)	Virological Status	MELD Score at Listing	CD4 T Cell (Cells/mL)	Nodules (n)	Largest Nodule (mm)	AFP (μg/L)	Time to Dropout (Months)	Cause of Dropout	OS After Listing (Months)
Male/46	HIV/HCV	9	520	1	20	7154	1	Portal tumoral thrombosis	11/deceased
Male/42	HIV/HBV	10	325	3	21	4	5	AIDS/infection	15/deceased
Male/47	HIV/HCV	17	410	1	35	37	6	Portal tumoral thrombosis	6/deceased
Male/43	HIV/HCV	18	140	4	32	203	6	Portal tumoral thrombosis	9/deceased
Male/51	HIV/HCV	10	180	1	30	98	14	Portal tumoral thrombosis	23
Male/56	HBV	31	–	1	30	181	1	Hepatic failure	1/deceased
Male/49	HCV	20	–	2	20	22	3	Hepatic failure	3/deceased
Male/62	HCV	7	–	2	15	8	5	Portal tumoral thrombosis	8
Male/43	HCV	14	–	1	13	60	8	Portal tumoral thrombosis	9/deceased
Male/50	HCV	8	–	1	17	10	3	Portal tumoral thrombosis	9/deceased
Female/55	HCV	12	–	4	35	55	11	Carcinomatosis	12/deceased
Female/65	HCV	8		3	35	15	4	Lymph node invasion	9/deceased

Drop-out 5/21 (23%) in HIV+ vs 7/65 (10%) in HIV-

Liver Transplantation for Hepatocellular Carcinoma: The Impact of Human Immunodeficiency Virus Infection

Eric Vibert,[1,2,4] Jean-Charles Duclos-Vallée,[1,2,4] Maria-Rosa Ghigna,[2,4,6] Emir Hoti,[1] Chady Salloum,[1] Catherine Guettier,[2,4,6] Denis Castaing,[1,2,4] Didier Samuel,[1,2,4] and René Adam[1,3,5]

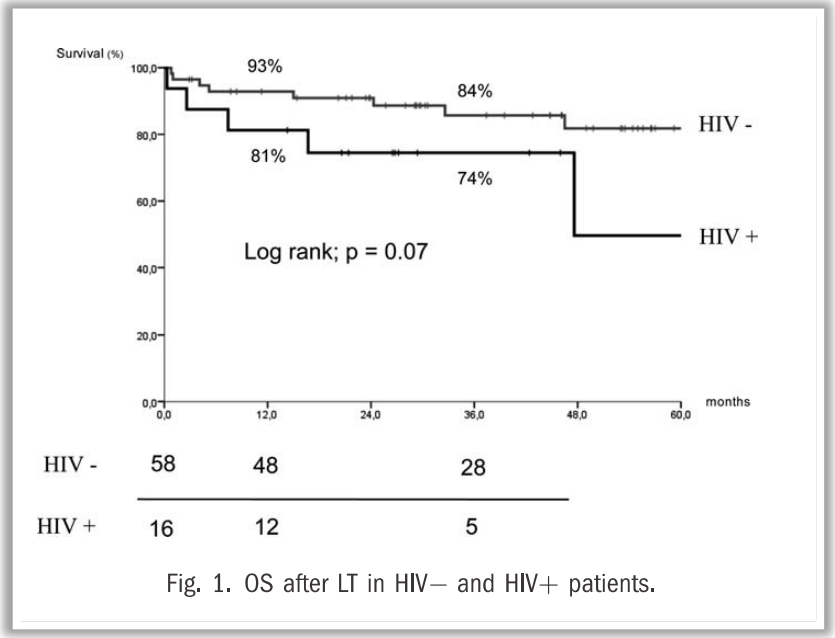


Fig. 1. OS after LT in HIV− and HIV+ patients.

