

Outcome of Patients with Hepatitis B Virus and Human Immunodeficiency Virus Infections Referred for Liver Transplantation

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The outcome of patients with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) referred for liver transplantation (LT) is unknown. A high frequency of lamivudine-resistant (LAM-R) HBV infection may increase the risk of liver-related death pre-transplantation and prophylaxis failure post-transplantation. We evaluated the association of LAM-R HBV on pre-transplant survival and post-transplant outcomes in 35 consecutive HIV-HBV coinfecting patients referred for LT between July 2000 and September 2002. At the time of referral, the median CD4 count was 273/mm³, MELD was 14, and LAM-R HBV infection was present in 67%. Among these referred patients, 26% were listed, 29% not listed due to relative/absolute contraindications; 26% not listed as too early for LT; 9% not listed as too sick for LT; and 11% died during transplant evaluation. Of the 9 listed patients, 4 remained listed, 1 died 18 months post-referral, and 4 were transplanted (11% of total) 3 to 40 months after listing. Of 17 evaluated but not listed patients, 5 died ($p=0.38$ compared to listed group) and all deaths were liver-related. All the HBV-HIV coinfecting patients, who were transplanted, are HBsAg negative and have undetectable HBV DNA levels on prophylactic therapy using hepatitis B immune globulin (HBIG) plus lamivudine, with and without tenofovir or adefovir, with median 33.1 months follow-up. Late referral and the presence of LAM-R HBV pre-transplantation are common in referred HIV-HBV patients. In HIV-HBV coinfecting patients undergoing LT, HBV recurrence is successfully prevented with combination prophylaxis using HBIG and antivirals. *Liver Transpl* 12:801-807, 2006. © 2006 AASLD.

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Liver disease is increasingly recognized as a significant cause of morbidity and mortality among HIV-infected individuals. As deaths due to HIV-related disease have declined, a proportionately greater number of HIV-infected persons are dying of liver-related complications. Both hepatitis C and hepatitis B have emerged as important contributors to liver-related complications.¹⁻³ In the largest study evaluating the impact of HBV infection on survival, liver-related mortality in HIV-HBV coinfecting men was found to be 14.2 per 1000 compared to 1.7 per 1000 ($p < 0.001$) in men with HIV-1

infection alone.² The rate of liver-related mortality was higher in the years since highly active antiretroviral therapy (HAART) was introduced^{2,3} and in those with low nadir CD4+ cell counts.²

Since the nucleoside analogue lamivudine has both anti-HIV and anti-HBV activity, many HIV-infected patients with HBV coinfection have received prolonged lamivudine therapy as a component of HAART. In HBV/HIV coinfecting patients, the incidence of lamivudine-resistant HBV is ~50% after two years of therapy^{4,5} and approaches nearly 100% after four years. The natural history of HBV disease in coinfecting patients is only partially known, but the development of lamivudine-resistant HBV infection may have significant negative

Abbreviations: DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; LAM-R, lamivudine-resistant; MELD, model of end-stage liver disease; Pre-LT, pre-transplantation; RNA, ribonucleic acid.

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consequences. Patients with HIV-HBV coinfection may be more likely to have lamivudine-resistant HBV infection and in patients with cirrhosis, liver decompensation may result in an urgent need for liver transplantation.⁶

Liver transplantation is the treatment of choice for individuals with end-stage liver disease. Historically, HIV infection has been considered a contraindication for liver transplantation due to the theoretical concerns of worsening HIV infection and risk of opportunistic infections in the setting of "dual" immunosuppression related to HIV and anti-rejection medications. With the advent of HAART and improved ability to prevent HIV-related complications, transplantation of HIV-infected individuals has been undertaken in a selected number of transplant programs. Recent single center reports has been positive,⁷⁻¹⁰ but with some concerns regarding patients with hepatitis C infection,^{9,10} who are at risk for recurrent disease post-transplantation, like non-HIV transplant recipients. A large NIH-sponsored study of the safety and efficacy of liver and kidney transplantation in HIV-infected individuals is underway and can be expected to provide a more comprehensive evaluation of outcomes in these patients.

