Solid Organ Transplantation from HBV-Infected Donors

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Abbreviations

- HBsAg = hepatitis B surface antigen
- anti-HBc = hepatitis B core antibody
- anti-HBs = hepatitis B surface antibody

Background

- The need for an expanded donor pool is mandated by organ shortages
- Use of donors with infections that can be easily managed in the recipient should be encouraged
- HBV-infected donors offer an opportunity to expand the donor pool, particularly in endemic countries

DON'T
WORRY
HBV
HAPPY

Considerations for Use of HBV-Infected Donors

- Definition of HBV-infected donors
  - HBsAg+
  - HBV DNA+ (or NAT+)
  - anti-HBc+
- Risk of *de novo* hepatitis B virus infection
  - Seroconversion
  - Acquisition of HBV DNA
  - HBV-related liver disease
  - Graft and patient survival

Risk of *de novo* hepatitis in liver recipients from hepatitis-B core antibody-positive grafts – a systematic analysis

Table 1. Study characteristics

Study	Patients	DNH (#)	Living donor (Y/N)	Prophylaxis (Y/N)	Type of prophylaxis
Barcena et al. (5)	23	1	N	N	NA
Castells et al. (6)	12	2	N	N	NA
Chen et al. (7)	24	3	Y	Y	Lam alone
De Feo et al. (8)	61	7	N	N	NA
Dickson et al. (2)	23	18	N	N	NA
Dodson et al. (10)	47	18	N	N	NA
Dodson et al. (9)	16	1	N	Y	HBIG alone, HBIG/lam
Donataccio et al. (11)	19	8	N	Y	HBIG alone
Douglas et al. (12)	9	3	N	N	NA
Fabrega et al. (13)	7	0	N	Y	HBIG/lam
Holt et al. (14)	12	0	N	Y	HBIG/lam
Celebi Kobak et al. (15)	16	0	Y	Y	Lam alone
Kwon et al. (16)	28	3	Y	Y	HBIG alone
Lee et al. (4)	14	3	Y	Y	HBIG alone
Loss et al. (17)	14	1	N	Y	HBIG/lam
Manzarbeitia et al. (18)	27	5	N	Y	HBIG alone
Nery et al. (19)	62	2	N	Y	Lam alone, HBIG/lam
Prakoso et al. (20)	18	0	N	Y	Lam alone, HBIG/lam[a]
Prieto et al. (21)	30	15	N	N	NA
Rokuhara et al. (22)	7	3	Y	N	NA
Roque-Afonso et al. (23)	22	5	N	Y	HBIG alone
Suehiro et al. (24)	22	0	Y	Y	HBIG/lam
Takemura et al. (25)	19	2	Y	Y	HBIG
Uemoto et al. (26)	19	12	Y	Y	HBIG
Wachs et al. (27)	7	4	N	N	NA
Yu et al. (28)	15	0	N	Y	Lam alone

Skagen et al. Clin Transplant 2011

Rates of *de novo* HBV Stratified by Liver Recipient HBV Status

Recipient status (n)	DNH		Odds ratio (95% CI)	p-Value
	No prophylaxis	Prophylaxis		
HBV naïve (213)	58% (81/140)	11% (8/73)	11.15 (4.98–25)	<0.0001
HBcAb−, HBsAb+ (78)	18% (6/34)	2% (1/44)	9.17 (1.1–83.3)	0.039
HBcAb+, HBsAb+ (106)	4% (3/70)	3% (1/36)	1.56 (0.16–15.62)	1.00
HBcAb+, HBsAb− (65)	14% (5/35)	3% (1/30)	4.83 (0.53–43.92)	0.21

DNH, *de novo* hepatitis B; HBV, hepatitis B; HBcAb−, hepatitis-B core antibody negative; HBsAb+, hepatitis-B surface antibody positive; HBcAb+, hepatitis-B core antibody positive; HBsAb−, hepatitis-B surface antibody negative.

Prophylaxis with HBIG and/or lamivudine significantly reduced rates of DNH in HBV naïve or vaccinated liver recipients

Skagen et al. Clin Transplant 2011

2007 Survey of Antiviral Strategies in Liver Transplant Recipients from anti-HBc+ Donors

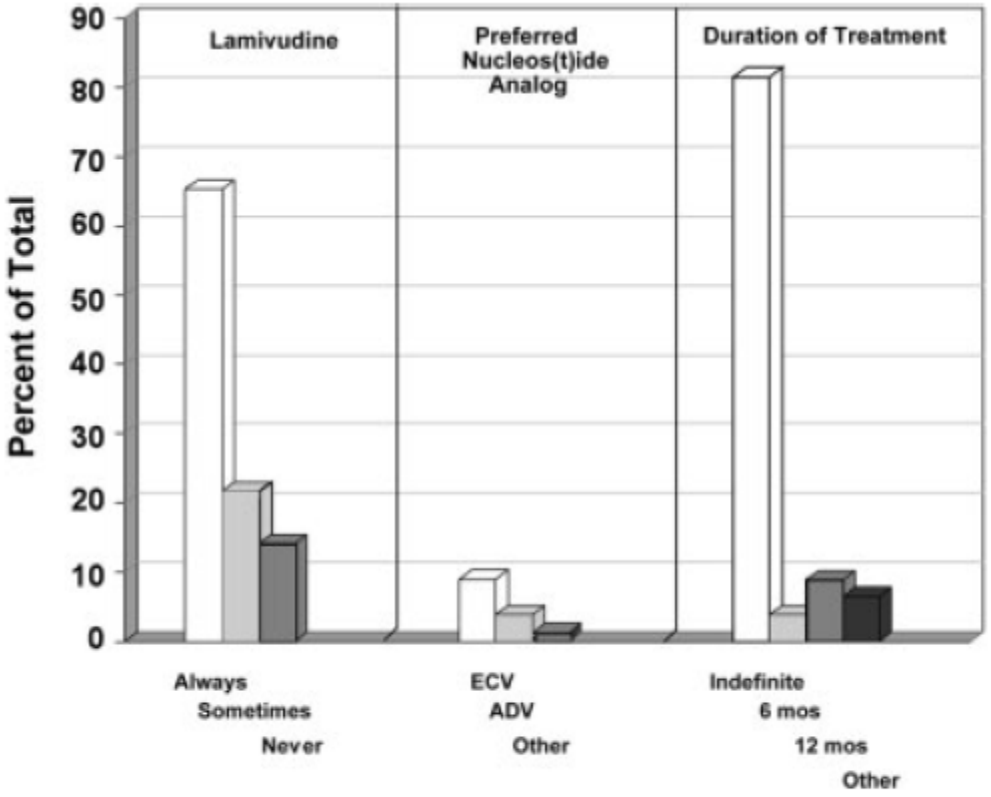


Figure 1. Preferred use of lamivudine and other nucleoside analogs as well as duration of use reported by 78 transplant physicians. Abbreviations: ADV, adefovir; ECV, entecavir;