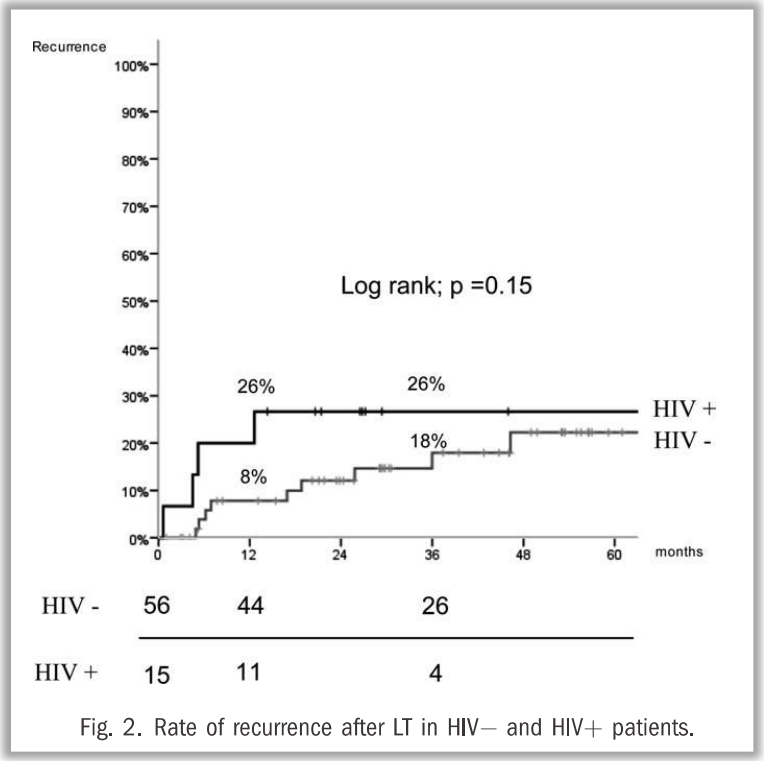


Fig. 2. Rate of recurrence after LT in HIV− and HIV+ patients.

Multicenter Italian Experience in Liver Transplantation for Hepatocellular Carcinoma in HIV-Infected Patients

Fabrizio Di Benedetto,[a] Giuseppe Tarantino,[a] Giorgio Ercolani,[b] Umberto Baccarani,[c] Roberto Montalti,[a] Nicola De Ruvo,[a] Massimiliano Berretta,[e] Gian Luigi Adani,[c] Matteo Zanello,[b] Marcello Tavio,[d] Nicola Cautero,[a] Umberto Tirelli,[e] Antonio D. Pinna,[b] Giorgio E. Gerunda,[a] Giovanni Guaraldi[f]

[a]Liver and Multivisceral Transplant Center, University of Modena and Reggio Emilia, Modena, Italy; [b]Liver and Multiorgan Transplant Unit, University of Bologna, Bologna, Italy; [c]Department of Medical and Biological Sciences and Liver Transplant Unit, University of Udine, Udine, Italy; [d]Division of Infectious Diseases, University of Ancona, Ancona, Italy; [e]Department of Medical Oncology, National Cancer Institute, Aviano (PN), Italy; [f]Infectious Diseases Clinic, University of Modena and Reggio Emilia, Modena, Italy

2004-2009: 30 HIV+ vs 125 HIV-

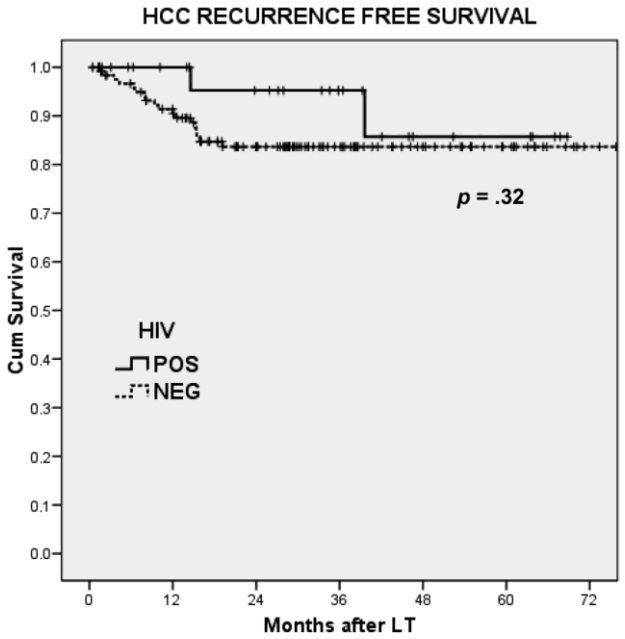


Figure 1. HCC recurrence-free survival of HIV-infected and HIV-uninfected patients.

