Review

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HBV-positive and HIV-positive organs in transplantation: A clinical guide for the hepatologist

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Summary

Organ transplantation is a life-saving treatment for patients with end-stage organ disease, a severe condition associated with a high risk of waitlist mortality. It is primarily limited by a shortage of available organs. Maximising available donors can increase access to transplantation. Transplantation from donors positive for HBV and HIV has increased in many countries. However, antiviral therapies need to be readily available for recipients after transplantation to prevent possible reactivation of the virus following the administration of immunosuppressive therapies. Furthermore, the intentional transmission of a virus has practical, ethical, and clinical implications. In this review, we summarise the current research, focusing on grafts from donors positive for the HBV surface antigen, antibodies against the HBV core antigen, and HIV, to help hepatologists and physicians interested in transplantation to select the best antiviral and/or prophylactic regimens for after transplantation.

Keywords: organ transplantation; HBV; HIV; non-optimal donors; antiviral therapy; antiviral prophylaxis.

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Introduction

Organ transplantation is the best and most cost-effective therapy for patients with end-stage organ failure.[1] Despite improvements in post-transplant outcomes through refinements in perioperative management and surgical techniques, waitlist mortality remains high.[2] As the number of donors is considerably lower than that of potential recipients, the use of expanded criteria grafts has increased.[3] Following a patient-tailored treatment strategy, transplantation programmes aim to offer the most suitable graft for the benefit of the individual recipient, while also expanding the criteria for organ acceptance and allocation.

Owing to powerful antiviral therapies, problems of organ shortage can be overcome by using grafts affected by HCV, HBV, or HIV.

Following a review on liver transplantation (LT) from HCV+ donors,[4] this manuscript summarises current research on grafts from donors positive for hepatitis B surface antigen (HBsAg), antibodies against the HBV core antigen (HBcAb), and HIV, to help hepatologists and physicians to select the best antiviral and/or prophylactic regimen for follow-up after transplantation. In the first part of this review, we discuss LT from HBV+ donors; in the second part, we discuss non-liver solid organ transplantation and cell transplantation from HBV+ donors; finally, in the last part, we discuss LT from HIV+ donors.

HBV+ donors in the LT setting

HBsAg+ donors

Transplanting livers from HBsAg+ donors might be an option to increase the number of liver donors, especially in endemic areas, such as the Far East and the Mediterranean basin. The prevalence of potential HBsAg+ donors (ranging from 0.5% to 7% of all potential donors) might cause the heterogenous spreading of such an infection worldwide.[5,6] A recent study from the US reported a prevalence of 0.7% among 38,166 potential donors and highlighted the net benefit of routine nucleic acid testing.[7] The number of potential good-quality grafts from HBsAg+ donors might increase in the future following the increased availability of high-barrier nucleos(t)ide analogues (NAs) that can arrest HBV disease progression.

Conversely, regarding HBcAb+ donors, only a few studies on LT, where grafts from HBsAg+ donors were used, have been published since the first report in 1994[5,8–27] (Table S1). HBsAg+ grafts used to be considered marginal organs due to active viral infection and the high risk of viral transmission without treatment. However, recently they have been shown to be safe, with good post-operative outcomes, especially when good-quality organs were transplanted through proper donor-to-recipient matching.[28]

The HDV status of the donor is unknown during donor assessment. In case the status of HBsAg+/HDV+ coinfected livers is known, they are not allocated due to the high risk of HDV recurrence after transplantation.[29]

HBsAg+ and HCV viraemic coinfected donor livers may be considered for transplantation after proper (histological) assessment of graft quality. The advent of direct-acting antivirals (DAAs)

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against HCV has enabled the transplantation of HCV viraemic livers, expanding the donor pool significantly, even for HCV- recipients.[4] Donor-derived HBV transmission, often undiagnosed during transplantation because of the window period, should be carefully evaluated in such cases.[30]

Recipients of HBsAg+ donors

Allocating HBsAg+ grafts to HBsAg+ recipients is the most reasonable choice since it does not significantly change postoperative management regarding prophylaxis against viral recurrence.[29]

Key point

Increasing liver transplantation from HBV+ donors, with adequate prophylactic antiviral therapy, in positive and negative recipients can decrease the national organ shortage.

Transplantation of HBsAg+ grafts into HBsAg- recipients is performed only during emergencies.[19,23] There have been a couple of reported cases of HCV viraemic, HBsAg- patients, with decompensated cirrhosis and high model for end-stage liver disease (MELD) scores, receiving an HBsAg+ graft without developing rapidly progressive cholestatic hepatitis.[10,13] Due to limited data, strong conclusions cannot be made; the risk is less pronounced following the introduction of DAAs. The available information suggests that transplantation of HBsAg+ grafts into HBsAg- recipients is safe, especially in endemic areas and in cases of emergency,[27] as the high-barrier NAs used for prophylaxis are highly effective. Effective therapeutic options for HDV might enable transplantation from HBsAg+ donors to this subgroup of patients, who cannot be provided grafts due to the risk of viral recurrence and subsequent graft loss.[29]

Prophylaxis after receiving HBsAg+ grafts

Retrospective studies from around the world provided optimal survival curves for patients who received good-quality HBsAg+ grafts when they maintained a persistently negative viremia post-operatively.[31] Case-control studies[19,22,24] did not find any difference in survival after transplantation of HBsAg+ or HBsAg- grafts, although a short follow-up time and the absence of granular data on the grafts allocated to the controls prevented any strong conclusion from being drawn.

The reappearance of serum HBsAg after LT needs to be managed; therefore, antiviral prophylaxis, preferably with high-barrier NAs, is important. Several cases reported the development of lamivudine-resistance post-LT, but such cases can be reduced significantly after applying high-barrier NAs. The benefits of the administration of long-term hepatitis B immune globulin (HBIG) and the timing of withdrawal are debated. Theoretically, HBIG is not useful because it lacks a neutralising effect after the reappearance of HBsAg,[8,11,12,17,25] and thus, it is not recommended (Fig. 1).