Indefinite use of lamivudine was the preferred antiviral strategy

2007 Survey of HBIG Use in Liver Transplant Recipients from anti-HBc+ Donors

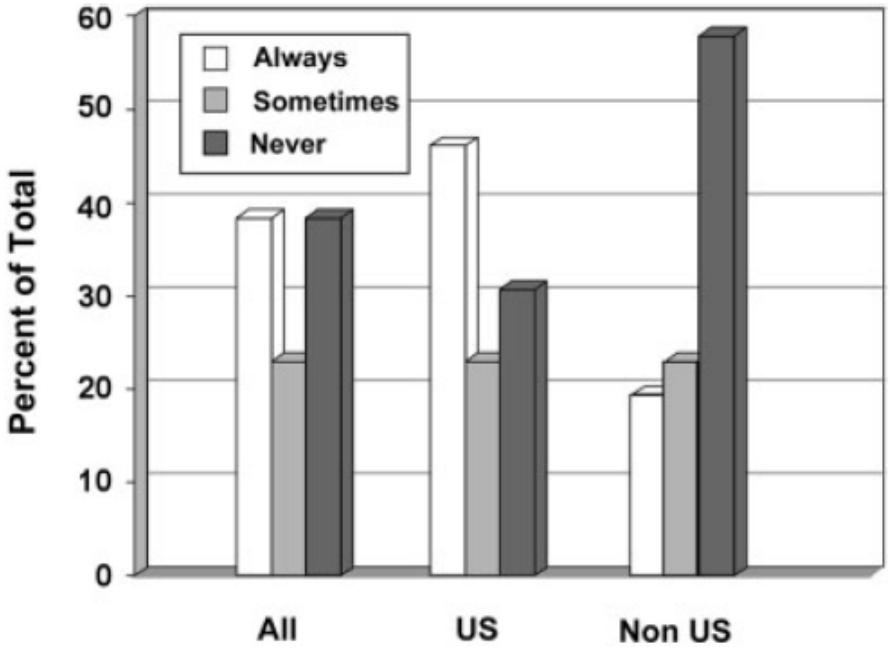


Figure 2. Use of hepatitis B immune globulin in the United States and other geographic regions as reported by 78 transplant physicians. The difference in hepatitis B immune globulin use in the United States versus other parts of the world is statistically significant at $P = 0.03$.

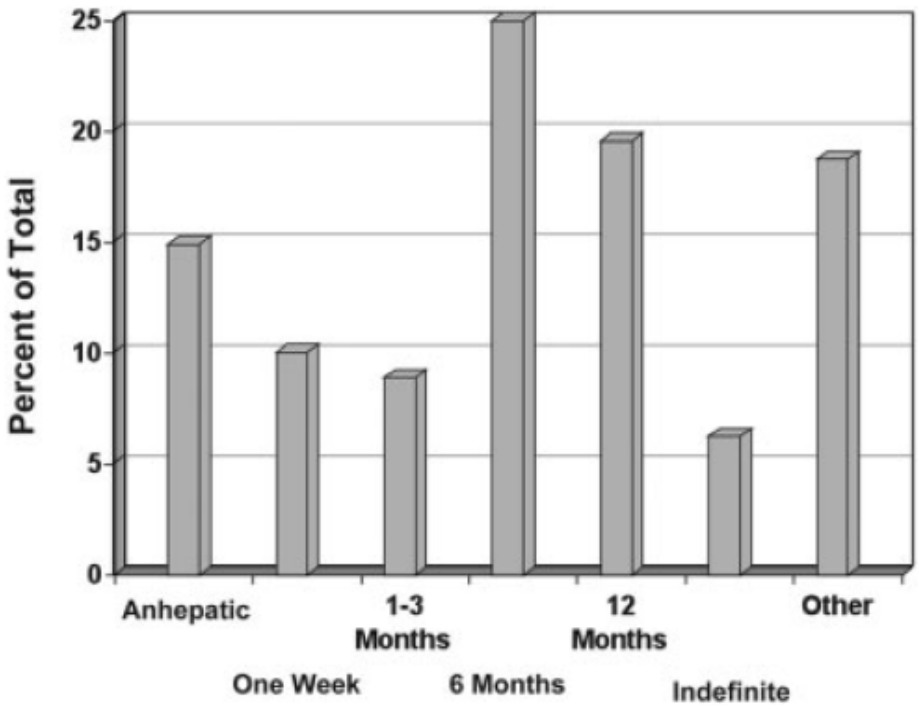


Figure 3. Duration of hepatitis B immune globulin use. Percentages are based on a total of 48 transplant physicians who reported using hepatitis B immune globulin.

HBIG use more common in United States compared to other parts of the world

Duration of HBIG use was variable but most commonly 6-12 months

Impact of anti-HBc+ Status on Renal Transplant Outcomes

Retrospective analysis of 24,661 kidney transplant recipients that included 763 anti-HBc- recipients from anti-HBc+ donors

TABLE 4. Incidence rates of recipient Anti-HBc Ab seroconversion

Donor Anti-HBcAb	No. of seroconversions	Person-year (yr)	Incidence rate/year (95% CI)	P^a
Negative (n=24,662)	287	54,002	0.005 (0.0047–0.0060)	
Positive (n=763)	17	1500	0.011 (0.0070–0.0182)	0.002

[a] Based on maximum likelihood test of the equality of rates.

TABLE 5. Incidence rates of recipient HBsAg seropositivity

Donor anti-HBc Ab Status	No. of seroconversions	Person-year	Incidence rate/yr (95% CI)	P^a
Negative (n=24,662)	161	54,190	0.003 (0.0025–0.0035)	
Positive (n=763)	2	1,531	0.001 (0.0003–0.0005)	0.23

Higher rates of anti-HBc (but not HBsAg) seroconversion

Donor anti-HBc status was not associated with graft failure or death in multivariable analysis

Fong et al. Transplantation 2002

Safety and Efficacy of anti-HBc+ Donors in Lung Transplantation

Single center retrospective study

29/456 (6.4%) LTx from anti-HBc+ donors

All received hepatitis B vaccine series prior to LTx

No post-LTx HBIG or antiviral therapy

TABLE 2. Hepatic function, viral serology, and polymerase chain reaction data for lung transplant recipients of HBcAb+[a] grafts

Recipient group	Elevated AST or ALT	Elevated T. bilirubin	HBsAg+	PCR HBV DNA +
HBcAb+ (alive)	1/21 (4.8%)	0/21 (0%)	0/21 (0%)	0/11 (0%)
HBcAb+ (deceased)	2/8 (25%)	2/8 (25%)	0/7 (0%)	0/3 (0%)

De novo HBsAg or HBV DNA detection not observed

Hartwig et al. Transplantation 2005

Safety and Efficacy of anti-HBc+ Donors in Lung Transplantation

- No significant differences in 30-day, 1-year, or 5-year survival rates
- No significant differences in 3- and 5-year incidence rates of bronchiolitis obliterans
- No significant differences in rates of early (<6m) or late (>6m) biopsy-proven rejection