In the past decade, the outcomes of patients with chronic HBV infection undergoing liver transplantation has undergone substantial improvements.¹¹ The availability of effective prophylactic therapies including lamivudine, adefovir and hepatitis B immunoglobulin (HBIG) has resulted in graft and patient survival comparable to those with non-viral diseases. A combination of HBIG and one or more nucleos(t)ide analogue(s) are commonly used for prophylaxis post-transplantation, and such regimens are effective in $\geq 90\%$ of transplant recipients.¹² However, most of these data were generated in patients without preexisting lamivudine-resistant HBV infection and it is unclear whether similar results can be obtained in the setting of drug-resistant HBV. Single center reports suggest the presence of pre-transplant lamivudine-resistant HBV is a risk factor for failure of prophylaxis post-transplantation.^{13,14}

In this study, we evaluated the outcomes of HBV-HIV infected patients referred for consideration of liver transplantation, the frequency of lamivudine-resistance among patients presenting for consideration of liver transplantation, and the pre- and post-transplant outcome of coinfecting patients undergoing liver transplantation.

STUDY METHODS

Study Design and Study Populations

This is a retrospective cohort study of consecutive HIV-infected persons with HBV coinfection referred for consideration of liver transplantation at the University of California San Francisco (UCSF) between July 2000 and September 2002. Referred patients had an initial intake interview with the transplant coordinator for HIV patients; the completion of this interview was the basis for inclusion in this study cohort. Patient outcomes in

the referred cohort were assessed up to June 2004. For those undergoing liver transplantation, patient and graft follow-up were assessed up to the date of last follow-up. The study was approved by the UCSF institutional review committee.

Study Endpoints and Data Collection

The primary study endpoints for referred patients were: (i) determination of the prevalence of lamivudine-resistant HBV infection at initial assessment, (ii) the pre-transplant survival of those referred for consideration of liver transplantation, and (iii) the proportion who were transplanted during the study period. Additional endpoints for the HBV-HIV coinfecting patients who underwent transplantation were: (i) frequency of post-transplant prophylaxis failure, defined as persistently detectable HBV DNA; and (ii) progression of HIV disease, defined by the development of opportunistic infections or neoplasms.

For the purposes of the study, lamivudine-resistant HBV infection was defined by a HBV DNA level greater than or equal to 10^5 copies/ml in a patient who had been on lamivudine therapy for at least 6 months. Sequencing for polymerase mutations was not performed. Among the liver transplant recipients, failure of prophylactic therapy was defined by a rise of HBV DNA by ≥ 1 log on 2 occasions or more, with measurements at least 2 weeks apart with or without the present of HBsAg in serum.

The following data were collected on all patients: (i) demographics - gender, race/ethnicity, age; (ii) HBV infection related - duration of HBV infection (based upon date of diagnosis, not risk factor information), duration of lamivudine therapy (if applicable), HBV DNA viral level on lamivudine (if applicable), current HBV DNA viral load, current anti-HBV drug therapy (lamivudine, adefovir, and later tenofovir were available during the study period); (iii) HIV-infection related - CD4 count; HIV RNA viral load, history of opportunistic infections or malignancies, history of lamivudine use as part of HAART; and (iv) transplant-related - history of significant cardiopulmonary disease or other non-HIV, non-liver comorbidities, history of drug and alcohol use, and adequacy of social support.

The usual criteria for listing for liver transplantation were applied, namely a Child-Pugh score of 7 or greater and/or small hepatocellular carcinoma.¹⁵ Additionally, HIV-specific criteria for liver transplantation utilized during the study period were (i) CD4 $> 100/\text{mm}^3$; (ii) undetectable HIV RNA (by sensitive quantitative assay) on HAART or predicted ability to suppress HIV replication post-transplantation based upon review of medication history and HIV resistance testing, (iii) absence of opportunistic infections or malignancies, and (iv) adequate functional status.