Treatment using tenofovir disoproxil fumarate, tenofovir alafenamide, and entecavir is currently preferred, depending on local availability, costs, pre-transplant treatments, renal function, and

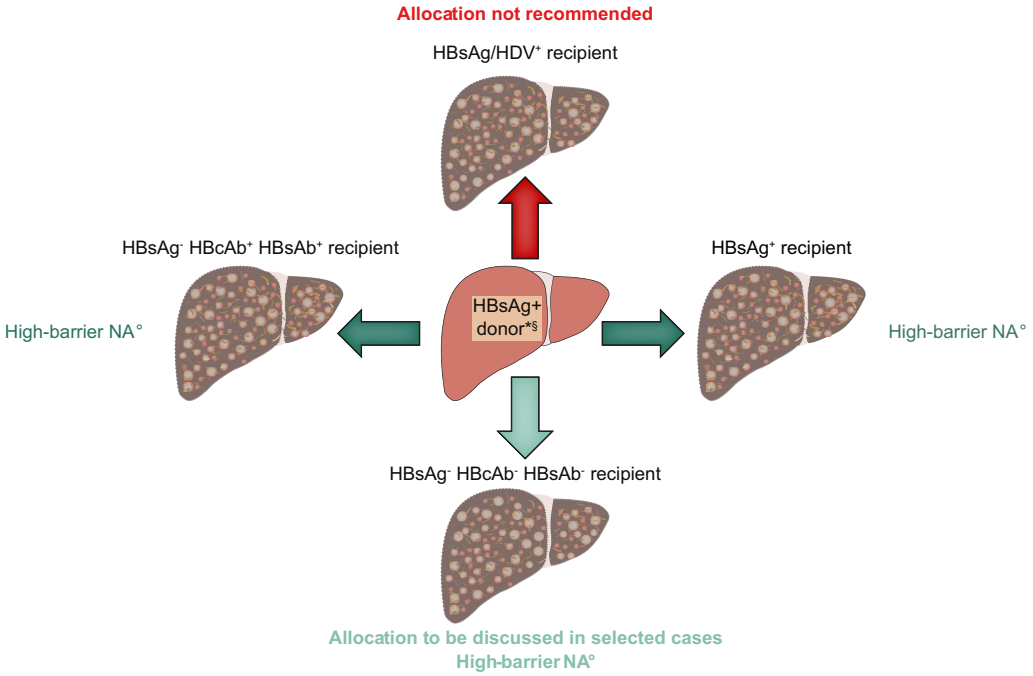

Fig. 1. Prophylactic strategies after liver transplantation using an HBsAg+ graft. The dark-green arrows indicate that LT is safe and effective; the light-green arrow indicates that LT is generally safe and effective but should be considered in specific cases (*e.g.*, urgent cases) or in endemic areas. The red arrow indicates that LT is not recommended. *Living donation should be carefully evaluated in specific cases, and HDV+ grafts should not be used for transplantation; §donor graft quality should be routinely assessed by liver biopsy; °the HBsAg appearance is highly expected after liver transplantation; therefore, HBIG should not be used when HBsAg reappearance is confirmed. HBIG, hepatitis B immune globulin; LT, liver transplantation; NA, nucleos(t)ide analogue.

bone health. Potential worsening of renal function after the co-administration of tenofovir disoproxil with nephrotoxic drugs (*e.g.*, aminoglycosides, ganciclovir), as well as potential interactions between tenofovir alafenamide and some antifungal/antimycobacterial agents, should be carefully considered, especially in the early postoperative phase. The risk of viral resistance to high-barrier NAs might be an issue in recipients with HBsAg reappearance after transplantation. Thus, such cases should be carefully evaluated and managed following the recommendations currently adopted for patients with chronic hepatitis B.[32]

The seroconversion to HBsAb was observed during follow-up. Loggi *et al.*[13] showed an HBsAg-, HBcAb+/HBsAb+ patient who turned HBsAg+ 3.5 months after receiving an HBsAg+ graft due to a reduced HBsAb titre; however, at month 18 post-LT, HBsAg clearance occurred concomitantly with the reappearance of a high HBsAb titre. The previous viral exposure might have elicited the immune response to HBV after LT, but this hypothesis was not confirmed in other studies.[23] More studies need to be performed to confirm this pathogenetic hypothesis.

Regarding postoperative follow-up, patients receiving HBsAg+ grafts have to be carefully monitored through per-protocol biopsies or by using non-invasive tools/serum biomarkers, with scheduled biochemical and sero-virological assessments (every 3 months in the first year, and then, every 3–6 months indefinitely, with liver ultrasound every 6–12 months).[7] Moreover, they should be provided life-long prophylaxis, which is associated with an unavoidable increase in costs. Fortunately, some studies have recently confirmed the cost-effectiveness of this procedure, especially for patients with high MELD scores and HBsAg- recipients who have received livers from HBV+ donors.[33] Additional studies are required to confirm this preliminary report.

Other important issues also need to be addressed. Further assessment is required to determine whether these patients are at a higher risk of *de novo* or recurrent postoperative hepatocellular carcinoma, given that HBV is oncogenic. The relatives of such patients must be informed about the risk of infectious disease transmission, especially if the patient becomes viraemic. Specific methods of treatment (*e.g.*, HBV vaccination) should be recommended. Viraemic grafts should be offered to adherent patients only when a strict follow-up by the local transplant team is guaranteed, and there is a certainty that the prescribed therapy will be available throughout life.

The transplantation of organs from HBsAg+ living donors has been proposed in very few cases. For good outcomes, donors should be selected carefully, and the histological/functional status of the graft should be extensively evaluated before surgery.