Hartwig et al. Transplantation 2005

Impact of anti-HBc+ Donors in Lung and Heart-Lung Transplant Recipients

Retrospective study of UNOS Database (1995-2007) comparing 13,233 recipients of anti-HBc- organs and 333 recipients of anti-HBc+ organs

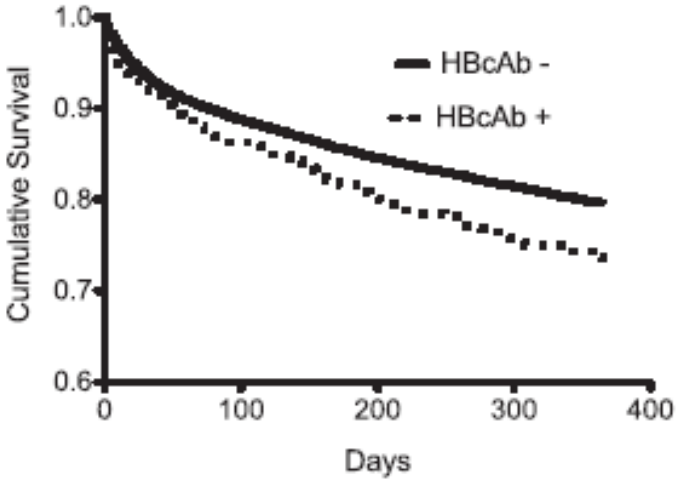


FIGURE 1. Unadjusted 1-year Kaplan-Meier survival analyses by hepatitis B core antibody status. $P=0.007$ by log-rank test.

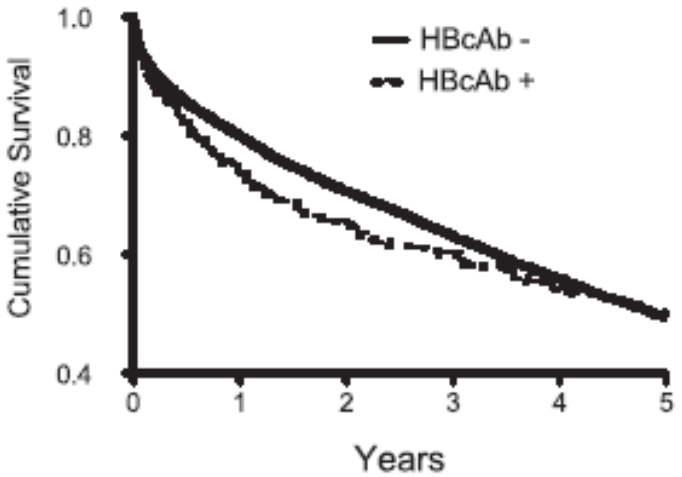


FIGURE 2. Unadjusted 5-year Kaplan-Meier survival analyses by hepatitis B core antibody status. $P=0.26$ by log-rank test.

But no difference in 1- or 5-year survival in adjusted analysis

Dhillon et al. Transplantation 2009

Acceptable Heart Transplant Outcomes from anti-HBc+ Donors

Publication Year	Recipients	HBV Transmission
1993	12	0
1995	7	0
2002	11	0
2005	25	0
2005	33	1
TOTAL	**88**	**1**

Kadian et al. 2nd International Congress of the Society of Organ Sharing 1993 (abstract)
Wachs et al. Transplantation 1995
Blanes et al. Transplantation Proceedings 2002
De Feo et al. Transplantation Proceedings 2005
Pinney et al. J Heart Lung Transpl 2005

American Journal of Transplantation 2015; 15: 1162–1172
Wiley Periodicals Inc.

doi: 10.1111/ajt.13187

Special Article

Solid Organ Transplantation From Hepatitis B Virus–Positive Donors: Consensus Guidelines for Recipient Management[†]

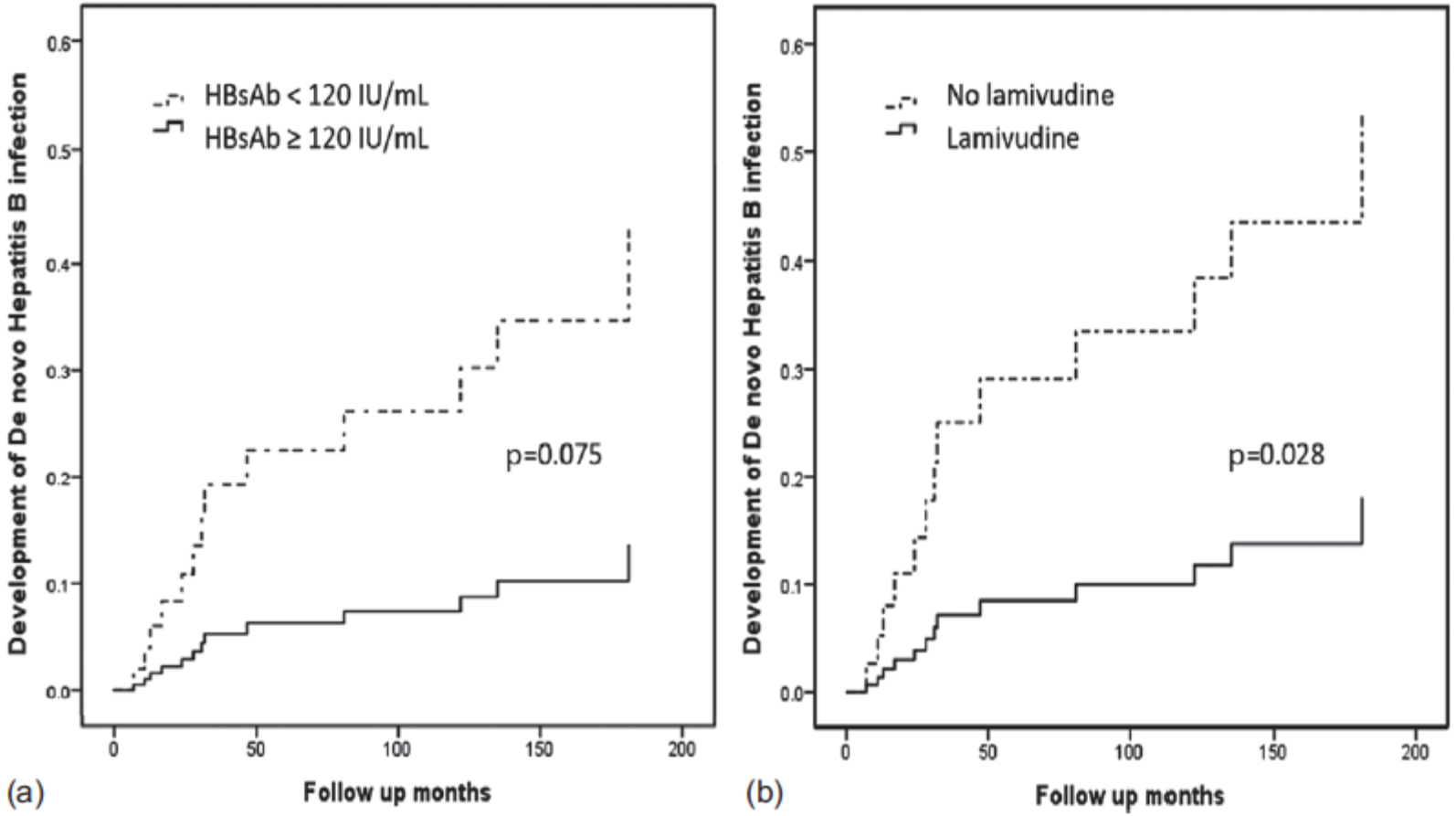
[†] *Endorsed by the American Society of Transplantation and the Canadian Society of Transplantation.*