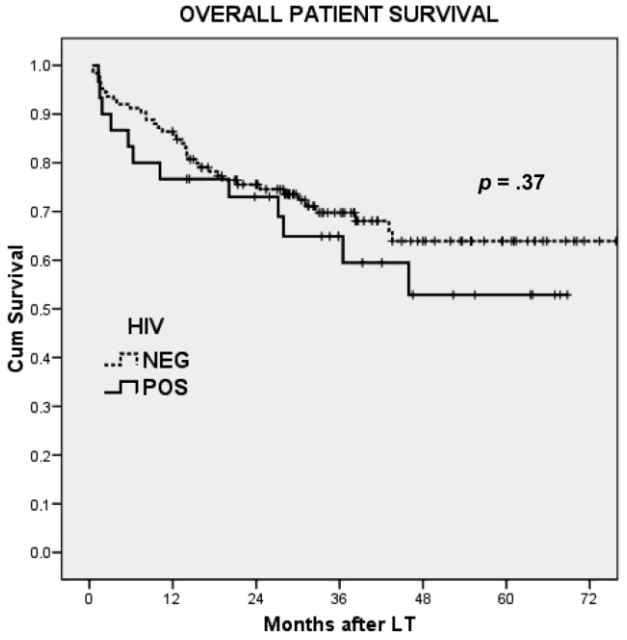


Figure 2. Overall survival of HIV-infected and HIV-uninfected patients.

Human Immunodeficiency Virus Infection Does Not Worsen Prognosis of Liver Transplantation for Hepatocellular Carcinoma

2002-2014: Spanish Multicentric Study:
74 HIV+ vs 222 HIV- trasplanted for HCC

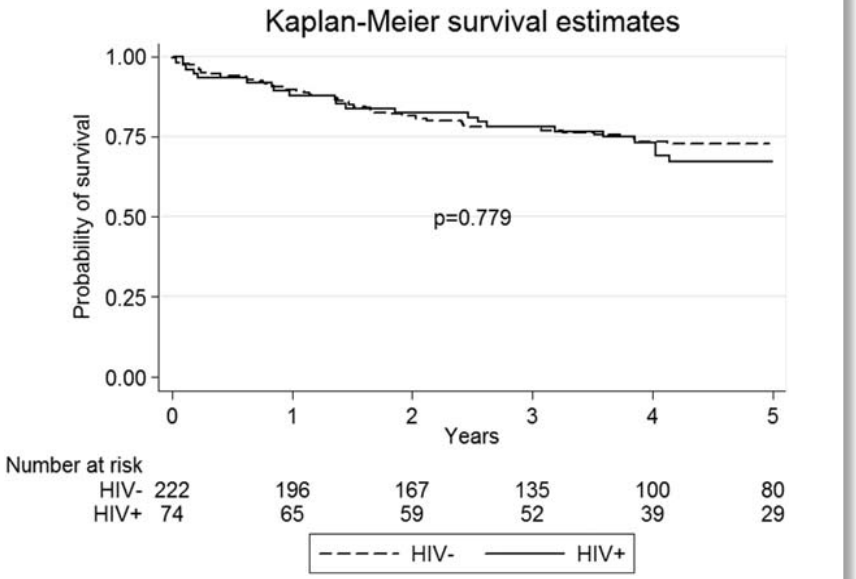


Fig. 1. Survival after liver transplantation in patients with and without HIV infection.

