UPDATE ON LIVER TRANSPLANTATION IN HIV 2013

JAMES O'BEIRNE

Royal Free Hospital

50 years of Liver Transplantation

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HOMOTRANSPLANTATION OF THE LIVER IN HUMANS

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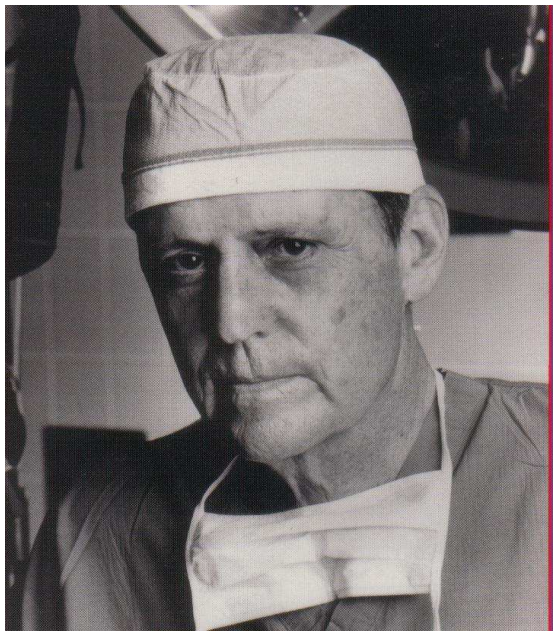
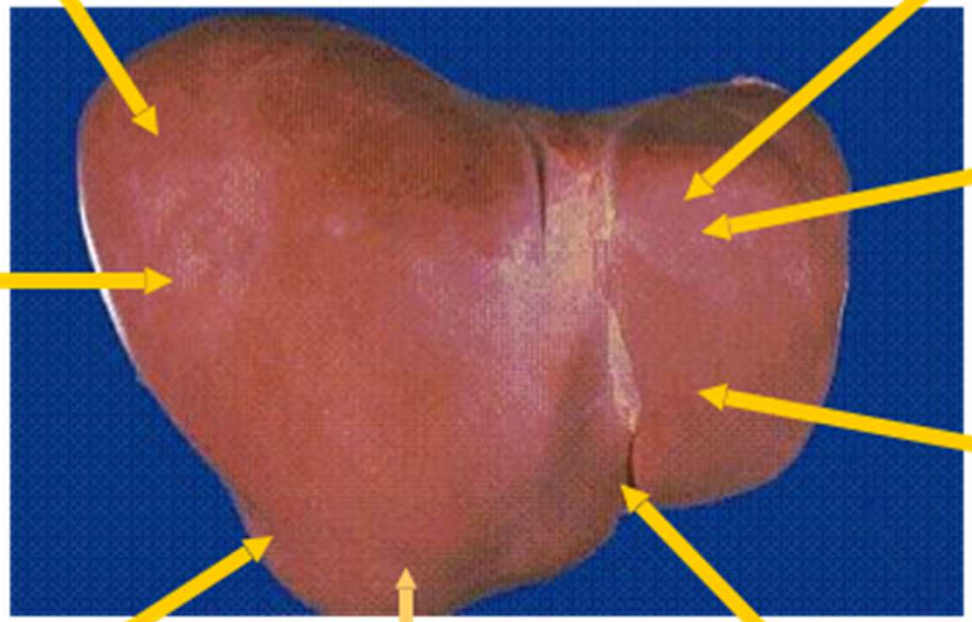
will be described. The first attempt resulted in failure at the operating table. The course of the second 2 patients establishes the feasibility of such an operation in humans, despite the fact that death occurred 22 and 7½ days after transplantation from pulmonary emboli.

- Surgical & Medical innovation
- Patient selection



Liver Disease in HIV-infected Patients



Opportunistic diseases[1]

HCV treatment[1]

HIV treatment[1]
NNRTIs, PIs, NRTIs

Hepatitis viruses[1]

Fatty Liver Disease[2]

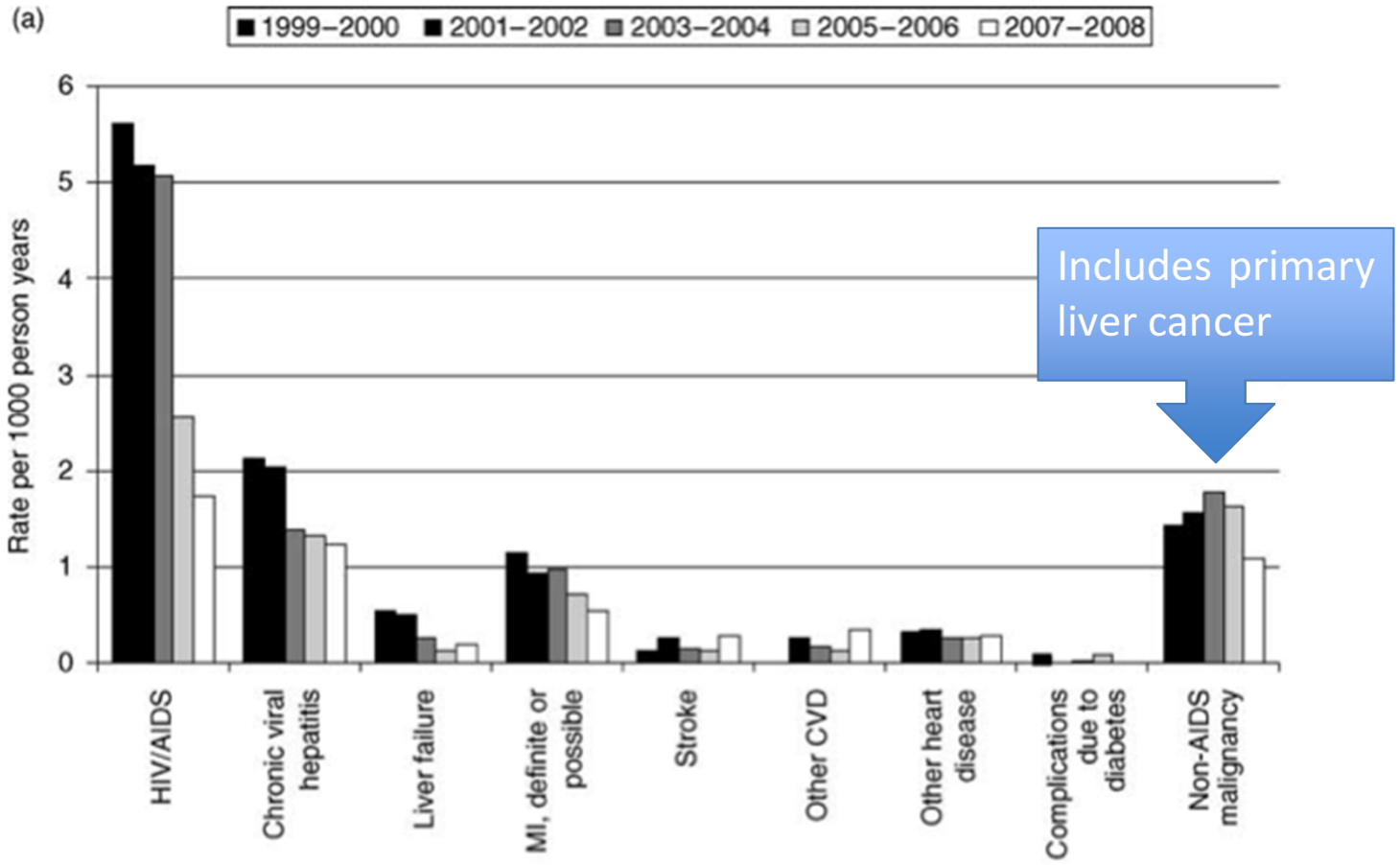
Immune reconstitution[3]