Organs from HBsAg– anti-HBc+ donors regardless of donor anti-HBs status should be considered for all adult transplant candidates after an individualized assessment of the risks and benefits and appropriate patient consent (strong; moderate).

Organs from HBsAg– anti-HBc+ donors should only be considered in emergent settings for pediatric transplant candidates in low prevalence areas after an individualized assessment of the risks and benefits and appropriate patient consent (strong; low).

Huprikar et al. AJT 2015

De novo hepatitis B virus infection after pediatric liver transplantations with hepatitis B core antibody-positive donors: A single-center 20-yr experience

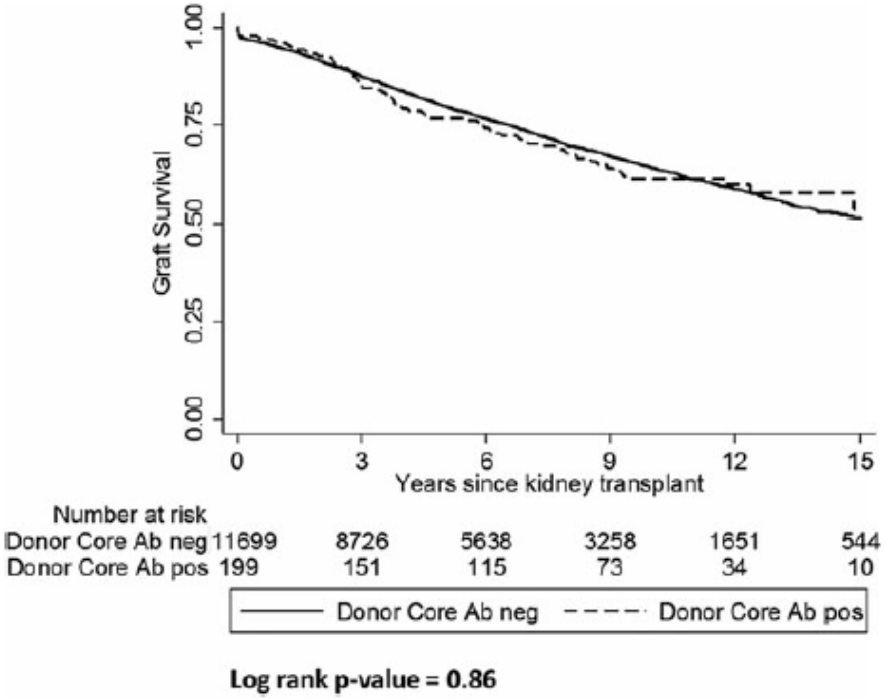


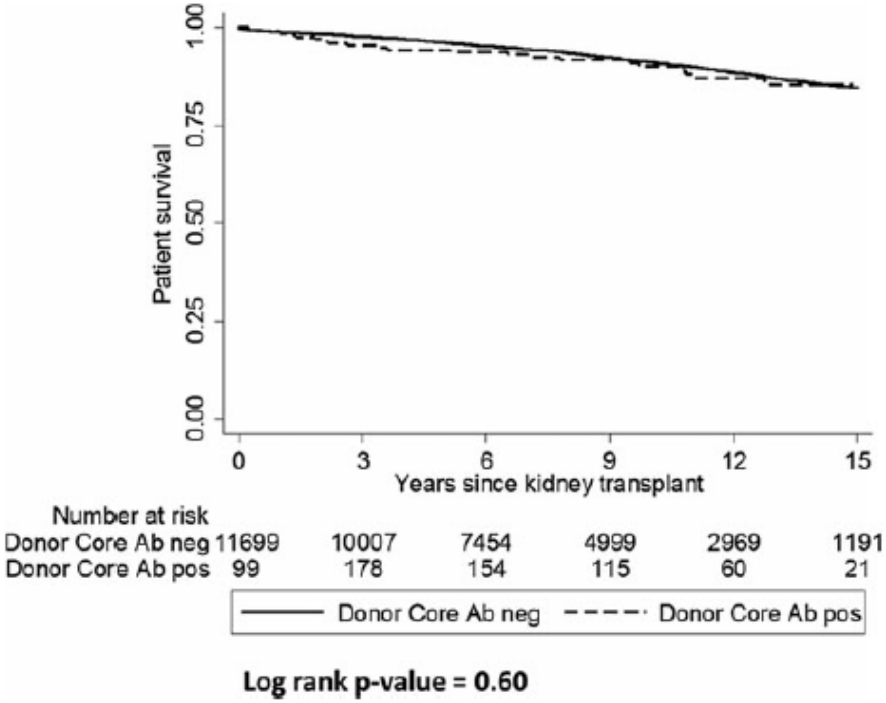
No graft failure due to *de novo* hepatitis B infection

Lee et al. Pediatr Transpl 2015

Outcomes Among Children Who Received a Kidney Transplant in the United States From a Hepatitis B Core Antibody–Positive Donor, 1995–2010

199 pediatric kidney transplant recipients
Scientific Registry of Transplant Recipients
1995-2010