Standardized Post-Transplant Protocols

Post-transplant management, including immunosuppressive therapy and HBV prophylaxis, were standard-

ized. Immunosuppression consisted of triple drug therapy using cyclosporine, mycophenolate mofetil and prednisone. Cyclosporine doses were adjusted to maintain trough blood levels between 200-250 ng/ml during the first three months, and 100-200 ng/ml after month 3. Mycophenolate mofetil was given at a dose of 1000-1500 mg daily for the first six months, and tapered off during the first year except if use of cyclosporine was limited by renal dysfunction. Bolus steroids (500 mg solumedrol) was administered at the time of surgery, and tapered to a maintenance dose (5 mg) within two months of the transplant. For patients with renal insufficiency, sirolimus was substituted for cyclosporine and the target sirolimus blood levels were 5-10 ng/ml. Induction with lymphocyte-depleting antibody therapy or interleukin-2 receptor antagonists was not used in any patients.

All HBV-HIV coinfecting patients received HBIG beginning in the operating room and continued post-transplantation on an indefinite basis. The dose of HBIG was 10,000 IU during the anhepatic phase, followed by 10,000 IU daily for six days and then 10,000 IU monthly. After the first year, if anti-HBs titers were >200 IU/ml the dose of HBIG was reduced to 5000 IU monthly and then to 2500 IU monthly. In addition to HBIG, patients received lamivudine, tenofovir, adefovir or combinations of drugs as prophylaxis. The specific regimen used was based on presence or absence of drug-resistant HBV pre-transplantation. Patients with lamivudine-resistant HBV initially received combination HBIG plus lamivudine and tenofovir or adefovir. Patients without lamivudine-resistance received HBIG plus lamivudine as initial therapy. Changes in antiviral therapy after the first six months post-transplantation were necessitated by concerns of virological breakthrough (HIV or HBV) or drug toxicity in two patients. Monitoring for HBV recurrence post-transplantation included measurement of HBsAg and anti-HBs prior to each dose. HBV DNA levels were measured every 6 months, if HBsAg became positive or if liver enzymes were elevated.

HAART was managed by an HIV specialist working with the transplant team. In most cases, HAART regimens used at the time of referral were continued prior to and following transplantation. HAART was restarted within the first week following transplantation in all patients.

Statistical Methods

Median, mean, range and standard deviation were used for the descriptive statistics, as appropriate. Analysis of categorical data was performed using the Fisher's exact test or Chi-square-test and the Mann Whitney U test was used for analysis of continuous variables. A p value of < 0.05 was considered statistically significant. Cumulative patient survival was calculated using Kaplan-Meier methods and the log-rank test used to compare groups. For the referred patients, censoring was performed at the date of last follow-up, death or date of liver transplantation. For transplanted patients, cen-

soring was performed at the time of last follow-up post-transplantation.

RESULTS

HBV-HIV Coinfected Patients Referred for Liver Transplantation

Baseline Characteristics

A total of 35 HBV-HIV coinfecting patients were referred for consideration of liver transplantation during the study period. All but one were male (97%), the majority were Caucasian (93%), and the median age was 46 years (range 28-55 years). The median duration from diagnosis of HBV infection was 11 years (range 1-28 years). The known duration of HIV infection closely mirrored that of HBV infection with a median duration of infection of 12 years (range 1-21 years).

At the time of referral, 83% of patients were receiving HAART with the remaining patients off HAART due to concerns regarding potential hepatotoxicity related to one or more HAART agents. The median duration of lamivudine treatment in those patients who had been on a lamivudine-containing HAART regime was 60 months (range <1-144 months). The median CD4 count was 276/mm³ (range 94-956/mm³) and HIV RNA was undetectable in 79% at the time of referral. The median HIV RNA in those with detectable viral loads was 148 copies/ml (range 140-250,040 copies/ml).

A total of 67% of patients met the criteria for lamivudine-resistant HBV infection based upon review of historical records of HBV DNA levels on lamivudine therapy. In three patients, insufficient virological data were available to determine whether lamivudine-resistance was present. At the time of referral, 48% of all patients were on an additional anti-HBV agent with activity against lamivudine-resistant HBV: 30% on tenofovir, 13% on adefovir and 4% on tenofovir and adefovir.