Pre-existing diseases[1]

Alcohol abuse/ IVDU[1]

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

Causes of death in HIV



1. Weber R, Sabin CA, Friis-Møller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch. Intern. Med. 2006;166:1632–1641.

HCV co-infection

- 1/3 rd of patients with HIV infection in Europe and the USA are co-infected with HCV
- 90% of deaths in HIV-positive patients with end-stage liver disease are attributed to HCV infection
  - HIV accelerates both HBV and HCV liver disease
  - HIV/HCV coinfection is associated with a reduced rate of spontaneous HCV RNA
  - More rapid rate of fibrosis progression
  - Following development of cirrhosis, the course of the liver disease is accelerated
  - median estimated survival time is only 13 months following the first decompensating event

1. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of Human Immunodeficiency Virus Infection on the Course of Hepatitis C Virus Infection: A Meta-Analysis. Clin. Infect. Dis. 2001;33:562–569.
2. Bonnard P, Lescure FX, Amiel C, Guiard-Schmid J-B, Callard P, Gharakhanian S, et al. Documented rapid course of hepatic fibrosis between two biopsies in patients coinfected by HIV and HCV despite high CD4 cell count. J Viral Hepat. 2007;14:806–811.
3. Sulkowski MS, Mehta SH, Torbenson MS, Higgins Y, Brinkley SC, de Oca RM, et al. Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults. AIDS. 2007;21:2209–2216.

HBV Co-infection

- 5-20% seroprevalence world wide
- Variable effect upon HIV progression/recovery after cART
- Faster fibrosis progression
- Increased rates of Hepatocellular carcinoma

1. Soriano V, Poveda E, Vispo E, Barreiro P. Hepatitis B in HIV-infected patients. Clin Liver Dis. 2013;17:489–501.
2. Thio CL, Seaberg EC, Skolasky R, Phair J, Visscher B, Muñoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002;360:1921–1926.

Hepatotoxicity is Seen With All Classes of ARV Drugs

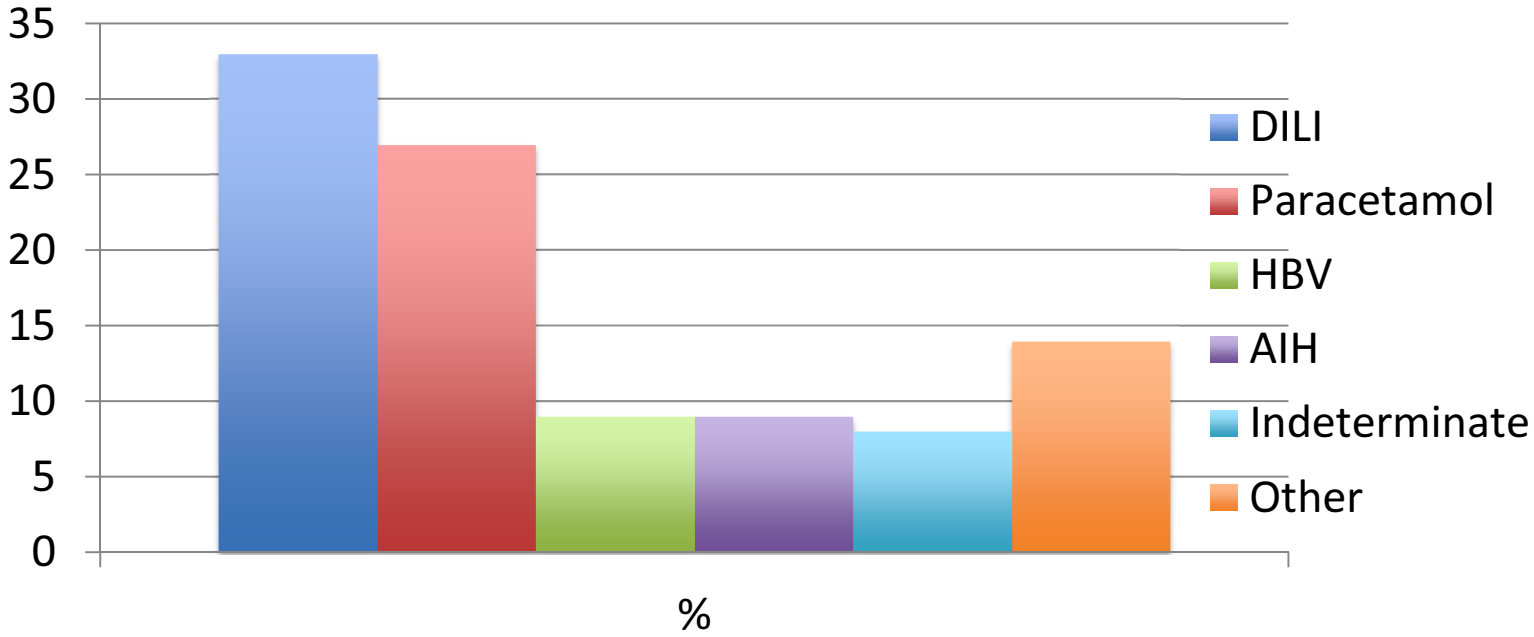
ACTG retrospective analysis of 21 trials on 10,622 patients

- **NRTI:** **6.3%; 95%CI (5.8-6.8%)**
- **NNRTI :** **8.2%; 95% CI (6.3-10.1%)**
- **Protease Inhibitors:** **6.2%; 95%CI (5.2-7.2%)**

- **Liver related death rate was 0.3% (2.5% of all deaths)**

Reisler K. AIDS Alert. 2001 Sep;16(9):118-9.