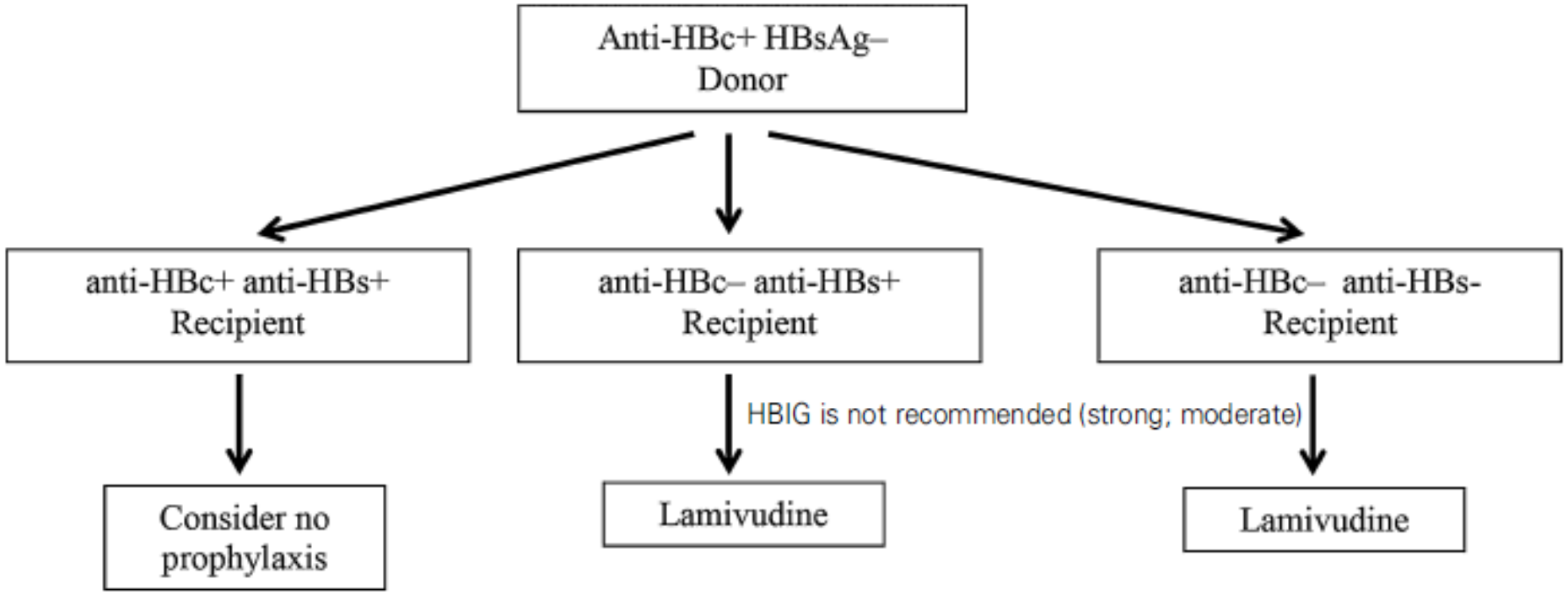




With median follow-up of 7.9 years, no significant differences in the adjusted graft or patient survival rates

Ruebner et al. JPIDS 2016

Guideline Algorithm for Use of Liver Grafts from anti-HBc+ Donors



Natural immunity **Vaccine immunity** **No immunity**

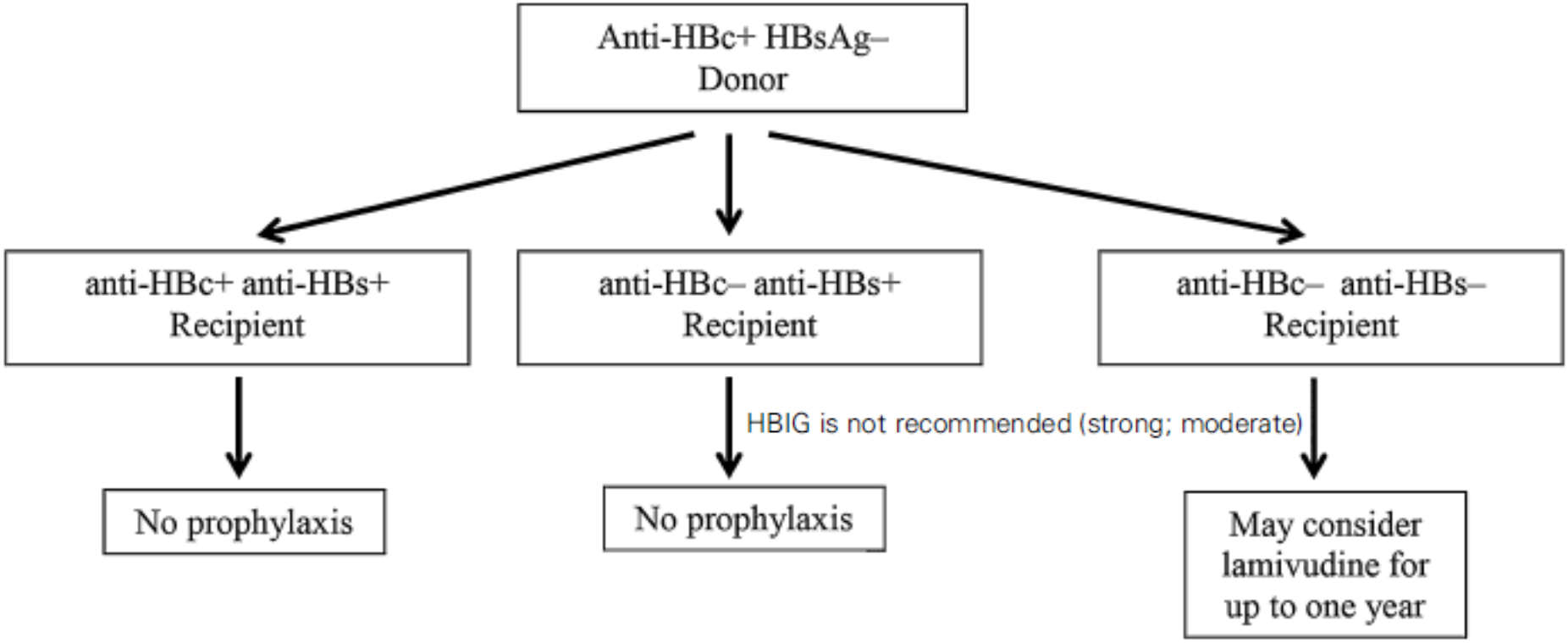
After transplantation, HBV vaccination is recommended for all non-immune transplant recipients (strong; low).

Huprikar et al. AJT 2015

Choice of lamivudine is based on evidence from a cost-effectiveness analysis

Wright et al. AJT 2014

Guideline Algorithm for Use of Non-Liver Grafts from anti-HBc+ Donors



Natural immunity **Vaccine immunity** **No immunity**

After transplantation, HBV vaccination is recommended for all non-immune transplant recipients (strong; low).

Huprikar et al. AJT 2015

Guideline Recommended Monitoring and Duration of HBV Therapy

Liver transplant recipients from anti-HBc+ HBsAg– donors (Figure 1)

HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely in all recipients regardless of current or prior prophylaxis strategy (strong; low).

Indefinite antiviral prophylaxis is recommended in HBV susceptible (anti-HBc– anti-HBs–) liver transplant recipients (strong; moderate).