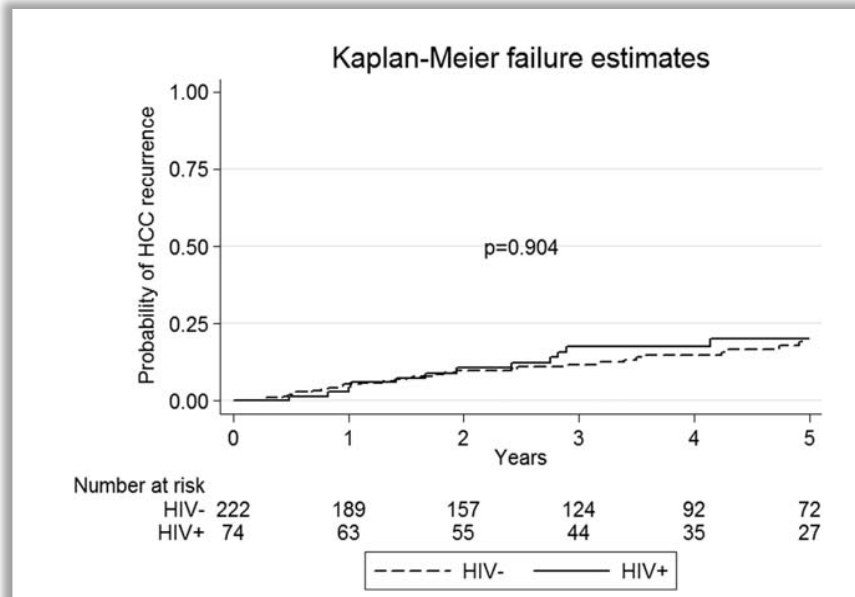


Fig. 2. HCC recurrence in liver transplant recipients with and without HIV infection.

International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Candidates

Norah A. Terrault, MD, MPH,[1] Geoff W. McCaughan, MD, BS, PhD,[2] Michael P. Curry, MD,[3] Edward Gane, MD,[4] Stefano Fagiuoli, MD,[5] James Y. Y. Fung, MD,[6] Kosh Agarwal, MD,[7] Les Lilly, MD,[8] Simone I. Strasser, MBBS, MD,[9] Kimberly A. Brown, MD,[10] Adrian Gadano, MD,[11] Paul Y. Kwo, MD,[12] Patrizia Burra, MD,[13] Didier Samuel, MD,[14] Michael Charlton, MD,[15] Mario G. Pessoa, MD,[16] and Marina Berenguer, MD[17]

(*Transplantation* 2017;101: 945–955)

Recommendation 4.1

We recommend that patients with HIV/HCV coinfection be offered liver transplantation for complications of HCC and/or decompensation.

Quality/Certainty of Evidence: Moderate
Strength of Recommendation: Strong

Recommendation 4.2

We recommend that patients with HIV/HCV coinfection on the waiting list for liver transplantation be treated with HCV antiviral therapy.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Strong

International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Recipients

Norah A. Terrault, MD, MPH,[1] Marina Berenguer, MD,[2] Simone I. Strasser, MBBS, MD,[3] Adrian Gadano, MD,[4] Les Lilly, MD,[5] Didier Samuel, MD,[6] Paul Y. Kwo, MD,[7] Kosh Agarwal, MD,[8] Michael P. Curry, MD,[9] Stefano Fagiuoli, MD,[10] James Y. Y. Fung, MD,[11] Edward Gane, MD,[12] Kimberly A. Brown, MD,[13] Patrizia Burra, MD,[14] Michael Charlton, MD,[15] Mario G. Pessoa, MD,[16] and Geoff W. McCaughan, MD, PhD[17]

(*Transplantation* 2017;101: 956–967)

Recommendation 4.1

We recommend that HIV/HCV coinfected liver transplant recipients be treated with combination DAA therapy early after liver transplantation.