Acute Liver Failure in HIV

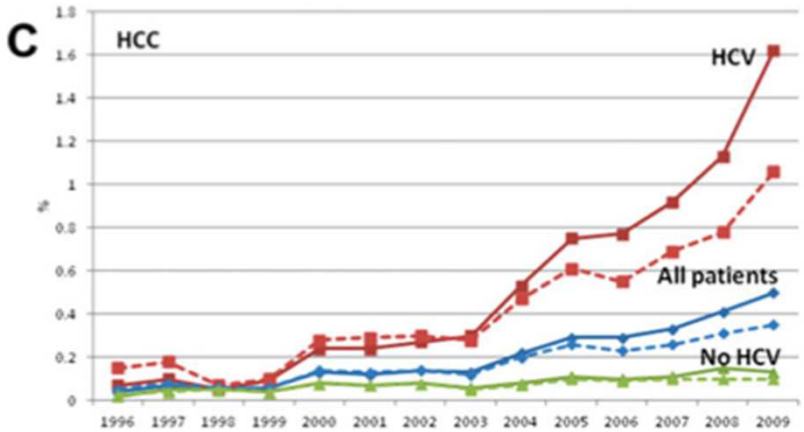


- HIV increases the risk of of ALF
- Efavirenz, Nevirapine, anti-TB etc….
- Usually severe in course
- 1.3% of Acute liver Failure in the USA (USALFSG)

1. Kramer JR, Giordano TP, Souchek J, El-Serag HB. Hepatitis C coinfection increases the risk of fulminant hepatic failure in patients with HIV in the HAART era. J Hepatol. 2005;42:309–314.
2. Clark SJ, Creighton S, Portmann B, Taylor C, Wendon JA, Cramp ME. Acute liver failure associated with antiretroviral treatment for HIV: a report of six cases. J Hepatol. 2002;36:295–301.

HCC

- Increasing prevalence esp. in HCV
- May have a more aggressive phenotype
  - Younger age at presentation
  - Higher Median AFP



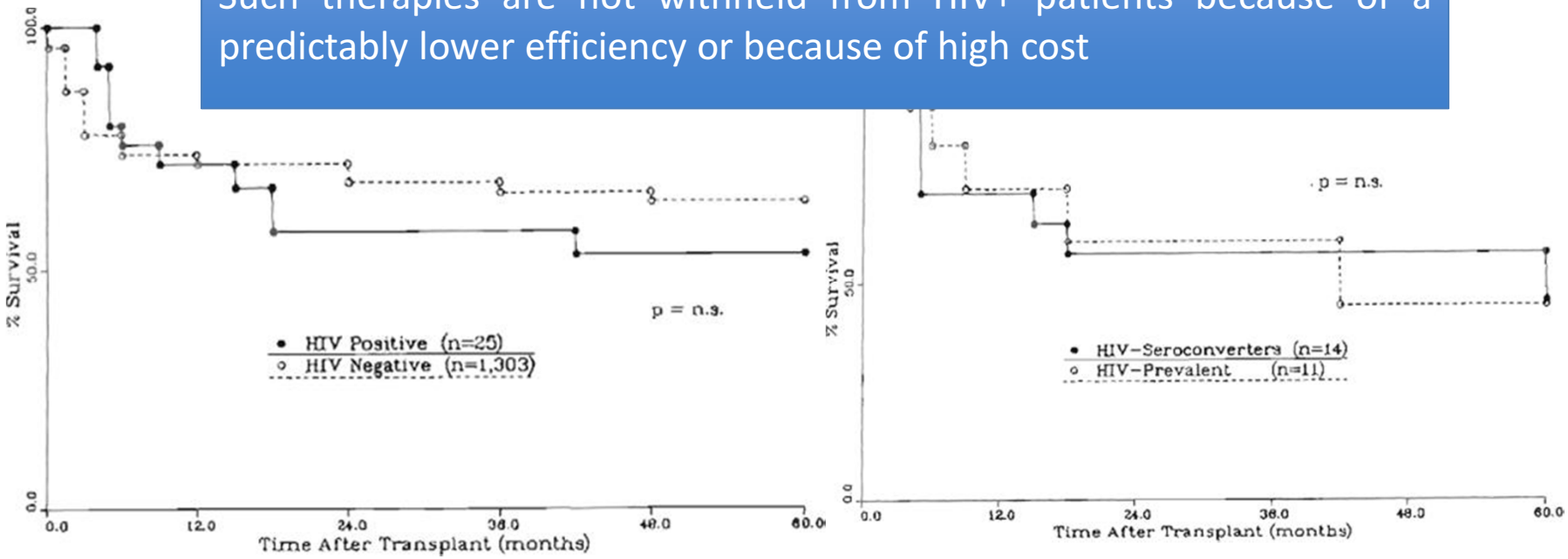
Initial presentation			
Liver mass on imaging (screening)	20 (31.7%)	104 (50.7%)	
Elevated AFP (screening)	11 (17.5%)	23 (11.2%)	0.048

1. Ioannou GN, Bryson CL, Weiss NS, Miller R, Scott JD, Boyko EJ. The prevalence of cirrhosis and hepatocellular carcinoma in patients with human immunodeficiency virus infection. Hepatology. 2013;57:249–257.

Liver Transplantation in HIV- historical aspects

- Pittsburgh 1990
- 25 p
- 11 i
- 14 i

In HIV+ patients who have no evidence of AIDS, transplantation can prolong meaningful life in the majority of patients but less reliably and less safely than in HIV− recipients.
It is self- evident that the same statement could be made about virtually every other major medical or surgical therapy available today. Such therapies are not withheld from HIV+ patients because of a predictably lower efficiency or because of high cost



1. Tzakis AG, Cooper MH, Dummer JS, Ragni M, Ward JW, Starzl TE. Transplantation in HIV+ patients. Transplantation. 1990;49:354–358.

Experience in the pre cART era

TABLE 1. HIV-positive patients at the time of transplantation, previously reported

No	Age	Center	Diagnosis	Immunosuppression	Rejection/Treatment	AIDS-Defining Illness	Outcome
1	48	Pittsburgh	N/A	C+P+OKT3	No	No	A:8m
2	15	Pittsburgh	HBV/HDV/NANB/H-A	C+P+OKT3	No	Yes: To (41 m); CMV (44 m)	D:44m
3	48	Pittsburgh	HBV/ALD/H-A	C+P	Yes:1 (OKT3+MoAb)	Yes: PCP (3 m)	D:4m
4	0.5	Pittsburgh	N/A	C+P+OKT3	No	No	D:9m
5	32	Pittsburgh	N/A	C+P+OKT3	No	Yes: immunoblastic sarcoma	D:8m
6	42	Pittsburgh	N/A	C+P	No	No	D:6m
7	3	Pittsburgh	N/A	C+P	No	No	A:68m
8	21	Pittsburgh	HBV/H-A	Not applicable	Not applicable	Not applicable	IOD
9	35	Mass. General	NANB/H-A	C+P+Az	Yes: 3 (steroids)	Yes: Cr (14 m); PCP (21 m)	D:27m
10	N/A	Deaconess	N/A	C+P	Yes: 3 (steroids+OKT3)	Yes: HSV, CMV	D:11m
11	N/A	Cambridge	ALD	C	Yes: 1 (steroids)	No	A:100m
12	35	Pittsburgh	HBV	T+C+P+PGE^1/PGE^2	Yes: 3 (steroids)	Yes: CMV	D:70d
13	N/A	Omaha	N/A	N/A	N/A	N/A	D:2m
14	N/A	Omaha	N/A	N/A	Yes	Yes: herpes zoster	A:9m