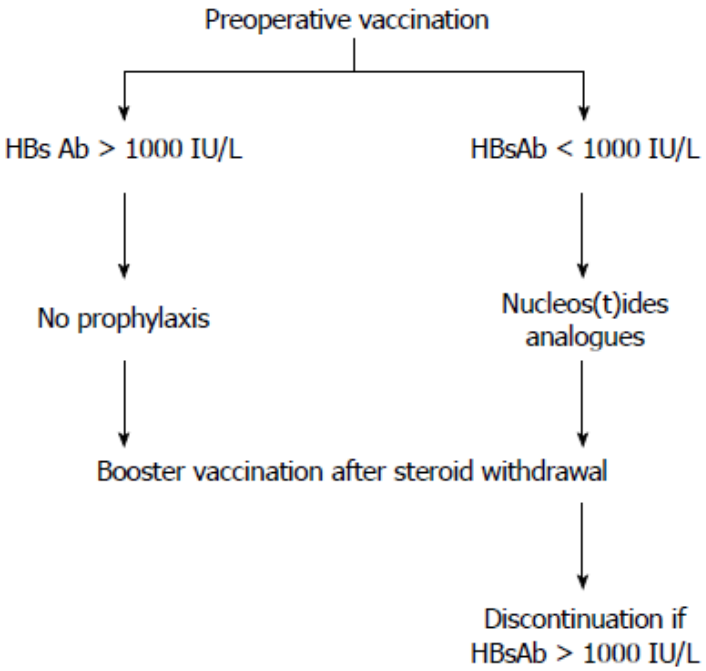
Discontinuation of prophylaxis may be considered after 1 year in recipients with confirmed persistence of immunity (anti-HBs $\geq$10 IU/mL) (strong; low).

Huprikar et al. AJT 2015

Active vaccination to prevent *de novo* hepatitis B virus infection in liver transplantation

Table 1 Published studies with HBsAb titers in patients receiving HBcAb(+) grafts

Patients	Lamivudine/HBIG	Vaccination Pre/post-LT	HBsAb cutoff (IU/L)	DNH	Follow-up (mo)
9/pediatric	HBIG	Yes/Yes	20	50% *vs* 0%[1]	26
30/pediatric	lamivudine	Yes/Yes	1000	15.7% *vs* 0%	57
11/adult	HBIG	No/Yes	1000	0%[2]	15
14/pediatric	HBIG	No/Yes	100	7.1%[3]	26.5
36/pediatric	N	Yes/Yes	200	30.7% *vs* 4.3%	52
41/adult	Lamivudine	Yes/Yes	1000	6.4% *vs* 0%	52
34/pediatric	N	Yes/Yes	1000	0%[4]	65



High titer anti-HBs >1000 IU/L highly protective

Lin et al. WJG 2015

Guideline Recommended Monitoring and Duration of HBV Therapy

Non-liver transplant recipients from anti-HBc+ HBsAg– donors (Figure 2)

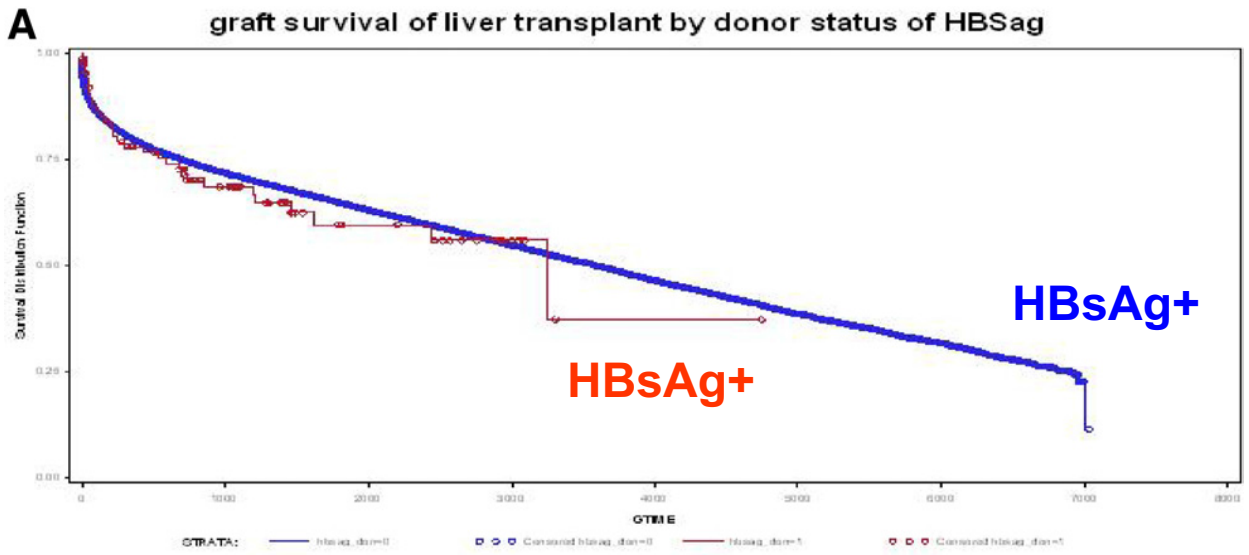
HBV DNA with or without HBsAg should be monitored every 3 months for 1 year (weak; low).

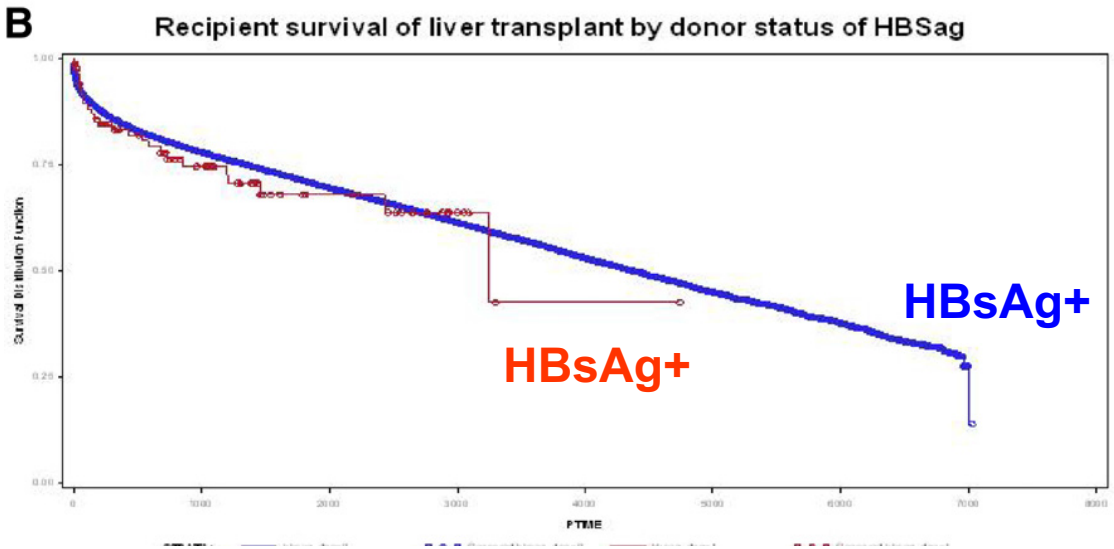
Antiviral prophylaxis for up to 1 year may be considered in HBV susceptible (anti-HBc– anti-HBs–) recipients (weak; low).