Quality/Certainty of Evidence: Low
Strength of recommendation: Strong

Drug-drug Interactions

Ciclosporin	■	■	■	■	■
Mycophenolate	■	■	◆	■	◆
Sirolimus	■	■	■	■	◆
Tacrolimus	■	■	■	■	■

Immunosuppressants	Atazanavir	Cobicistat (with ATV or DRV)	Darunavir	Fosamprenavir	Indinavir	Lopinavir	Nelfinavir	Ritonavir	Saquinavir	Tipranavir
Azathioprine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Ciclosporin	■	■	■	■	■	■	■	■	■	■
Mycophenolate	■	◆	■	■	■	■	■	■	■	■
Sirolimus	■	■	■	■	■	■	■	■	■	■
Tacrolimus	■	■	■	■	■	■	■	■	■	■

Immunosuppressants	Dolutegravir	Elvitegravir/cobicistat	Maraviroc	Raltegravir
Azathioprine	◆	◆	◆	◆
Ciclosporin	◆	■	■	◆
Mycophenolate	◆	◆	◆	◆

www.hiv-druginteractions.org

Drug-drug Interactions

EASL 2018

Drug-drug interactions between HCV DAAs and antiretroviral drugs.

		SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir disoproxil fumarate	◆	■	■	◆	◆	■	◆
	Tenofovir alafenamide	◆	◆	◆	■	◆	■	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	●	●
	Etravirine	◆	◆	●	●	●	●	●
	Nevirapine	◆	◆	●	●	●	●	●
	Rilpivirine	◆	◆	◆	■	◆	◆	◆
Protease inhibitors	Atazanavir/ritonavir	◆	◆*	◆*	■	●	●	●
	Atazanavir/cobicistat	◆	◆*	◆*	●	●	●	●
	Darunavir/ritonavir	◆	◆*	◆*	■	●	■*	●
	Darunavir/cobicistat	◆	◆*	◆*	●	●	◆*	●
	Lopinavir/ritonavir	◆	◆*	◆*	●	●	●	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■*	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	◆	◆
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

Drug-drug interactions between HCV DAAs and immunosuppressants.

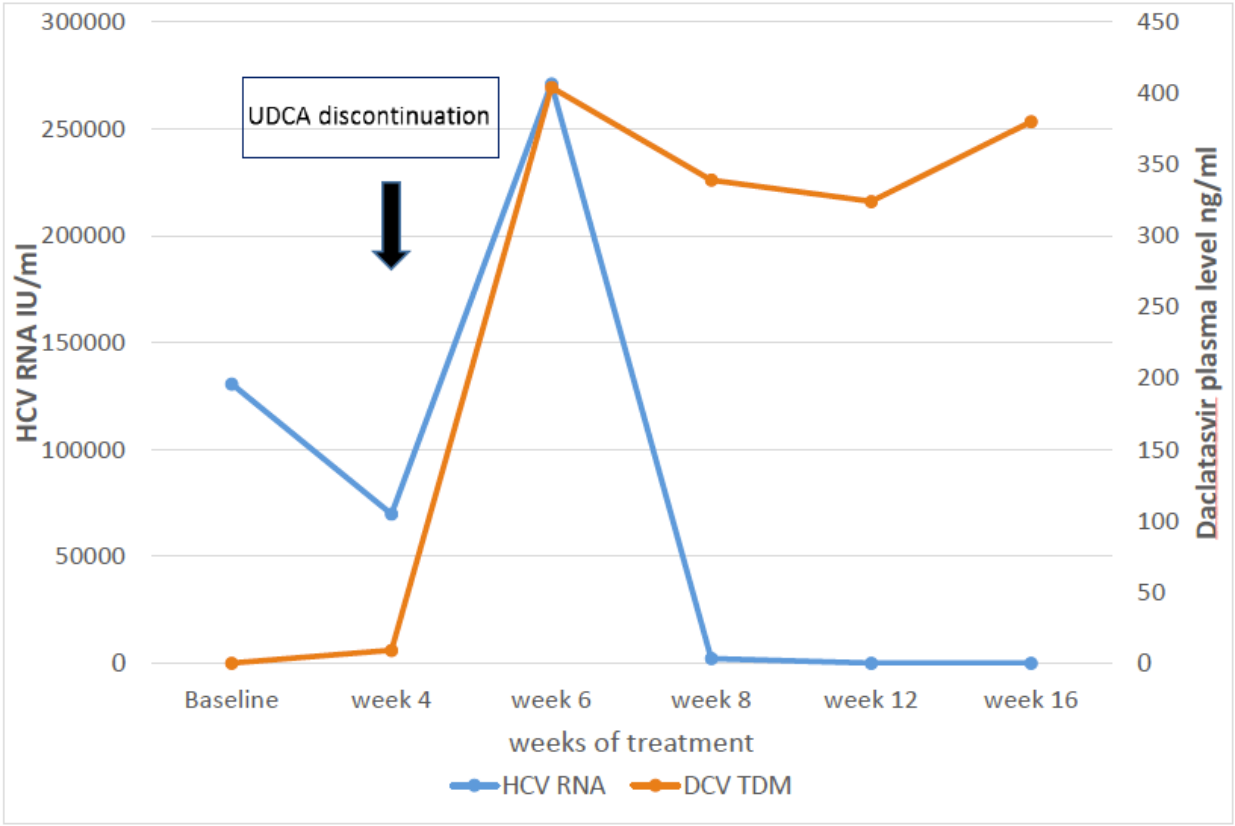
	SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
Azathioprine	◆	◆	◆	◆	◆	◆	◆
Cyclosporine	◆	◆	◆	■	●	●	■
Etanercept	◆	◆	◆	◆	◆	◆	◆
Mycophenolate	◆	◆	◆	■	◆	◆	◆
Sirolimus	◆	◆	◆	■	■	■	■
Tacrolimus	◆	◆	◆	■	■	■	■