UK Experience

- 1st case HIV+ve Haemophiliac transplanted at Kings College Hospital - 1996

TABLE 2. Summarized data of HIV-positive liver transplant patients at King's College Hospital

No	Age	Sex	Diagnosis	CD4 pre-OLT	HIV-RNA pre-OLT	Immunosuppression	Rejection	AIDS-Defining Illness	Outcome
1	36	M	HCV+H-A	280[a]	N/A	T+P	Yes	Yes (PCP-1 year pre-OLT)	D:25m
2	26	M	HCV+H-A	160[a]	N/A	C+P+Az->C+P->T+P->T	Yes	?Yes (weight loss > 10% post-OLT)	D:15m
3	39	F	HCV	>500[a]	Undetectable	T+P	Yes	No	D:6m
4	40	M	Acute HBV	124[a]	25,000[b]	T+P->T	No	No	A:24m
5	30	M	NANB	172[a]	132,690[b]	T+P->T	Yes	No	A:4m

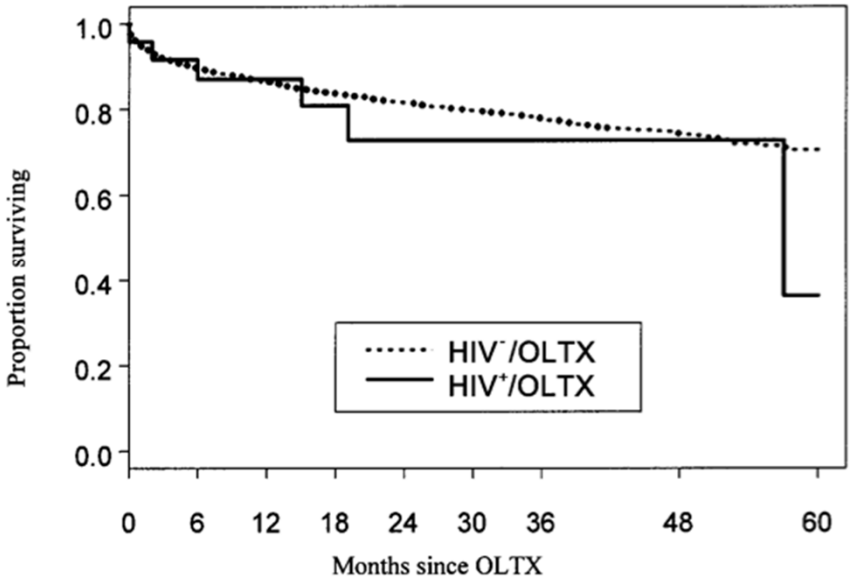
[a] Cell-count/ml.
[b] Copies/ml.

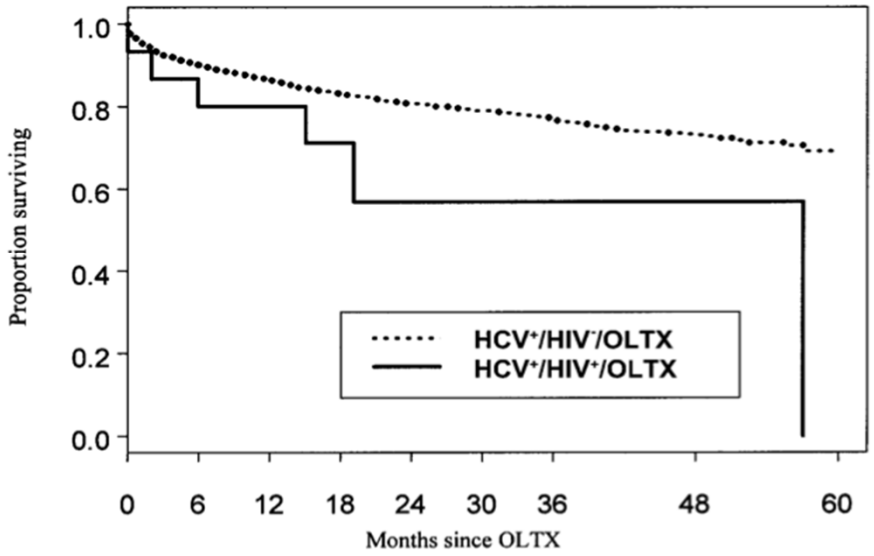
TABLE 3. Antiretroviral therapy

Pt no	Diagnosis	Pre-OLT (Duration)	Post-OLT (Duration)
1	HCV/H-A	None	saquinavir (9 m), zidovudine (5 m), 3TC
2	HCV/H-A	None	zidovudine (14 m)
3	HCV	lamivudine/zidovudine (1 year)	lamivudine, zidovudine, stavudine
4	Acute HBV	lamivudine (2 days)	zidovudine, indinavir, didanosine, nevirapine, stavudine
5	NANBNC	zidovudine, lamivudine, abacavir (6 days)	zidovudine, lamivudine, abacavir

Prachalias AA, Pozniak A, Taylor C, Srinivasan P, Muiesan P, Wendon J, et al. Liver Transplantation in Adults Coinfected With Hiv. Transplantation. 2001;72:1684.