Outcome of Referred Patients

Of the 35 patients referred for consideration of liver transplantation, nine (26%) were wait-listed, 10 (28%) had contraindications for liver transplantation, nine (26%) were too early for transplantation (did not meet minimal listing criteria), three (9%) were too sick to be considered for transplantation (intubated and/or multi-organ failure) and four (11%) died during the evaluation process (Figure 1). Contraindications for liver transplantation were commonly related to non-HIV issues rather than HIV issues. Only three of the referred patients had conditions related to their HIV infection that were specific contraindications to liver transplantation during the study period: 2 had a history of Kaposi's sarcoma and 1 had a CD4 count less than 100/mm³.

After the initial referral and with a median follow-up of 7.5 months (mean 10, range 0-48 months), 10 patients died, all of liver-related complications. In addition to the four deaths occurring during the evaluation

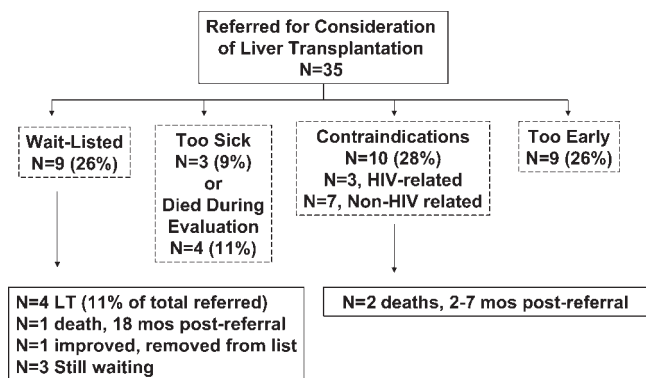


Figure 1. Outcome of 35 HBV-HIV coinfecting patients referred for consideration of liver transplantation. A total of 26% (N=9) were considered candidates for transplantation (absence of transplant-related or HIV-related contraindications) and met listing criteria.

process, all three patients judged to be too sick for liver transplantation at the time of referral died, as well as two patients with contraindications and one patient listed for liver transplantation. The overall 1-year cumulative survival from time of referral was 67%, with the majority of deaths occurring within three months of referral (Figure 2a). Treatment with adefovir or tenofovir prior to or at the time of referral was on the only factor identified as predictive of survival with or without transplantation (Table 1 and Figure 2b).

Of the nine patients who were listed for liver transplantation, four (11% of entire referral population) underwent liver transplantation, two with deceased donors and two with living donors. Two patients were removed from the list, one due to liver-related complications leading to death 18 months post-referral, and one due to significant improvement in the status of his liver disease on adefovir therapy. Five patients remained wait-listed.

Post-Transplant Course of HBV-HIV Coinfecting Patients

The pre-transplant features of the four HIV-HBV coinfecting liver transplant recipients are shown in Table 2. The median biological MELD score at the time of transplantation ranged from 16 to 28. All patients were on HAART and anti-HBV therapy at the time of transplantation and had undetectable HBV DNA levels by HBV quantitative assay.

Overall cumulative patient and graft survival were 100%. All patients received prophylactic therapy for HBV using HBIG plus lamivudine with or without adefovir or tenofovir. HBV antivirals were started concurrent with reinitiation of HAART post-transplantation. In all patients, the same antivirals used pretransplantation were continued post-transplantation and all patients have remained HBsAg negative, anti-HBs positive and without evidence of HBV recurrence after a median follow-up of 33 months (range 18-48 months) (Figure 3). Changes in anti-HBV therapy post-transplantation