HBcAb+ donors in LT

The HBcAb+ condition requires prior exposure to HBV and causes a lifelong hepatocyte infection due to the presence of covalently closed circular DNA (cccDNA) in the hepatocyte that cannot be cleared by the host immune response.[34] Therefore, HBcAb+ grafts were viewed as marginal organs. However, due to the worsening global organ shortage, the allocation of HBcAb+ livers has increased substantially in endemic countries like those in the Far East (where the prevalence is roughly 50% of all organs),[35,36] the Mediterranean basin (where HBcAb+ grafts comprise about 15% of all organs),[37] and in low-endemic countries, like the USA (where the prevalence increased from 1.8% in 1994 to 6% in 2006).[38]

Determining the optimal allocation of HBcAb+ grafts

The development of HBV recurrence or a *de novo* viral infection significantly affects the survival of the graft and the patient. After the introduction of a high-barrier NA, such risks are minimised considerably. Moreover, since the risk varies with the serostatus of the pre-LT recipient, the current guidelines recommend tailored prophylactic algorithms.[29,39] Transplanting an HBcAb+ graft into an HBsAg+ recipient might be safe and effective, given that post-transplant prophylaxis remains the same. A study showed that HBcAb positivity increased the risk of post-LT viral recurrence by twofold; however, in that study, more than 60% of patients received HBIG monoprophylaxis.[40] HBV-naive recipients are at the greatest risk of *de novo* infection without prophylaxis, followed by HBcAb+/HBsAb- and HBcAb-/HBsAb+ patients (47%, 13%, and 9%, respectively). Conversely, HBcAb+/HBsAb+ recipients have a negligible risk of *de novo* infection (1.4%), making antiviral prophylaxis unnecessary (Fig. 2).

A recent hypothesis suggested considering the prognostic value of the HBsAb serostatus of recipients during patient selection for lifelong prophylaxis.[41] While an aforementioned systematic review[39] showed that HBsAb detectability through vaccination reduces, but does not abolish, the risk of *de novo* HBV infection, a recent study on the recipients of LTs from living donors showed that active pre-operative immunisation can effectively prevent *de novo* HBV infection, provided high HBsAb serum levels are maintained after surgery.[42]

Determining the best prophylaxis after LT

A monoprophylaxis regimen might be the most reasonable option for HBsAg- recipients receiving an HBcAb+ graft. Unlike when receiving HBsAg+ donors, no circulating HBsAg-coated virions requiring neutralisation by HBIG will be present in HBsAg- recipients of HBcAb+ grafts. No randomised, comparative studies are available regarding the choice of NA. Lamivudine has been used as a

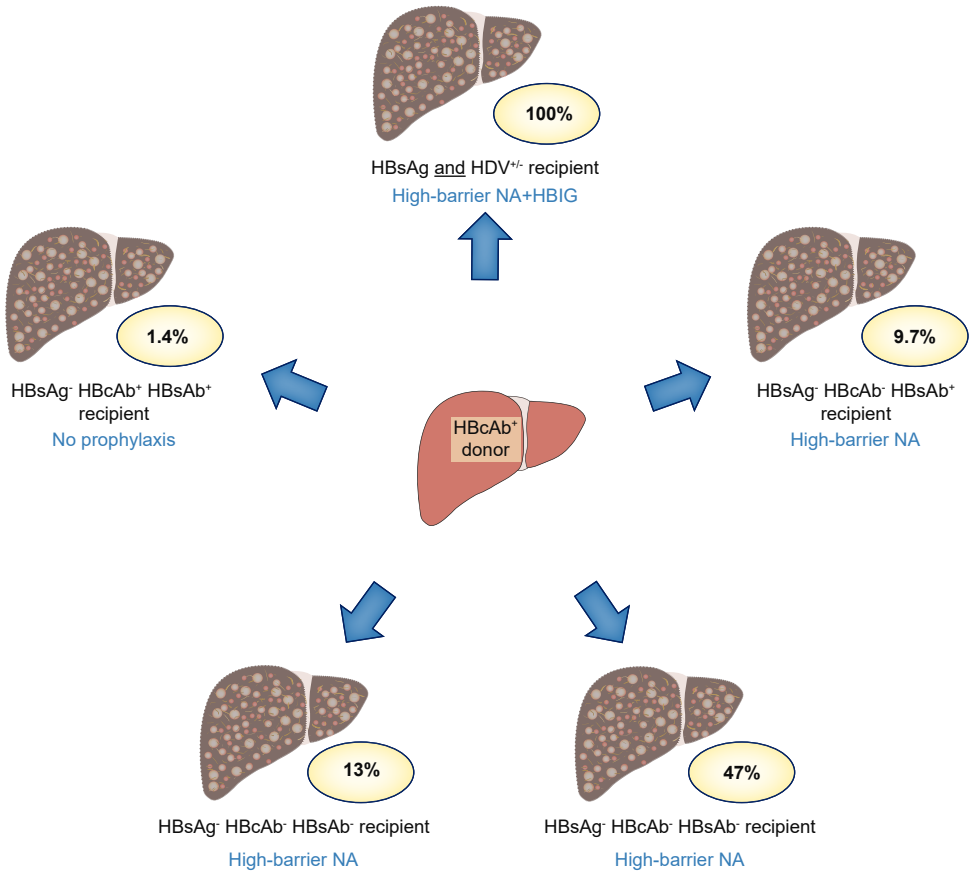

Fig. 2. Prophylactic strategies after liver transplantation using an HBcAb+ graft. Circles indicate the probability of *de novo* infection without prophylaxis. NA monoprophylaxis should be proposed to adherent patients with persistently negative HBV DNA and HBsAg for the long-term follow-up after liver transplantation. HBIG, hepatitis B immune globulin; NA, nucleos(t)ide analogue.

Key point

Kidneys from HBV viraemic donors should only be transplanted to recipients with protective HBV immunity (HBsAb >10 IU/L) during transplantation, and the antibody titre should be monitored immediately after transplantation, one month after transplantation, and then, every three months to verify the necessity of a booster dose of vaccine or antiviral prophylaxis until HBsAb levels are above 10 IU/L.

cost-effective treatment in patients receiving HBcAb+ grafts. The increased global availability of high-barrier NAs at low cost has made this a safer treatment option.[36,43] A complete withdrawal of prophylaxis is not recommended and requires the evaluation (and monitoring) of intrahepatic cccDNA; it might be performed when serum biomarkers, which are reliable surrogates of intranuclear DNA,[44] are available.