Survival of HIV+ LT recipients in the post HAART era

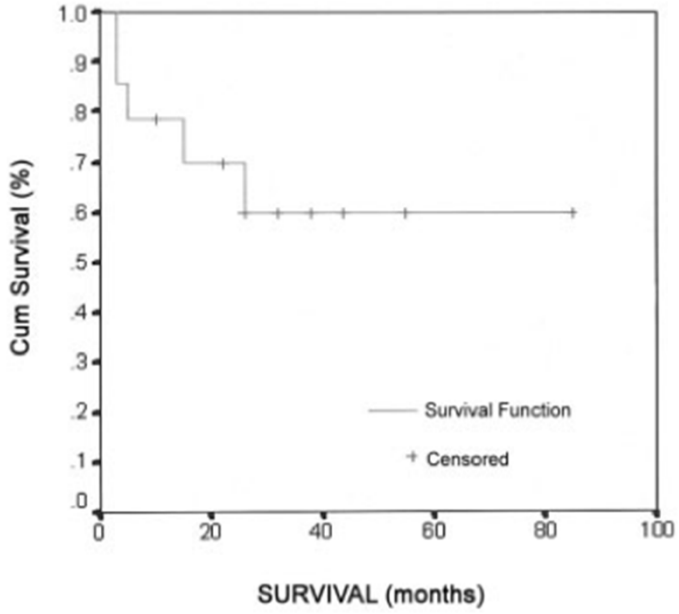


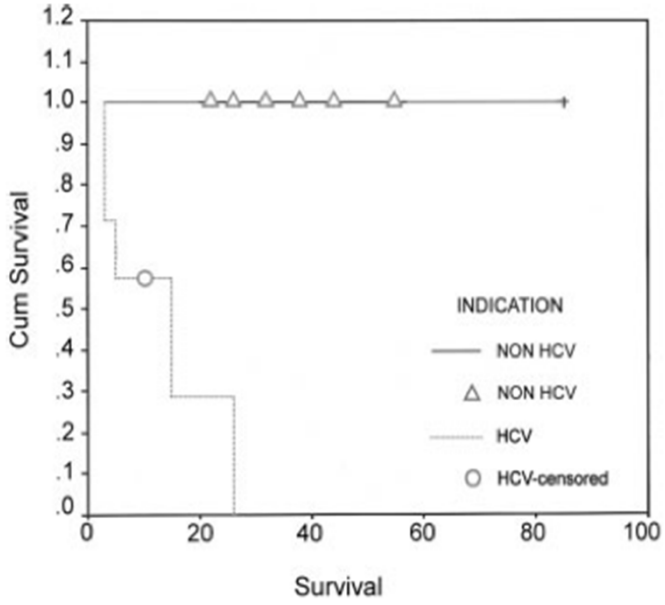


- N=24 US/UK experience

Fung J, Eghtesad B, Tom KP, DeVera M. Liver transplantation in patients with HIV infection. Transplantation. 2004;

Impact of HCV co-infection on LT outcome





Norris S, Taylor C, Muiesan P, Portmann BC, Knisely AS, Bowles M, et al. Outcomes of liver transplantation in HIV-infected individuals: the impact of HCV and HBV infection. Liver Transpl. 2004;10:1271–1278.

Outcomes

TABLE 3. Post-LT Outcomes for HIV-Positive Patients (All Etiologies)

Authors	n	Patient Survival (%)* 1 Year	2 Years
Neff et al.[59] (2003)	16	100	80
Ragni et al.[60] (2003)	24	87	73
Rafecas et al.[61] (2004)	4	100	—
Norris et al.[62] (2004)	14	79	70
Moreno et al.[63] (2005)	4	100	—
Schreibman et al.[64] (2007)	15	73	—
Vennarecci et al.[65] (2007)	12	83	58
Mindikoglu et al.[58] (2008)	138	80	70

*The survival rates are based on Kaplan-Meier or actuarial estimates.

Table 1. The 1-, 3- and 5-year survival rates in published series of liver transplantation for HIV/HCV coinfection.

Study (year)	n	1-year survival (%)	3-year survival (%)	5-year survival (%)	Ref.
Ragni *et al.* (2003)	15	80	57	–	[31]
de Vera *et al.* (2006)	27	67	56	33	[49]
Vennarecci *et al.* (2007)	12	83	58	–	[50]
Duclos-Vallée *et al.* (2008)	35	–	73	51	[51]
Terrault *et al.* (2012)	89	76	60	–	[35]
Miro *et al.* (2012)	84	88	–	54	[32]
Baccarani *et al.* (2012)	26	–	78	68	[52]

Dannhorn E, O'Beirne JP. Liver transplantation for HIV/HCV coinfection: where is the controversy? Future Virology. 2013;8:639–648.

Joshi D, O'Grady J, Taylor C, Heaton N, Agarwal K. Liver transplantation in human immunodeficiency virus-positive patients. Liver Transpl. 2011;17:881–890.

Current UK guidelines for liver transplantation in HIV

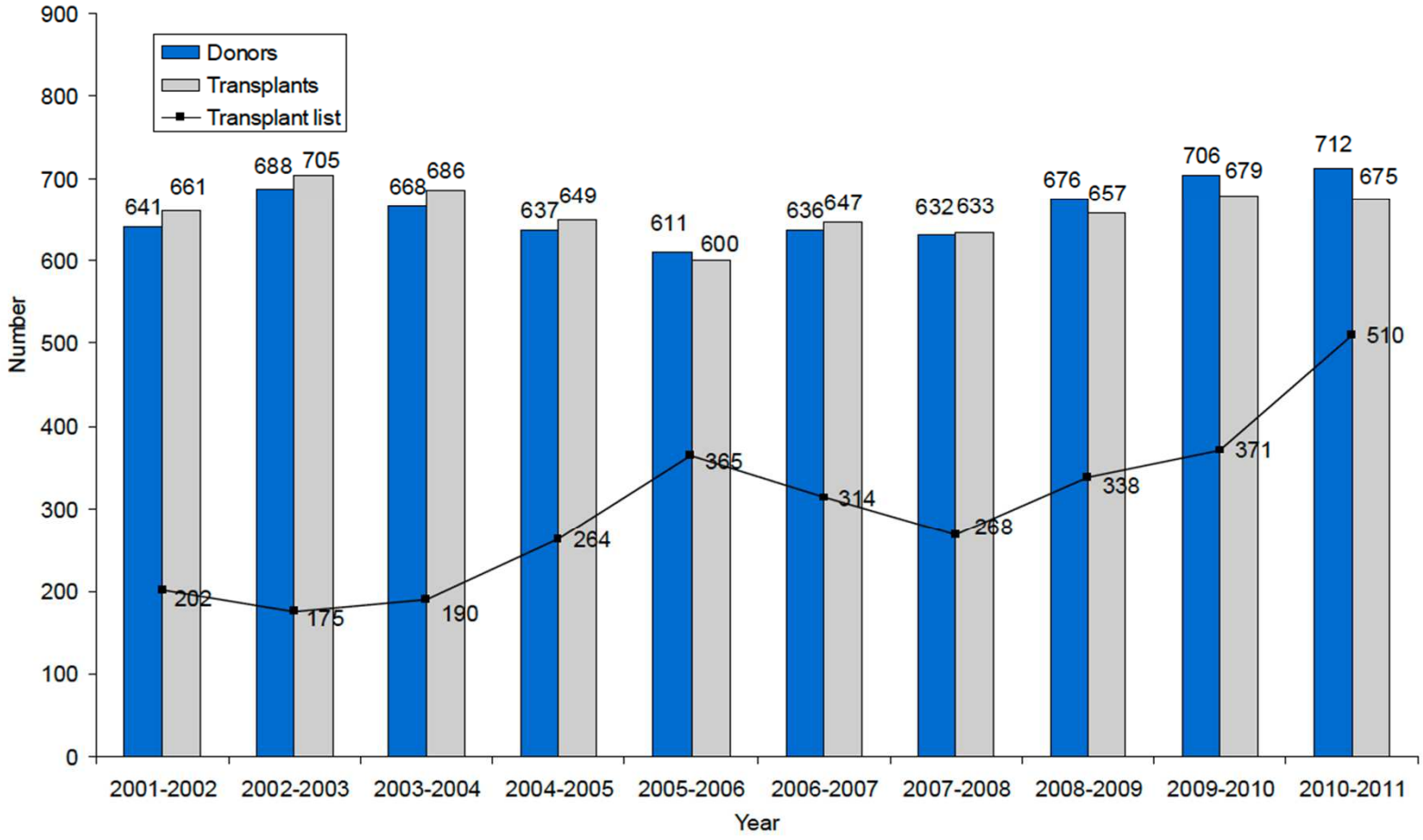
Box 1. UK guidelines for consideration of liver transplantation in HIV infection (in addition to the usual indications and contraindications).