Huprikar et al. AJT 2015

Liver Transplantation From Hepatitis B Surface Antigen-Positive Donors

R.F. Saidi, N. Jabbour, S.A. Shah, Y.F. Li, and A. Bozorgzadeh





UNOS Database 1990-2009:

68 D+R+
24 D+R-

No difference in patient or graft survival

Saidi et al. Transpl Proc 2013

Guideline Recommendations for Use of HBsAg+ Donors

Organs from HBsAg+ donors may be carefully considered in all adult transplant candidates after an individualized assessment of the risk and benefits and appropriate patient consent (weak; low).

HBsAg+ livers should only be considered when significant donor liver disease has been ruled out by histology (strong; low).

Indefinite prophylaxis with entecavir or tenofovir is recommended for all recipients (strong; low).

HBIG should be considered in all recipients when the anti-HBs titer is <100 IU/L (strong; low).

HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely (strong; low).

Huprikar et al. AJT 2015

Use of Hepatitis B Surface Antigen–Positive Grafts in Liver Transplantation: A Matched Analysis of the US National Database

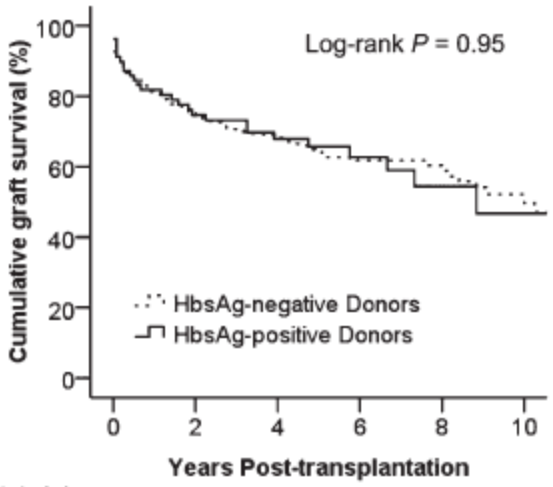
Zhiwei Li,* Zhenhua Hu,* Jie Xiang, Jie Zhou, Sheng Yan, Jian Wu, Lin Zhou, and Shusen Zheng

U.S. Scientific Registry of Transplant Recipients Database: 1987-2010

15 D+R+

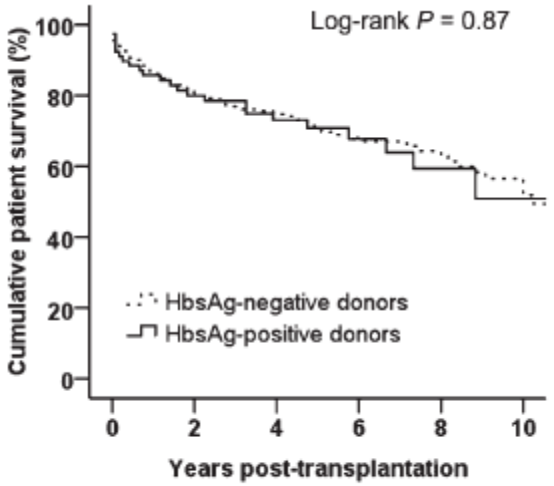
63 D+R-

A



Patients at risk (n)						
HbsAg-negative	312	203	144	60	40	21
HbsAg-positive	78	51	36	19	11	4

B



Patients at risk (n)						
HbsAg-negative	312	218	155	67	44	24
HbsAg-positive	78	54	38	20	11	4

Use of HBsAg+ grafts not associated with worse patient or graft survival

HBIG associated with better survival in recipients of HBsAg+ grafts

Li et al. Liver Transpl 2014

Liver grafts from hepatitis B surface antigen-positive donors: A review of the literature

Elisabetta Loggi, Fabio Conti, Alessandro Cucchetti, Giorgio Ercolani, Antonio Daniele Pinna, Pietro Andreone

- 17 published studies
- Preferentially allocated to HBsAg+ recipients
  - Most recipients with serologic persistence
  - Antiviral therapy is paramount
  - But no significant HBV related disease
- Promising results in HBsAg- recipients

Loggi et al. WJG 2016

Liver Transplantation
HBsAg+ Donors and HBsAg+ Recipients

Ref.	Patient No.	Prophylaxis		Outcome at the last FU			Median FU (mo)
		Nucleos(t)ide Analogue	HBIg	HBV disease	HBsAg	HBV-DNA	
Franchello *et al*[13]	3	LMV LMV + ADV (n = 1)	Yes	No (n = 1) Yes (HDV =2)	Persistence	Negative HDVRNA +	19
Ho *et al*[17]	1	LMV + ADV	No	No	Persistence	Negative	24
Hwang *et al*[16]	1	LMV + ADV	Yes	Mild	Persistence	Negative	64
Soejima *et al*[15]	1	LMV	Yes	No	Persistence	Negative	48
Jiao *et al*[24]	2	LMV	Yes	Mild	Persistence	Negative	48
Jang *et al*[25]	6	LMV + ADV	Yes	No	Persistence	Negative	22.5
Bahde *et al*[14]	1	LMV + ADV	Yes	HDV cirrhosis	Persistence	Negative HDVRNA +	50
Loggi *et al*[23]	6	LMV + ADV LMV + TDF	Yes	No	Persistence	Negative	42
Choi *et al*[26]	8	LMV (n = 2) ETV (n = 6)	Yes	No	Persistence (n = 6) Loss (n = 2)	Negative	25.5
Ju *et al*[27]	23	ETV	Yes	No	Persistence (n = 17) Loss (n = 1)	Negative	NA
Saidi *et al*[28]	68	NA	NA	NA	NA	NA	NA
Li *et al*[29]	15	NA	NA	NA	NA	NA	NA
Yu *et al*[31]	38	Not specified	Yes	No	Persistence	Negative	NA
Jeng *et al*[32]	13	ETV	No	No	Persistence	Negative	46

HDV infection may be a contraindication for use of HBSag+ donor

Loggi et al. WJG 2016

Liver Transplantation
HBsAg+ Donors and HBsAg- Recipients

Ref.	Patient No.	Etiology of liver disease	Prophylaxis		Outcome at the last FU			Median FU (mo)
			Nucleos(t)ide Analogue	HBIg	HBV disease	HBsAg	HBV-DNA	
Gonzalez *et al*[12]	1	Crypto	NO	Yes	Mild	Negative	Negative	24
Loggi *et al*[22]	1	HBV	LMV	No	No	Negative	Negative	18
Loggi *et al*[23]	4	HCV (n = 3) PBC (n = 1)	LMV LMV + ADV	Yes	Mild	Negative	Negative	42 (12-60)
Saidi *et al*[28]	24	NA	NA	NA	Survival similar to controls	NA	NA	NA
Li *et al*[29]	63	HCV (n = 34) NASH (n = 2) Alcohol (n = 6) Other (n = 17)	NA	NA	Survival similar to controls	NA	NA	NA
Krishnamoorthi *et al*[30]	15	NA	NA	NA	Survival similar to controls	NA	NA	NA
Yu *et al*[31]	4	NA	NA	NA	Survival similar to controls	NA	NA	NA
Jeng *et al*[32]	1	HCV	ETV	No	No	Negative	Negative	12