The impact of HBcAb+ grafts on survival

The impact of HBcAb+ grafts on post-transplant survival is debated. The development of good prophylactic strategies has reduced the risk of *de novo* infection after LT. Moreover, such occurrences can be safely and effectively treated with high-barrier NAs. Therefore, the attention has shifted from HBV recurrence to the hypothesis that HBcAb+ status might reflect suboptimal graft quality. This hypothesis was proposed in a large prospective study, where the effect of organs transplanted from HBcAb+ donors on the post-operative survival of recipients was only considered after they were allocated to HBsAg- recipients (mainly hepatitis C recipients).[37] A recent study from a highly endemic HBV-prevalent area demonstrated a similar 10-year graft survival status (76.8% *vs.* 74.8%, respectively) for HBcAb+ grafts, without any difference in primary non-function, graft dysfunction, or hepatocellular carcinoma.[36] This study considered both living and deceased donor LTs, including young donors. Studies have suggested that HBcAb+ grafts should not be discarded, especially at times of organ shortage.

HBV+ donors in non-liver solid organ transplantation

HBsAg+ donors

Transplanting an HBsAg+ graft into an HBsAg- recipient is associated with a significant risk of *de novo* infection. In areas endemic for HBV infection, where HBsAg+ rates are high (10–20%), the exclusion of HBsAg+ donors would considerably reduce the donor pool.[45] This issue is less significant in western countries where organs from HBsAg+ donors are not transplanted regularly. The successful transplantation of deceased-donor or living-donor HBsAg+ kidneys has been reported in several

studies, including in recipients with pre-existing immunity through vaccination or previous HBV infection (Table 1). A retrospective study compared the outcomes between kidney transplant (KT) recipients with HBsAb titres above 10 IU/L, who received either HBsAg+ (with absent or minimal viral replication; n = 43) or HBsAg- (n = 86) grafts. Regardless of the status of the HBsAg donors, there were neither cases of *de novo* HBV infection nor significant differences in graft and patient survival after a median follow-up of 58 months. Moreover, recipients who received kidneys from HBsAg+ donors with no HBV prophylaxis (n = 20) showed outcomes comparable to those treated with lamivudine only (n = 21) or lamivudine along with HBIG (n = 2).[46] Tuncer *et al.* highlighted the importance of HBsAb titre >10 IU/L in recipients and did not find cases of HBV infection in 35 HBV-immune patients who underwent KT from HBsAg+ living donors (with undetectable serum HBV DNA) without antiviral prophylaxis or HBIG administration.[47] The protective role of immunisation was

Table 1. Studies on non-liver solid organ transplantation with HBsAg+ donors.

	Study	Organ transplanted	Donor(s) characteristics	Recipient(s) characteristics	Antiviral treatment	Post-transplant outcome	Relevant findings
Tuncer *et al.*, 2012	Retrospective study	Kidney	35 HBsAg+ living donors (with undetectable serum HBV-DNA)	35 HBsAg– recipients with anti-HBs titres above 10 IU/L	No use of antiviral prophylaxis or HBIG	No cases of HBV *de novo* infection	
Chancharoenthana W *et al.*, 2014	Retrospective, longitudinal study	Kidney	43 HBsAg+ donors (with absent or minimal viral replication) and 86 HBsAg- donors	129 HBsAg- recipients with anti-HBs titres above 100 IU/L	21 HBsAg+ organ recipients were treated with lamivudine. 2 HBsAg+ organ recipients received lamivudine in combina-tion with HBIG	No cases of HBV *de novo* infection	Regardless of the HBsAg donor status, no significant differences in graft and patient survival after a median follow-up of 58.2 months.
Wang *et al.*, 2021	Retrospective study	Kidney	83 HBsAg+ donors (viraemia not reported; histology not reported)	83 HBsAg– recipients, including 20 without a protective anti-HBs titre	All recipients received antiviral prophylaxis (average duration 1–3 months)	Two recipients became HBsAg+ and tested positive for HBV-DNA	The 2 patients who became HBsAg+ did not have a protective anti-HBs titre
Wang *et al.*, 2004	Retrospective study	Heart	32 HBsAg+ donors	2 HBsAg- recipients without a docume-nted protective anti-HBs titre 4 HBsAg+ recipients 26 anti-HBs+ recipients	Only 1 HBsAg- and anti-HBs- recipient received post-operative HBIG All HBsAg+ recipients received antiviral prophylaxis	One of the 2 patients who did not have previous HBV infection or anti-HBs titre experienced a hepatitis infection Becoming HBsAg+	
Chen *et al.*, 2012	Retrospective study	Heart	3 HBsAg+ donors	3 HBsAg- recipients (no information about anti-HBs titre)	Perioperative HBIG	One recipient became HBsAg+	
Shin *et al.*, 2014	Retrospective study	Heart	6 HBsAg+ donors	6 HBsAg- recipients with a documented anti-HBs titre (except for 1 patient whose serologic data was missing)	Perioperative HBIG	No cases of HBV *de novo* infection	
Eichenberger *et al.*, 2020	Case report	Lung	1 HBsAg+ viraemic deceased donor	1 HBsAg- recipient with anti-HBs titres above 100 IU/L	HBIG immediately before and after transplantation daily for 5–7 days. Antiviral prophylaxis was started immediately after surgery.	No *de novo* HBV infection (duration of the follow-up not mentioned)	
Belga *et al.*, 2020	Case report	Lung	1 HBsAg+ with low-level HBV-DNA	1 HBsAg-recipient without a protective anti-HBs titre	HBIG immediately before and after transplantation daily for 5–7 days. Antiviral prophylaxis was started immediately after surgery	HBV serology after 12 months showed positive anti-HBc and anti-HBs, but negative HBsAg and HBV-DNA	

HBIG, hepatitis B immunoglobulin.

further demonstrated in a recent study performed in a large Chinese cohort. HBsAg- individuals (n = 83), including 20 without a protective HBsAb titre, underwent KT from HBsAg+ donors. Although all patients received antiviral prophylaxis (average duration 1–3 months), after a mean follow-up of 36 months, 2 recipients (2.4%; n = 83) became HBsAg+ and tested positive for HBV DNA. The 2 patients lacked a protective HBsAb titre.[48] These results confirmed that protective immunity is crucial to prevent *de novo* HBV infection.