- Meets conventional criteria for listing for liver transplantation[†] and:
  - CD4 counts of 200 cells/ml, or 100 cells/ml in the presence of portal hypertension
  - Absence of HIV viremia[‡]
  - Absence of AIDS-defining illness after immune reconstitution
  - Antiretroviral therapeutic options available if HIV disease reactivates

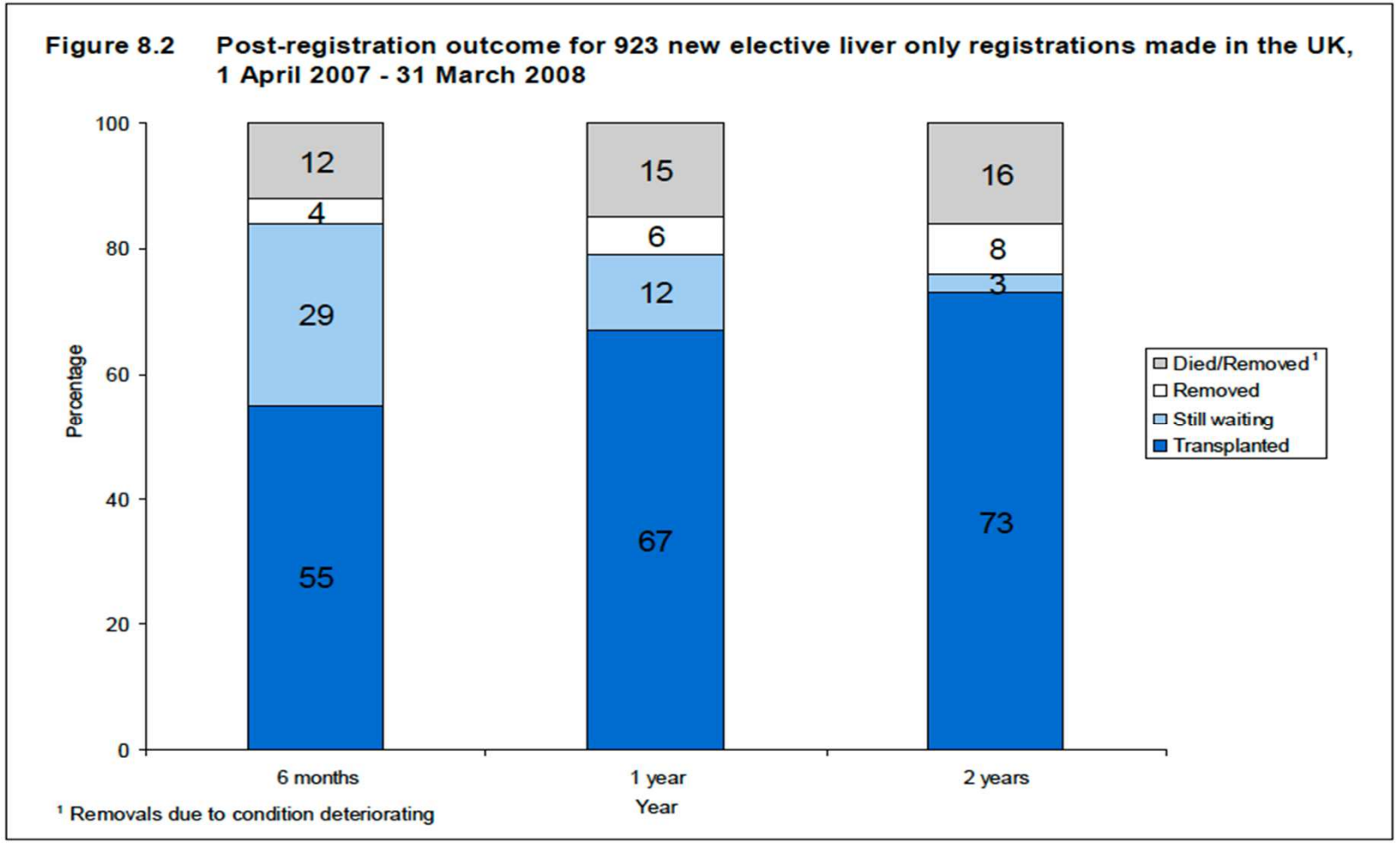
[†]UK Model for End-Stage Liver Disease score >49, diuretic-resistant ascites or other variant syndrome, hepatic encephalopathy or hepatocellular carcinoma within accepted criteria.
[‡]Except in de novo presentation of HIV infection in cases of acute liver failure.
Adapted with permission from [30].

UK Liver Transplant – number of transplants and number on waiting list

Figure 8.1 **Deceased donor liver programme in the UK, 1 April 2001 - 31 March 2011**
Number of donors, transplants and patients on the active transplant list at 31 March



Outcome of patients wait listed for Liver transplant in the UK



Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

- 27 HIV+ve patients undergoing LT (17 with HCV, 2012 n=26)
- 37% HCC
- Median Age 45 years
- MELD at LT = 15
- Median donor age 48 years

Low MELD at listing and LT
Younger donors

Baccarani, U., Scudeller, L., Adani, G. L., Viale, P. & Tavio, M. Is liver transplantation feasible in patients coinfected with human immunodeficiency virus and hepatitis C virus? Liver Transpl 18, 744

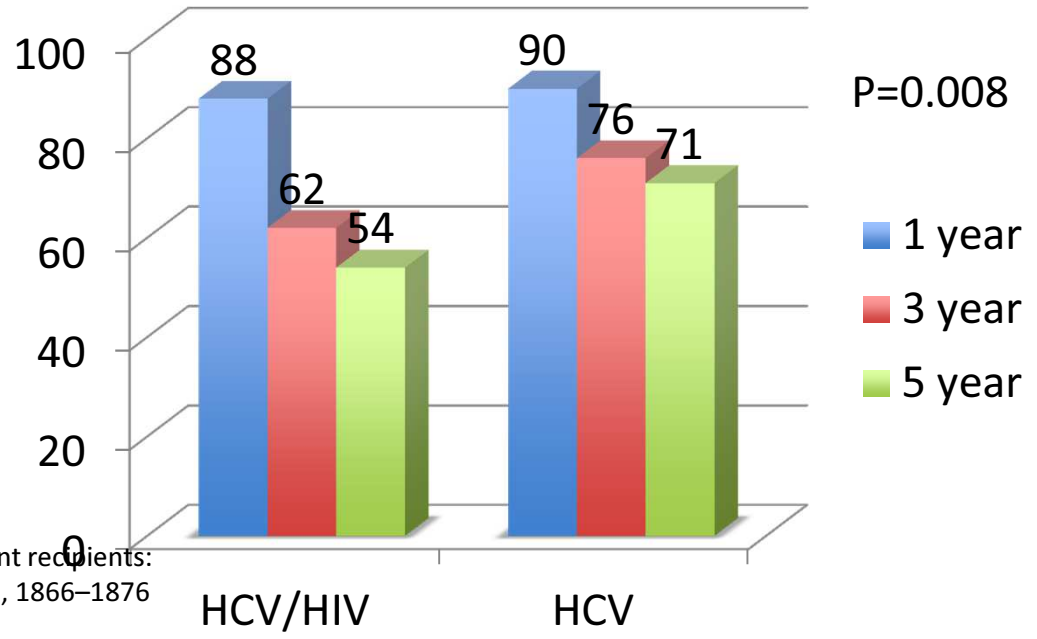
Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