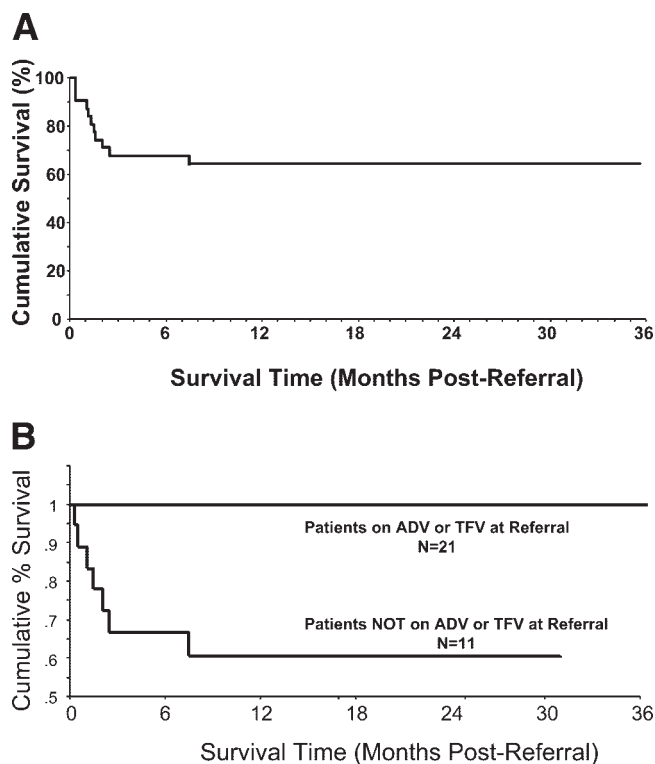


Figure 2. (A) Overall cumulative patient survival in 35 HBV-HIV coinfecting patients referred for consideration of liver transplantation. Patients undergoing liver transplantation are censored at the time of transplantation. (B) Cumulative patient survival in HBV-HIV coinfecting patients referred for consideration of liver transplantation who were on a drug with efficacy against lamivudine-resistant HBV (adefovir or tenofovir) at time of referral versus those not on adefovir or tenofovir at time of referral. Patients who underwent liver transplantation were censored at the time of transplantation. Differences in survival with or without transplantation were significantly different between groups ($p=0.031$ by log-rank test). At one year after referral, 38% of referred patients had died; all were in the group not on adefovir or tenofovir at the time of referral and most occurred in the 3-6 months following referral.

were required in two patients. One patient developed a transient low-level increase in HBV DNA at month nine post-transplantation. HBsAg was negative and anti-HBs positive during this period and repeat testing of HBV DNA was undetectable. However, tenofovir was added to lamivudine and HBIG to reduce the possibility of any future virological escape. A second patient developed acute interstitial nephritis and progressive renal dysfunction at month 6 post-transplantation. Tenofovir was discontinued due to concerns of possibly toxicity and adefovir was not considered an option in the setting of new onset renal dysfunction. This patient was maintained on higher dose HBIG infusions (increased from 5000 IU monthly to 10,000 IU monthly) to provide a higher anti-HBs titers and lamivudine was continued. There has been no evidence of HBV infection; HBsAg remains negative and HBV DNA levels undetectable.

HIV viral loads remained undetectable in all patients on continuous HAART. One patient required interruption in HAART due to concerns regarding renal toxicity

TABLE 1. Comparison of Clinical Features at Time of Referral in Survivor and Non-Survivors

Clinical Features At Time of Referral	Survivors N = 25	Non-Survivors [‡] N = 10	P Value
MELD score (median, range)	14.5 (6-26)	14 (8-27)	0.76 [†]
CD4 count (median, range)	273 (94-956)	290 (107-605)	0.38 [†]
LAM-R HBV infection (%)	61%	74%	0.71*
On HAART (%)	88%	70%	0.20*
On adefovir and/or tenofovir (%)	44%	0%	0.03*

[‡]Three patients with insufficient data to determine if LAM-R excluded: all were non-survivors.

[†]Mann-Whitney U test.

*Fisher-Exact test.