Based on the available data, although they were from studies that differed in pre-and post-transplant patient management, we suggest that KT from HBV viraemic allografts should only be considered for recipients with protective HBV immunity (HBsAb >10 IU/L) at the time of transplantation. The antibody titre should also be monitored immediately after transplantation, 1 month after transplantation, and then, every 3 months to verify the necessity of a booster dose of vaccine or antiviral prophylaxis until HBsAb levels are above 10 IU/L. Moreover, the aforementioned data suggest that antiviral prophylaxis is not mandatory in all HBsAg+ graft recipients, but the assessment of the status of immunosuppression should be performed, especially for desensitisation using T cell- and/or B cell-depleting agents.[49]

Data on the transplantation of thoracic organs from HBsAg+ donors is limited (Table 1). Most of the available data are related to heart transplantation from overlapping cohorts living in Korea. From an analysis of HBsAg+ heart transplants (n = 41 recipients), only 2 recipients (4.8%) were reported to be HBsAg+. One out of 3 HBsAb- recipients and 1 out of 7 recipients who were HBcAb+ before transplantation became HBsAg+; neither of the patients had received HBIG or antiviral prophylaxis. No case of HBsAg positivity was observed in the group of HBsAb+ recipients.[50–52] Data on lung transplantation from HBsAg+ donors came from 2 case reports that described emergency transplantation from 2 HBsAg+ donors with variable levels of serum HBV DNA to an HBsAg- and an HBcAb- recipient, with no documented immunisation before transplantation in 1 case. In both cases, the recipients received HBIG daily for 5–7 days immediately before and after transplantation; entecavir administration was started immediately after surgery. After 12 months, the HBsAg- recipient was positive for HBcAb and HBsAb, but negative for HBsAg and HBV DNA. In the HBcAb- patient, *de novo* HBV infection was not detected, but the length of the follow-up was not mentioned.[53,54] However, the use of HBsAg+ grafts during lung and heart transplantation is currently restricted and generally limited to emergency cases. Given the paucity of data on the transplantation of thoracic organs from HBsAg- donors, no specific suggestions can be made.

HBcAb+ donors

Ideally, HBcAb+ organs should be transplanted into HBcAb+ and/or HBsAg+ recipients, but this strategy would yield a small donor pool. Assuming the appropriate management of recipients, the risk of HBV transmission from HBcAb+/HBsAg- grafts to HBV-naïve patients is low/moderate in KT and even lower in thoracic organ transplantations.[28,55,56] Immunisation against HBV infection and HBsAb titre levels before transplantation are key ways to minimise the risk of HBV transmission from HBcAb+ grafts.[28]

The most robust evidence on the risk of transmission, and related outcomes with HBcAb- recipients is in KT. However, studies on KT are generally characterised by a lack of information on the pre-transplant HBV serological status of the recipients and considerable heterogeneity in recipient management. In a systematic review of 9 studies comprising 1,385 patients who received KT from HBsAg+/HBcAb+ donors, HBV serological markers developed in only 45 patients (3.24%), and 4 patients turned HBsAg+ (rate of seroconversion was 0.28%) with no evidence of symptomatic hepatitis. Although they did not investigate the impact of HBsAb status or the use of antiviral prophylaxis in recipients, they reported similar transplant outcomes in patients with HBsAg or HBcAb seroconversion as for HBsAb+ recipients.[57] The largest study that evaluated the status of HBsAg- kidney recipients from the United Network for Organ Sharing database between 1994 and 1999 – reported a similar rate of HBsAg acquisition in 763 recipients of HBcAb+ grafts compared to 24,661 recipients of HBcAb- organs (0.001 *vs.* 0.003, $p = 0.23$). In that study, no difference in survival was found between the recipients of HBcAb+ and HBcAb- organs after conducting a multivariable-adjusted analysis.[58]

In most centres, kidneys are transplanted from HBcAb+ donors to candidates with documented immunity to HBV, *i.e.* with HBsAb >10 IU/L through vaccination or previous exposure. This titre confers immunity against *de novo* HBV infection. In 3 recent studies, no cases of HBsAg seroconversion were found in 236 HBcAb+ kidney recipients with protective HBV immunity (HBsAb >10 IU/L) during transplantation.[59–61] Therefore, vaccination can prevent the risk of transmission in KT. However, many patients with renal failure have an impaired immune response, resulting in a suboptimal response to standard recombinant vaccines.[62] Thus, antiviral prophylaxis might still play a role in non-immune recipients of HBcAb+ grafts, as suggested by the guidelines.[28] The optimal duration of antiviral prophylaxis is unknown, but the risk is generally restricted to the early post-transplantation period (6–12 months).

The administration of HBIG is an alternative to antiviral prophylaxis. One study reported no cases

of HBsAg seroconversion following the administration of a single dose of HBIG in 18 KT recipients with HBcAb+ grafts.[63] However, further studies are needed to confirm that the use of HBIG is a safe and effective alternative to antiviral prophylaxis in non-immune recipients of HBcAb+ grafts.

Studies on HBV in thoracic transplantation are limited. An analysis of a large cohort of lung and heart-lung transplants was performed to compare the results of 13,233 recipients of organs from HBcAb- donors with 333 recipients of organs from HBcAb+ donors. Although 1-year mortality was higher in the latter group in an unadjusted analysis, there was no significant difference in 5-year mortality, and HBcAb status did not affect mortality 1 and 5 years after transplantation.[64] In 2 other studies, no case of *de novo* HBV infection was reported among 36 recipients of HBcAb+ lungs who were vaccinated against HBV before transplantation or received antiviral prophylaxis after transplantation.[65,66] Early studies, including those on patients who underwent heart transplantation from HBcAb+ donors without prophylaxis, did not report any incidence of HBV transmission in cohorts of more than 80 patients; however, some of the patients were vaccinated before transplantation.[67–70] The indications for prophylaxis in recipients of non-liver HBV+ solid organs are summarised in Table 2.