Inadequate daclatasvir blood levels in a liver transplantation recipient treated with sofosbuvir and daclatasvir in association with ursodeoxycholic acid: a case report.

Bussini L.[1], Guardigni V.[1,2], Badia L.[1,2], Francalanci E.[1], Rinaldi M.[1], Conti M.[3], Viale P.[1,2], Verucchi G.[1,2]

The known interaction between DCV and UDCA seems to have led to a complete loss of therapeutic efficacy of DCV.

Careful monitoring of co-medication is mandatory in patients treated with DAAs after LT.



- TDM can play a key role in this setting, allowing an early identification and correction of sub-optimal drug exposition.

Liver transplantation from HIV+ donor to HIV+ recipient

	UK	Swizerland	U.S.
Transplant year	2011	2015	2016
Pubblication	NEJM Letter to editor	AJT case report	News articles
Outcomes	Transiet HIV viral increase No rejection reported	HIV viral suppression No rejection reported	-
Patient survival	3y	5m	-

Hathorn N.Engl.J.Med. 2016, Calmy Am.J. Transplant 2016, http://www.hopkindmedicine.org

Liver transplantation from HIV+ donor to HIV+ recipient: a case report

G. Travi[1], M.Merli[1], M.C. Moioli[1], A. Pazzi[1], A. Lauterio[2], R. De Carlis[2], S. Di Sandro[2], F. Ferla[2], L. De Carlis[2,4], A. De Gasperi[3], M. Puoti[1]

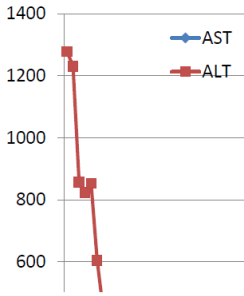
[1] SC Malattie Infettive, ASST Grande Ospedale Metropolitano Niguarda, Milano

Ospedale Niguarda — Sistema Socio Sanitario Regione Lombardia

CASE REPORT

- M, 50 years old
- Multifocal HCC: 2011 and 2016
- 11 months on the waitlist
- Stage C3 (CDC)
- ARV: 2005 TDF/FTC+EFV→ Jan 2015 rilpivirine→ 2017 dolutegravir. HIVR negative
- HCV-HBV-HDV+, MELD 10, Child -Pugh score was A6.
- Donor: M, 52 years old man, HIV+. ARV: ABC/3TC+DTG (first regimen, no failure). Last available HIVRNA: negative; CD4 count 501 cells/mm3 (23%)
- HIVRNA at day
  No coinfection
- Donor/Recipie