TABLE 2. Pre-Transplant Features of Liver Transplant Recipients

	Age at LT(Yrs)	Laboratory MELD*	LAM-R HCC Present	Pre-LT Anti-HBV Therapy	HBV DNA Level at Time of LT [†]	AST, ALT at Time of LT	CD4 Pre-LT (per mm ³)	HIV RNA Pre-LT (copies/ml)	
Patient #1	50	17	No	Yes	Adefovir	<10 ⁶ copies/ml	78, 45	439	<75
Patient #2	53	16	No	No	Lamivudine	<10 ⁶ copies/ml	40, 24	175	<50
Patient #3	47	28	No	Yes	Tenofovir	<4700 copies/ml	83, 41	313	<75
Patient #4	43	28	Yes	Yes	Tenofovir Lamivudine	<4700 copies/ml	39, 37	104	NA

Abbreviations: Pre-LT, pre-transplantation; LAM-R, lamivudine-resistant; MELD, model of end-stage liver disease; HCC, hepatocellular carcinoma.

[†]HBV DNA assays with different limits of detection were used during the study period.

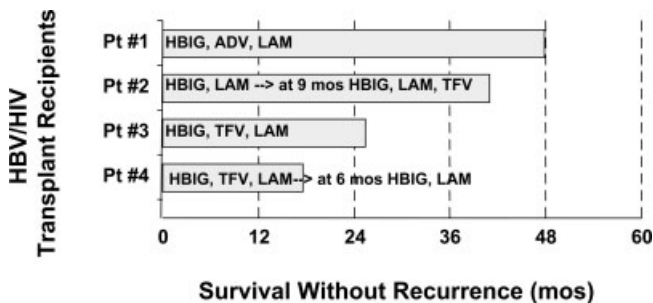


Figure 3. The post-transplant course and prophylactic therapy used for each patient is shown. The follow-up ranged from 18 to 48 months. All patients remain HBsAg negative and anti-HBs positive. In patient #2, HBV DNA became transiently positive (HBV DNA level at nine months) but without presence of HBsAg; tenofovir was added to HBIG and lamivudine and the patient has remained HBsAg negative and anti-HBs positive in subsequent follow-up. Patient #4 developed acute interstitial nephritis and renal dysfunction at 6 months and tenofovir was discontinued due to concerns of renal toxicity; patient is being maintained on lamivudine and HBIG.

and HIV RNA levels were transiently positive while the patient was off HAART but became undetectable again once HAART was resumed. There have been no episodes of acute rejection and there have been no emergent opportunistic infections. The median CD4 count on last follow-up was 315/mm³ (range 125 to 505/

mm³), which was equal to or higher than pre-transplant values in all patients.

DISCUSSION

In the era prior to the development of HAART, HIV-infected patients were largely excluded from consideration of liver transplantation due to relatively high mortality rates.^{16,17} However, with continued advances in the understanding of HIV pathogenesis and the recognized benefits of HAART, as well as concurrent advances in immunosuppression and management of post-transplant complications, there are an increasing number of transplant programs undertaking the transplantation of HIV-infected patients.^{7,8,10,18-19} Recent reports have highlighted the unique aspects of clinical management in these patients, including the interactions between immunosuppressive agents and antiretroviral drugs,²⁰⁻²² the importance of adequate HIV suppression post-transplantation, and the risk of recurrent HCV disease.^{7,18,19} HBV coinfection is an important cause of liver failure in HIV-infected patients² and a clear understanding of the unique aspects of HBV treatment are essential to optimize pre- and post-transplant outcomes. Our study highlights the importance of timely referral for consideration of liver transplantation, the high frequency of lamivudine-resistant HBV

infection in these patients, and the key role of agents such as adefovir and tenofovir in the management of HBV-HIV coinfecting patients with decompensated liver disease.

This study is the first to assess the outcomes of HBV-HIV coinfecting patients referred for liver transplantation. We found that only 26% of referred patients are eligible candidates. This low rate of ineligibility reflects, in part, a lack of knowledge on the part of referring physicians regarding the indications and appropriate timing for referral for liver transplantation. While 20% of referred patients did not meet minimal listing criteria for liver transplantation and were referred too early, an equal percent were referred too late with liver-related deaths occurring before the transplant evaluation could be completed. Since transplantation in HIV-infected individuals is relatively "new" as a treatment option for end-stage liver disease, there is a need to educate referring gastroenterologists and infectious disease specialists regarding the indications and contraindications for transplantation in this population.