Allogeneic haematopoietic stem cell transplantation

The treatment of haematological malignancies has changed substantially in recent decades, and haematopoietic stem cell transplantation (HSCT) has become very common. HBV can be transmitted by HBsAg+ grafts to HBV-naïve recipients or those who have lost protective immunity. Such transmission is generally fatal because of the primary disease of the patients and the immunodeficiency associated with pre-transplant conditioning therapy and immunosuppressive drugs used after transplantation to prevent the onset of graft-*vs*.-host disease. A high HBV viral load in the donor and the absence of HBsAb in the recipients are important risk factors associated with the development of HBV-related hepatitis post-HSCT.[71,72] In HBV endemic areas, excluding HBsAg+ donors significantly limits the use of allogeneic HSCT, especially when an HBsAg+ donor might be the only option. A 3-level approach was proposed to manage HBsAg+ donor transplantation at the Fifth European Conference on Infections in Leukaemia (ECIL-5), which established the possibility of using organs from such a donor pool provided that HBsAg- recipients were vaccinated before transplantation and that both the donor and the recipient underwent antiviral therapy to reduce HBV DNA before HSCT in the donors and suppress HBV DNA after HSCT in the recipients.[73] Following these recommendations, Hui *et al.* showed that HBV-related hepatitis occurred in 2 recipients (6.9%; n = 29) who received stem cells from HBsAg+ donors, whereas, in the control group that underwent HSCT without antiviral prophylaxis, the incidence was 48% (12 of 25 recipients).[74] Another study performed in an Asian cohort, showed a similar 5-year cumulative incidence of HBV-related hepatitis among patients who received stem cells from HBsAg+ donors and matched control recipients who received stem cells from HBsAg- donors (8.5% [95% CI −0.9% to 17.9%] *vs.* 7.9% [95% CI −0.9% to 16.7%]; $p = 0.939$). The HBsAg+ donors received antiviral treatment, and HBIG was administered to the HBsAg- recipients.[75] Moreover, Shen *et al.* demonstrated that HBIG, combined with long-term antiviral prophylaxis, effectively prevented *de novo* HBV infection in 67 HBsAg- patients who received grafts from double-positive HBsAg and HBcAb donors. None of the HBsAg- patients developed HBV infection after HSCT.[76]

Therefore, through appropriate management of donors and recipients, the risk of HBV-related hepatitis following HSCT from HBsAg+ stem cells can be reduced. This might enable patients in need to receive allo-HSCT in HBV-endemic areas. However, considering the paucity of data, clinical trials are needed to establish the most effective management methods when accepting stem cells from HBsAg+ donors.

Information on the effects of HSCT from HBcAb+ donors to HBV- recipients is lacking. A study reported the absence of HBV transmission in a cohort of HBV-naïve children undergoing prophylaxis through vaccination and/or HBIG administration when receiving HSCT from HBcAb+ donors.[77] Another study showed that HBV- recipients receiving stem cells from HBcAb+ donors had a 10.5% higher risk of developing HBV-related hepatitis after transplantation compared to the recipients receiving transplants from HBV- donors.[78]

Key point

Preliminary data suggested that antiviral prophylaxis should also be provided to the hematopoietic stem cell transplant (HSCT) recipients if they receive transplants from HBcAb+ve donors, regardless of the HBcAb status of the recipient.

Table 2. Indications for the management of recipients of HBV+ grafts in non-liver solid organ transplantation.

	Recipient status		
Donor status	**HBsAg-/HBsAb-**	**HBsAg+**	**HBsAg-/HBsAb+/HBcAb±**
HBsAg+	Not recommended	High-barrier NA prophylaxis	Can be used without high-barrier NA prophylaxis, only if careful monitoring and antiviral therapy at the earliest sign of HBV recurrence
HBsAg-/HBcAb+	High-barrier NA	High-barrier NAprophylaxis	Can be used without high-barrier NA prophylaxis with careful monitoring and antiviral therapy at the earliest sign of HBV recurrence

NA, nucleos(t)ide analogue.

Table 3. Indications for the management of recipients of HBV+ grafts in hematopoietic stem cell transplantation.

	Recipient status		
Donor status	**HBsAg-/HBsAb-**	**HBsAg+**	**HBsAg-/HBsAb+/ HBcAb±**
HBsAg+	Not recommended (In urgent cases: pre transplant vaccination+ life-long high-barrier NA +HBIG at transplant in recipients and pre transplant high-barrier NA in living donor)	High-barrier NA prophylaxis	Can be used without high-barrier NA prophylaxis, only if careful monitoring and antiviral therapy at the earliest sign of HBV recurrence
HBsAg-/HBcAb+	Pre-transplant vaccination+ high-barrier NA+ HBIG at transplant	High-barrier NA prophylaxis	Can be used without high-barrier NA prophylaxis if HBcAb-. NA prophylaxis if HBcAb+

HBIG, hepatitis B immunoglobulin; NA, nucleos(t)ide analogue.

In a more recent study from Italy, 11 out of 15 HBV- patients undergoing allo-HSCT with stem cells from HBcAb+/HBsAg- donors were treated with lamivudine. One of the remaining 4 patients who did not receive lamivudine experienced HBV reactivation.[79] Therefore, the transmission of HBV infection from HBcAb+/HBsAg- donors is possible. The ECIL-5 had suggested that antiviral prophylaxis should also be provided to recipients if they receive transplants from this pool of donors, regardless of the HBcAb status of the recipient; however, further studies are needed regarding this. The current indications from a few published studies are summarised in Table 3.

HIV donors in transplantation

A new source of donors for the HIV+ recipient

Combination antiretroviral therapy (cART) has increased the survival of HIV+ individuals and changed the status of AIDS from a fatal disease to a chronic condition. The transplant community has been relatively slow in recognising this change,[80] but the need for transplantation in HIV+ recipients has increased considerably. Owing to cART, many HIV+ individuals no longer suffer from AIDS but instead develop end-stage kidney and liver disease due to the comorbidities associated with chronic infections. Despite early reluctance to perform transplantation due to logical concerns regarding immunosuppressing individuals who might already be immunosuppressed, several multicentre trials demonstrated comparable allograft and survival outcomes between HIV- and HIV+ recipients following kidney,[81] liver,[82] and pancreas transplantation.[83] Importantly, the negative impact of HCV/HIV coinfection has been abrogated with the advent of DAAs.[84] This has significantly increased the number of HIV+ candidates on the waiting lists, which highlights the importance of new donor sources for HIV+ individuals waiting for solid organ transplants, as well as the need to expand the donor pool to new sources of HIV-infected donor organs.

Key point

Transplantation of HIV+ donor organs is increasing since they are as efficacious and safe as their HIV- counterparts.