- Prospective multicentre cohort study
- 84 HCV/HIV co-infected LT patients 2002-2006 matched with non-HCV controls
- Majority Genotype 1
- MELD at listing 15 MELD at LT 16
- DRI 1.4
- Donor age (median) 52

Biopsy proven rejection
38% HCV/HIV 20% HCV

Factors significant in multivariate analysis:

MELD
Genotype 1
Transplant centre experience



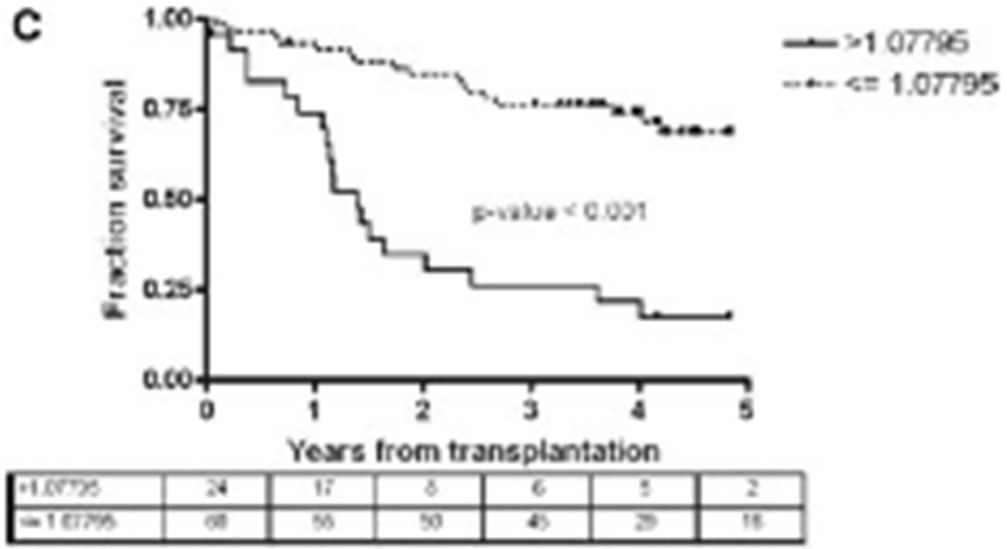
Miro, J. M. et al. Outcome of HCV/HIV-coinfected liver transplant recipients: a prospective and multicenter cohort study. Am J Transplant 12, 1866–1876 (2012).

Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

- Exp ([(0.81966∗ if genotype = 1] + [0.05748∗ MELD pre-OLT] + [1.03540 if center <1 OLT in HIV-infected patients/year])
- Risk score cut-off of 1.07795 classified the 84 recipients as having a low risk

  (n = 60 patients, 69%) or a high risk of death (n = 24 patients 31%)

5 yr survival of Risk score < 1.077
=69%



Miro, J. M. et al. Outcome of HCV/HIV-coinfected liver transplant recipients: a prospective and multicenter cohort study. Am J Transplant 12, 1866–1876 (2012).

Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

- Prospective study 89 patients 2003-2010
- 2 control groups
  - Matched
  - High risk group (>65 years old)

	HCV/HIV	HCV
Age	49	54
BMI	25	28
MELD@LT	20	20
HCC %	30	30
Genotype 1 %	80	80
Donor Age	37	42
NHBD %	17	4

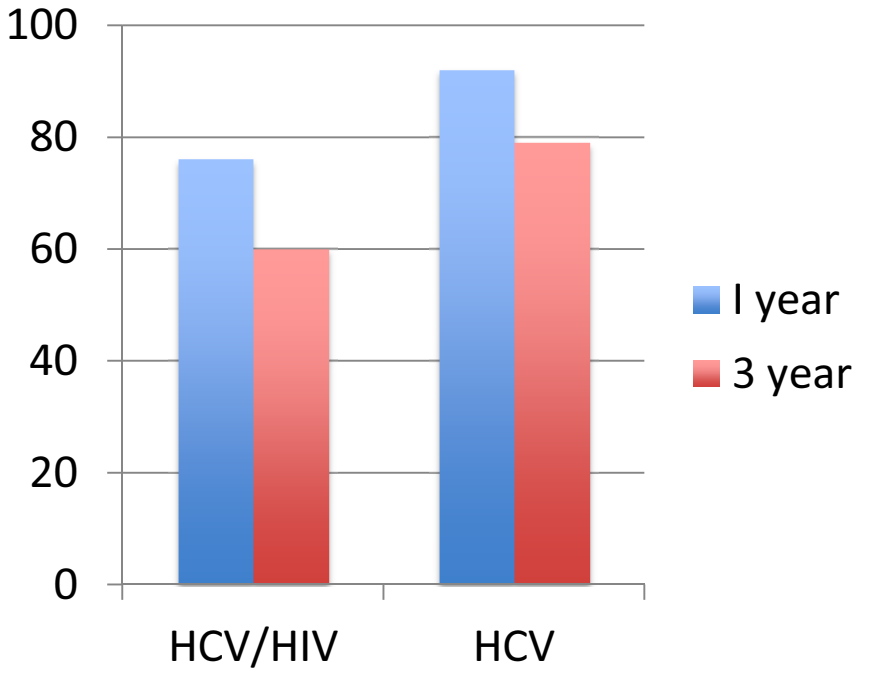
Terrault, N. A. et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. Liver Transpl 18, 716–726 (2012).

Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

Multivariate analysis of factors associated with mortality:

CLKT
BMI<21
Anti-HCV positive donor
Older donor age

In patients without these risk factors survival no different to HCV patients >65 yrs



Biopsy proven rejection
39% HCV/HIV 24% HCV

Terrault, N. A. et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. Liver Transpl 18, 716–726 (2012).

LT for HCV/HIV co-infection

Box 2. Pretransplant and donor variables associated with increased risk of graft loss and mortality in coinfected liver transplant recipients.

Pretransplant/recipient variables

- Genotype 1 HCV infection
- Combined liver–kidney transplant†
- BMI <21 kg/m^2
- Center volume (<1 HIV-positive liver transplant/year)

Donor variables

- Higher donor age
- Donation after circulatory death donor
- HCV-positive donor

†*Reflecting renal dysfunction in the recipient.*

Box 3. Characteristics of HIV/HCV-coinfected patients associated with good outcomes following liver transplantation.

- Normal renal function
- BMI >21
- MELD <25
- Non-genotype 1 HCV

MELD: Model for End-Stage Liver Disease.