Recipients with HBV immunity (anti-HBc+ and/or anti-HBs+) are likely the best candidates to receive an HBsAg+ liver graft

Loggi et al. WJG 2016

Entecavir Monotherapy with HBsAg+ Liver Grafts

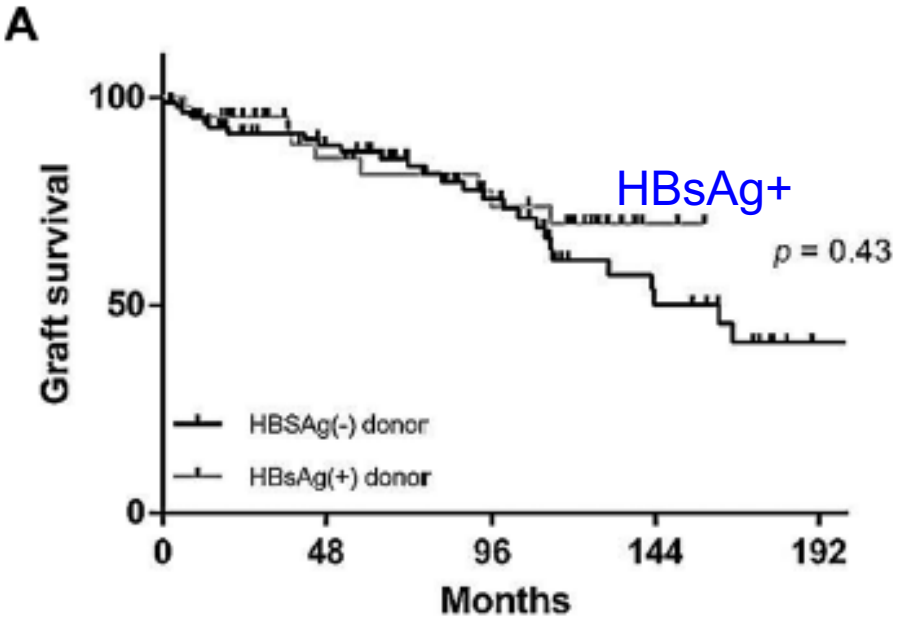
Table 4. Post transplant individual laboratory data of recipients at the end of 1 year with relation to underlying HBV activity.

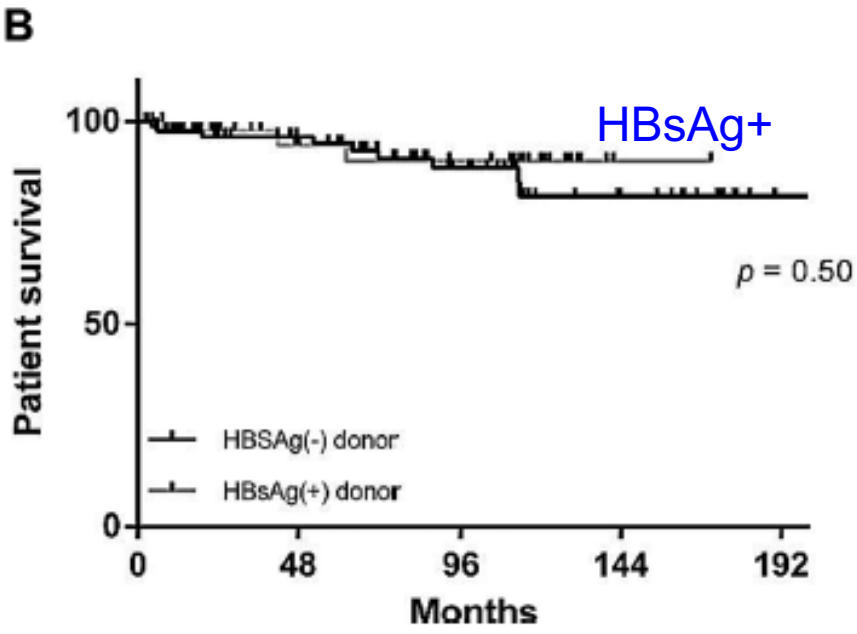
Case no.	Diagnosis	Recipient's pre-transplant viral assay		Recipient's post-transplant viral assay and liver functions after 1 year					Present status of patient
		HBsAg	HBV-DNA	HBV-DNA (IU/ml)	AST (IU/ml)	ALT (IU/ml)	T.Bil (mg/dl)	INR	
1.	ALF+HCC	15.31	1600 IU/ml	<12	19	24	0.57	0.98	A
2.	ALF	>250	>1M IU/ml	<12	23	23	0.46	1.16	A
3.	HCC (HBV+HCV)	1.93	<12 IU/ml	<12	31	18	1.5	1.04	A
4.	HCC	76.2	20000 IU/ml	<12	28	61	0.57	1.1	E*
5.	HCC	122.98	<12 IU/ml	<12	51	76	1.34	1.14	A
6.	ALF	>250	30000 IU/ml	<12	18	13	0.51	1.13	A
7.	HCC	>250	11000 IU/ml	<12	24	23	0.45	1.03	E*
8.	HCC	>250	<12 IU/ml	<12	102	150	2.4	0.97	A
9.	ALF	>250	>1M IU/ml	<12	16	16	0.66	1.02	A
10.	HCC	>250	<12 IU/ml	<12	20	43	0.32	0.92	A
11.	HCV related ESLD+HBV	NR	<12 IU/ml	<12	149	145	1.85	1.1	A
12.	HBV ESLD	>250	<12 IU/ml	<12	21	14	0.56	1.04	A
13.	HBV ESLD	73.39	11000IU/ml	<12	57	53	0.42	1.1	A
14.	HCC	>250	200 IU/ml	<12	22	22	0.59	1.0	A

Jeng et al. Ann Transplant 2015

The Outcomes of Kidney Transplantation in Hepatitis B Surface Antigen (HBsAg)–Negative Recipients Receiving Graft From HBsAg-Positive Donors: A Retrospective, Propensity Score-Matched Study

HBV immune KT recipients (HBsAg- and anti-HBs >100 miU/mL) : HBsAg+ donors (n=43) vs. HBsAg- donors (n=86)





KT recipients from HBsAg+ donors with no HBV prophylaxis (n=20) had similar outcomes with those treated with lamivudine alone (n=21) or lamivudine in combination with HBV immunoglobulin (n=2).

Chancharoenthana et al. AJT 2014

Summary

- Organ transplantation using organs from anti-HBc+ donors is safe
  - Highest risk of de *novo* HBV infection is observed in liver transplantation
  - Lamivudine prophylaxis may only be needed in liver recipients with vaccine or no immunity
  - HBIG is not recommended
- Evidence base for use of HBsAg+ donors continues to increase

Thank you!

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