The increasing demand for solid organ transplantation in HIV+ recipients

As the status of HIV has changed from a fatal disease to a chronic condition, the number of people with well-controlled HIV who are candidates for solid organ transplants has increased considerably.[85–87] HIV-associated nephropathy is a common indication for KT in young HIV-infected people of African descent,[88] and it is identified through kidney biopsy in approximately 20% of HIV+ patients in the United States.[89] Coinfection with hepatitis B is associated with membranous nephropathy, and IgA nephropathy might be directly associated with an HIV infection.[90,91] Progression to end-stage renal failure is further exacerbated by nephrotoxicity associated with cART and prophylaxis. Unfortunately, waiting times for KT are long, and dialysis is associated with poorer allograft and patient survival.[92] Lengthy waiting times might be even more problematic for HIV-infected recipients. Although more recent studies have shown an improvement in the survival duration for HIV-infected patients on dialysis,[93] earlier transplantation from HIV-infected donors can greatly benefit HIV+ patients. In the US, the HIV Organ Policy Equity Act (HOPE), which was made a part of federal law in 2013, has enabled such early transplantations.[94]

After the status of an HIV infection changed to a chronic condition, liver diseases became a leading cause of death among HIV+ patients with non-alcoholic fatty liver disease, co-infected with HBV and/or HCV.[95–98] Some studies have shown that progression to end stage liver disease (ESLD) is faster in HIV+ people.[95,96,99,100] The faster progression of the disease is exacerbated by drug-induced hepatotoxicity, the development of lamivudine-resistant HBV, and immune restoration hepatitis.[101–104] Unfortunately, HIV-infected candidates with ESLD, who are on the waiting list for transplantation, are often at a high risk of death.[105,106] With an increase in the number of all potential recipients on LT waiting lists, poor survival is even more problematic since the MELD scores necessary for the allocation of a liver are high. By the time the HIV+ candidate achieves the MELD score required for allocation of the liver of a deceased donor, clinical deterioration might be so severe that they might not meet the inclusion/exclusion criteria of most transplant centres based on CD4 counts and HIV viral load. By providing access to HIV+ donors, the HOPE Act has enabled transplantation from deceased donors at a lower MELD score, thus increasing the likelihood of better post-transplant outcomes.

The early experience with HIV-infected deceased donors

The transplantation of organs from HIV+ deceased donors (D+) was pioneered by Dr Elmi Muller in Cape Town, South Africa, in 2008[107,108] in response to the lack of funding for haemodialysis in HIV+ recipients (R+) in the public sector. Based on the early success of KT of HIV- donor organs into HIV+ individuals,[81] Dr Muller recognised that organs from HIV+ donors, who were on life support and met the criteria for brain death, could potentially be used for transplantation. South Africa has an extremely high incidence of HIV infection, with a prevalence of 19% and over 7 million HIV+ people.[109] Since the HIV+ recipients were largely in the public sector, transplantation was the only survival option; HIV-infected donors permitted early access to donor organs due to the high prevalence of HIV. In a pilot study, the first 4 HIV D+/R+ deceased donor transplants were associated with excellent outcomes, and no evidence of superinfection with more resistant strains of HIV or opportunistic infections transmitted by the D(+) organ was found following kidney transplantation.[107,108] In follow-up studies, long-term detection of the donor-strain virus was not observed in 25 HIV D(+)/R(+) recipients in the South African study, although the donor-strain virus was sporadically detected in 32% of recipients.[110]

The safety and efficacy of kidney transplantation in South Africa prompted US centres to change federal laws, which had prohibited the utilisation of tissue or organs from HIV-infected recipients. Based on the 500–600 viable HIV-infected recipients in the US annually,[111] the team from Johns Hopkins facilitated the rapid passage of the HOPE Act to permit the transplantation of organs procured from HIV-infected donors.[112] This increased the donor pool substantially, which was necessary to meet the demand for organs and reduce the disproportionate mortality observed among HIV+ individuals on the transplant waiting lists. A report on HIV+ deceased donor organs in the US described 92 HIV+ donors between March 2016 and March 2020, with 177 organs donated (131 kidneys and 46 livers).[113] There were no restrictions on donor HIV viral load or CD4 counts, although the presence of an opportunistic infection suggested a contraindication. Most of the HIV+ donors (90%) were on cART. Major mutations for drug resistance were present in 42% of donors. Importantly, integrase strand transfer inhibitors were present in only 4% of donors, which was fortunate since antiretroviral therapy in the HIV+ recipients is most frequently based on the integrase inhibitor to minimise the inter-drug interactions between antiretroviral agents and immunosuppressive agents.

The first NIH multicentre clinical trials (D+/R+) were initiated for KT recipients in 2018 (NCT03500315) and LT recipients in 2019 (NCT03734393) and included 160 HIV+ KT recipients and 80 HIV+ LT recipients. Although results on safety and efficacy are pending, the OPTN registry reported the trends during the first 2 years after the HOPE Act was passed. The 1-year patient and graft survival of 71 (D+/R+) KT and 31 (D+/R+) LT recipients were comparable to the outcomes of D-/R+ kidney and liver transplant recipients.[114] The chance of superinfection from the donor HIV strain, donor-derived infections, and HIV-associated disease in the donor liver or kidney remains a concern, but the safety and efficacy data from the US pilot trials performed with HIV+ donors for liver[115] and kidney[116] transplantation showed promising results. Importantly, both pilot studies showed that there was no loss of viral control following transplantation with an HIV+ donor. The HIV+ KT recipients showed excellent outcomes after receiving transplants from HIV+ and HIV- donors, although there was a higher incidence of rejection in the HIV+ cohort. There were also no statistical differences in the 1-year outcome following LT from either HIV+ or HIV- donors, but the incidences of opportunistic infections, infectious hospitalisations, and cancers were higher in the cohort transplanted from HIV+ donors. More definitive data should be available from the HOPE trials conducted by the NIH in the future. The results of those trials might help to formulate informed consent. Outside South Africa and the US, there have been scattered reports of excellent early outcomes following D+/R+ deceased donor kidney and liver transplantation.[117–121]