Achievable in the UK?

High rate of DCD grafts – 20%
Older donors
UKELD

Dannhorn E, O'Beirne JP. Liver transplantation for HIV/HCV coinfection: where is the controversy? Future Virology. 2013;8:639–648.

Hope for the future?

- Photon-1 114 G1 (4% cirrhotic) 42 G3 (14% cirrhosis) HIV co-infection
- Sofosbuvir 400mg od + RBV 1000-1200mg
  - 12 weeks G3
  - 24 weeks G1
- SVR12
  - G1 76%
  - G3 67%
- Well tolerated
- No interactions with wide range of ARV
- No resistance mutants in viral breakthrough patients

MS Sulkowski, M Rodriguez-Torres, JP Lalezari, et al. All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV (PHOTON-1). 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Washington, DC, November 1-5, 2013. Abstract212

Sofosbuvir and Ribavirin for the Treatment of Established Recurrent Hepatitis C Infection After Liver Transplantation: Preliminary Results of a Prospective, Multicenter Study

- Phase 2 Multicenter post LT
- 80% Genotype 1
- 88% treatment experienced
- 40% cirrhotic, 23% bridging fibrosis
- Sofosbuvir 400 mg od with increasing RBV as tolerated
- SVR 4 77%
- No immunosuppressant interactions
- 15% anaemia
- No death or graft loss

MR Charlton, EJ Gane, MP Manns, et al. Sofosbuvir and Ribavirin for the Treatment of Established Recurrent Hepatitis C Infection After Liver Transplantation: Preliminary Results of a Prospective, Multicenter Study.*64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Washington, DC, November 1-5, 2013. AbstractLB-2*

Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection after Liver Transplantation

- 61 patients - multicentre
- Mostly HCC with G1 HCV 77% treatment experienced
- Median MELD of 8
- Sofosbuvir 400 mg od and RBV 1000-1200mg/day
- Upto 48 weeks treatment whilst awaiting LT
- 91% were HCV RNA –ve after 12 weeks of therapy
- 64% of patients HCV RNA –ve at time of LT were HCV-RNA negative 12 weeks post LT
- Only 1 patient rendered HCV RNA negative for > 30 days relapsed after LT
- Well tolerated

MP Curry, X Forns, RT Chung, et al. Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection after Liver Transplantation.64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Washington, DC, November 1-5, 2013. Abstract213

Lessons from the past that inform the future

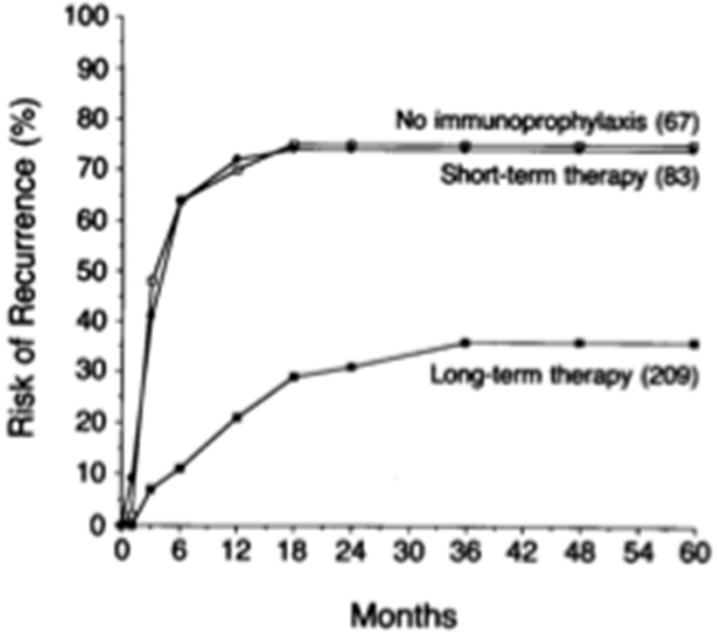


Figure 2. Actuarial Risk of Recurrence of HBV, According to the Duration of Passive Prophylaxis with Anti-HBs Immune Globulin.

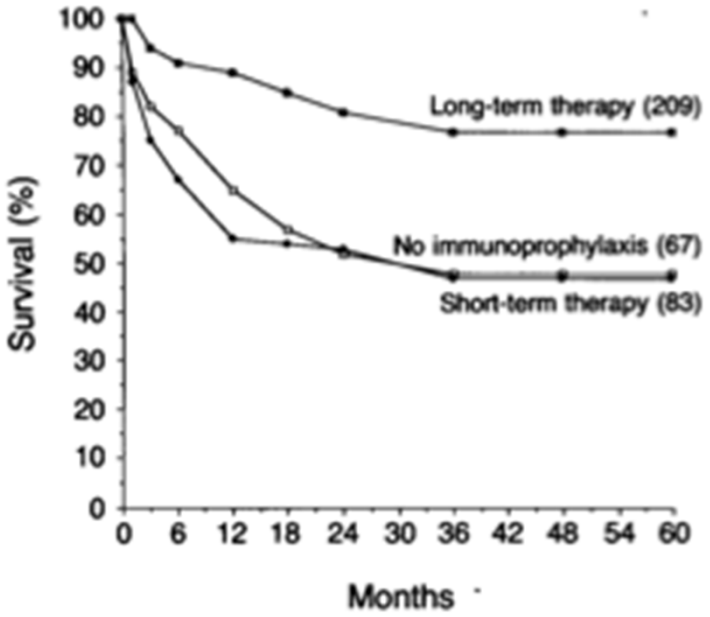


Figure 4. Actuarial Survival, According to the Duration of Passive Prophylaxis with Anti-HBs Immune Globulin.

1842 THE NEW ENGLAND JOURNAL OF MEDICINE Dec. 16, 1993

LIVER TRANSPLANTATION IN EUROPEAN PATIENTS WITH THE HEPATITIS B SURFACE ANTIGEN

DIDIER SAMUEL, M.D., RAINER MULLER, M.D., GRAEME ALEXANDER, M.D., LUIGI FASSATI, M.D., BÉATRICE DUCOT, M.D., JEAN-PIERRE BENHAMOU, M.D., HENRI BISMUTH, M.D., AND THE INVESTIGATORS OF THE EUROPEAN CONCERTED ACTION ON VIRAL HEPATITIS STUDY*

Barriers to LT

- Must meet the conventional listing criteria for liver transplantation in the UK
- Which means……
  - Stable methadone but no heroin, crack or cocaine/ other recreational drugs
  - Alcohol – risk of relapse, need for abstinence (life long) even where alcohol is a co-factor eg. in HCV

www.odt.nhs.uk/pdf/liver_selection_policy.pdf

Conclusions

- Liver disease (including HCC) is prevalent and will continue to rise in HIV infected individuals
- Current results support the use of LT in selected individuals although results in HCV co-infection are currently sub-optimal
- DAAs offer hope for the future although data is limited
- Multidisciplinary approach mandatory