As anticipated, lamivudine-resistant HBV infection was common among coinfecting patients. Adefovir, tenofovir and entecavir are active against lamivudine-resistant HBV and are safe agents in patients with decompensated liver disease.^{6,13,23,24} In our study, 30% of patients were on treatment with adefovir or tenofovir for lamivudine-resistant HBV at the time of referral. Those patients on antiviral drugs with efficacy against lamivudine-resistant HBV had a higher likelihood of survival than those not receiving these agents, suggesting that untreated lamivudine-resistant HBV infection can have serious clinical consequences. This argues strongly for regular monitoring of HBV DNA levels in HBV-HIV coinfecting patients, so that virological breakthrough can be detected early and new anti-HBV therapies instituted before clinical deterioration. Ongoing control of HBV replication long-term will be of equal importance in maintaining stability of liver disease in coinfecting patients. In this regard, the use of anti-HBV drugs (alone or in combination) with goal of minimizing the risk of drug resistance would be the optimal treatment strategy, especially in patients with cirrhosis who may decompensate when drug-resistant HBV infection develops.

Control of HBV replication in the setting of active liver disease (elevated serum aminotransferase levels and/or presence of necroinflammation on liver histology) has been associated with stabilization of clinical status in those with decompensation. In patients with wild-type HBV infection, treatment with lamivudine prior to transplantation has been associated with improvement in survival and delays in the need for transplantation.²⁵⁻²⁷ Similarly, treatment of lamivudine-resistant HBV infection in non-HIV infected patients with adefovir results in significant improvements in total bilirubin, prothrombin time and albumin levels and stabilization or improvement in Child-Pugh score in the majority of patients.²³ However, clinical improvements lag behind suppression of HBV DNA replication and patients typically require approximately six months of

treatment to derive clinical benefits. In our study, the majority of deaths occurred within three months of referral, suggesting the clinical state of these patients was too advanced to obtain the clinical effects of effective HBV suppressive therapy. However, one listed patient with lamivudine-resistant HBV infection who was treated with adefovir improved significantly to the point that liver transplantation was no longer needed and the patient was removed from the list.

The optimal anti-HBV therapy in patients with HIV coinfection is not known. Several approved anti-HIV agents have anti-HBV activity, including lamivudine, tenofovir, and emtricitabine. The use of one or more agents in the treatment of HIV infection has important implications for control of HBV infection and vice versa. The use of lamivudine as HIV therapy in a patient with unrecognized HBV infection could limit future HBV treatment choices because of the development of lamivudine-resistant HBV. Likewise, the treatment of HBV infection with lamivudine or tenofovir alone in a coinfecting patient will lead to HIV resistance to these agents and thereby compromise future anti-HIV treatment options. Both hepatologists and HIV treatment providers need to be aware of the potential impact of nucleos(tide) analogue choices in the management of both HBV and HIV infections.

Our limited experience indicates patients with HIV-HBV coinfection can successfully undergo liver transplantation without progression of viral disease, even in the setting of lamivudine resistance. Combination therapy using nucleos(tide) analogues plus HBIG was highly effective in the prevention of HBV recurrence post-transplantation. These results add to the evidence of excellent short and longer-term outcomes of HBV-HIV coinfecting transplant recipients.^{8,9,28}

In summary, we have found the HIV-HBV coinfecting individuals referred for liver transplantation had a high prevalence of lamivudine-resistant HBV infection and that use of drugs to suppress HBV replication in these patients (i.e. adefovir and tenofovir) was associated with improved survival. This emphasizes the importance of control of HBV replication in the setting of decompensated liver disease. The availability of an increasing number of drugs with both HIV and HBV activity (e.g. lamivudine, tenofovir, emtricitabine) increases both the opportunities to use drug combinations to control HBV infection pre and post-transplantation, but also may lead to the emergence of multidrug resistant HBV in the future. Ongoing close monitoring of HBV replication status in HBV-HIV coinfecting patients will be essential in identifying the emergence of drug-resistant HBV and in making therapeutic decisions to minimize the risk of liver-related complications.

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