AST/ALT

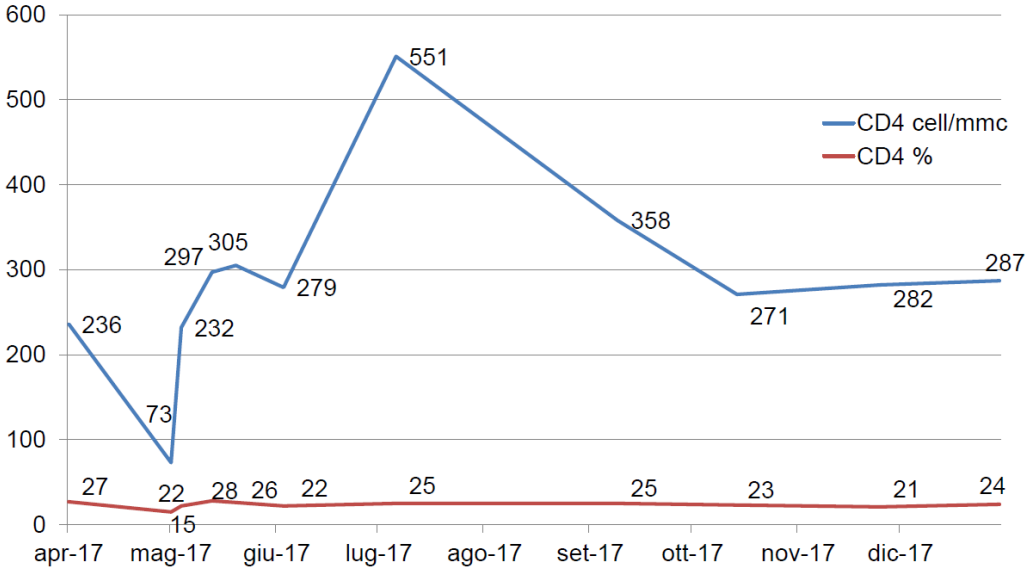


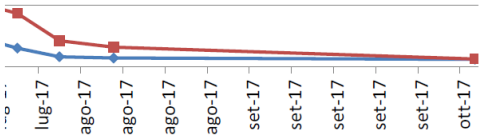
AST-ALT-bilirubine values

Date	AST	ALT	bilirubine
27/05/17	89	1278	1,06
28/05/17		1231	5,77
29/05/17		857	1,26
30/05/17		824	1,16
31/05/17	290	854	1,45
01/06/17	96	605	1,67
03/06/17		287	1,37
05/06/17	75	268	1,44
06/06/17		264	1,56
08/06/17	50	209	1,26
15/06/17	26	76	1,41
29/06/17	24	40	1,45
06/07/17	28	51	1,46
12/07/17	47	102	1,14
19/07/17	93	203	0,92
25/07/17	61	173	1,46
01/08/17	33	85	1,2
10/08/17	29	64	1,2
09/10/17	25	26	0,7

CD4

HIVRNA TND during follow up





Donatore deceduto con Infezione da HIV

Modifica dell'articolo 3 del decreto 2 agosto 2002, recante: «Criteri e modalita' per la certificazione dell'idoneita' degli organi prelevati al trapianto (art. 14, comma 5, legge 1 aprile 1999, n. 91)».

Criteri aggiuntivi di eleggibilità del donatore deceduto con infezione da HIV

- Storia conosciuta di infezione da HIV
- Se in ART. disponibilità degli schemi terapeutici effettuati
- Nessuna evidenza di patologie opportunistiche e/o neoplasia correlata all'infezione da HIV in atto
- Idoneità dell'organo documentata istologicamente
- Possibilità da parte dell'equipe infettivologica di individuare un adeguato regime ART da iniziare nel ricevente, sulla base della storia clinica e farmacologica del donatore e del ricevente, assicurando che tale regime sarà tollerato, efficace e sicuro
- Carica virale e conta CD4: nessuna restrizione

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Current doubts

- HIV superinfection from donor to recipient
- Different HIV subtypes and viral tropism
- Drug resistance transmission
- Antiretroviral Therapy
- Ethic problems