Liver and kidney transplantations from HIV-infected living donors can greatly minimise the time spent on dialysis in ESRD and maximise outcomes. Similarly, HIV+ donors provide the opportunity for LT in recipients with lower MELD scores before a significant deterioration in patient health, which could terminate transplant candidacy. Unfortunately, HIV+ candidates have a 47% lower chance of receiving a living donation KT compared to non-affected candidates on the waiting list.[122] Since many HIV-infected potential recipients have HIV-infected partners, the opportunity for transplantations from living donors can increase if people with well-controlled HIV serve as donors. Importantly, the HOPE Act also changed federal laws to permit living HIV+ donors to donate a kidney or a liver lobe. Although a prospective clinical trial with HIV+ living kidney donors was initiated in 2018 (NCT03408106), there are concerns that HIV-infected donors might have a higher risk of ESRD after donation due to HIV-associated diseases in the remaining kidney. Muzaale *et al.*[123] assessed the cumulative incidence of ESRD in people with well-controlled HIV and no diabetes, hypertension, or hepatitis C and compared it to matched HIV- people. Although there was a slightly higher risk of ESRD in people with HIV, it was comparable to other risk factors that were not contraindications to donation, such as tobacco use. In the US, the first 2 living donor operations

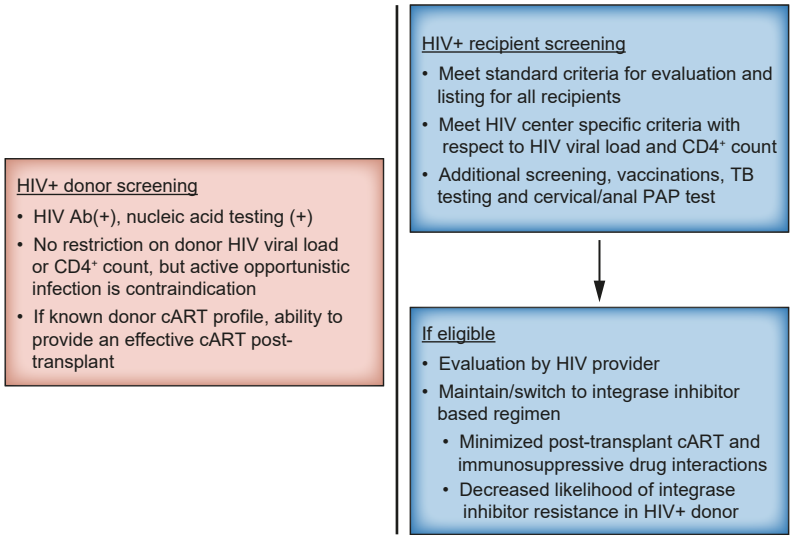

Fig. 3. The proposed algorithm for management of the HIV-positive solid organ transplantation. cART, combination antiretroviral therapy.

between HIV- kidney donors and recipients were performed at Johns Hopkins University in 2019, with excellent early outcomes.[124,125] The first living donor liver operation between an HIV+ donor (mother) and her 11-month-old HIV- child with ESLD, secondary to biliary atresia, was conducted in South Africa in 2017. The early outcomes, in this case, were favourable for the donor and the recipient, and HIV was undetectable in the child – who received cART – 1 year after transplantation.[126]

In conclusion, the inclusion of HIV+ deceased donors was initiated in the US by the HOPE Act, which facilitated earlier transplantation of organs to the increasing number of HIV+ people suffering from ESRD and ESLD. Such candidates face higher waitlist mortality and can greatly benefit from earlier transplantation made possible by increasing the donor pool to include HIV+ donors (Fig. 3). Long-term results from the initial trials in South Africa and the US are pending, but the early outcomes of HIV+ donations demonstrated that the transplantations were safe and efficacious, comparable to the transplantations of their HIV- counterparts. Although transplantations from HIV+ living donors are permitted in the US, the incidences of such transplantations are relatively low, perhaps due to the greater availability of and good early outcomes observed with HIV+ deceased donors.

Ethical point of view

Regarding the ethical point of view, the 4 basic principles that we should consider when assessing a procedure include autonomy, beneficence, non-maleficence, and justice.[127]

By obtaining the patient's informed consent (autonomy),[128] removing the cause of morbidity, decreasing the mortality, increasing the patient's quality of life (beneficence), using an effective antiviral therapy after transplantation (non-maleficence), and increasing the size of the organ pool to reduce the suffering of patients with end-stage organ dysfunction (justice), all the above principles are met. We recommend that full informed consent, including detailed information on the benefits and potential harms, should be discussed with the transplant candidate and their family. They should be informed about the potential risk of transmission of infectious diseases. This consent should be obtained during waiting list registration.

Conclusions

The disparity between the availability of organs and the need for them can be addressed by broadening the criteria for the donation of organs and expanding the size of the donor pool. Owing to the development of reliable antiviral therapies, problems of organ shortage can be overcome by using grafts affected by HCV, HBV, or HIV. In this review, we summarised all the data published to date on the use of these organs, except those positive for HCV, as mentioned in the introduction. Transplantations from HBV-+ donors are regularly performed with the appropriate prophylaxis schemes prescribed by expert hepatologists from the transplant centres. However, the donation of HIV- organs is uncommon, although the safety and efficacy of such transplantations are comparable to those from HIV- donors. A multidisciplinary approach with trained hepatologists and infectious disease specialists in the local transplant team is essential to determine the optimal allocation of infected organs, prescribe the best prophylactic treatment after transplantation, assess patient's adherence, and treat recurrent/*de novo* infection, if it occurs. This resembles a tailored approach that can be implemented as part of modern personalised transplantation strategies.

Abbreviations

cART, combination antiretroviral therapy; cccDNA, covalently closed circular DNA; ESLD, end stage liver disease; ESRD, end-stage renal disease; HBcAb, antibodies against the HBV core antigen; HBIG, hepatitis B immune globulin; HBsAb, antibodies against HBsAg; HBsAg, HBV surface antigen; HOPE, HIV Organ Policy Equity; HSCT, haematopoietic stem cell transplantation; KT, kidney transplant; LT, liver transplantation; MELD, model for end-stage liver disease; NA, nucleos(t)ide analogues.

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Authors' contributions

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Supplementary data

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