The Strategy and Efficacy of Prophylaxis Against Hepatitis B Virus Recurrence After Liver Transplantation in the Era of High Potent Nucleos(t)ide Analogues: A Meta-Analysis

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Keywords: Hepatitis B virus, liver transplantation, prophylaxis, high potent nucleos(t)ide analogues, meta-analysis

Posted Date: May 28th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-30067/v1>

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Abstract

Background: High potent nucleos(t)ide analogues (HP NAs) with or without hepatitis B immunoglobulin (HBIG) is the standard prophylactic therapy for avoiding the HBV recurrence after liver transplantation (LT). While the clinical impact of HP NAs-based prophylaxis has not been well documented, the optimal treatment strategy is currently debated. This meta-analysis aims to evaluate clinical outcome of LT recipients under HP NAs-based regimens and investigate different prophylaxis schemes.

Methods: We followed PRISMA statement to conduct this study. Two reviewers independently searched relevant literature via PubMed, EMBAES, MEDLINE, Web of Science, and Google Scholar. Studies were included if they observed HBV recurrence under HP NAs-based regimens in patients who received HBV-related LT. Primary and secondary outcome were HBV recurrence, HCC recurrence, all-cause and HBV-recurrence related mortality. Incidence with 95% confidence intervals was aggregated and assessed by fixed effect model/random effect model. Subgroup analysis was applied to examine the impact of different treatment strategies.

Results: 26 studies (n=2374) were included, with a pooled HBV recurrence rate of 0.92% (95% CI 0.47%-1.48%). Studies with and without HBV viremia or HDV superinfected patients demonstrated comparable HBV recurrence (p=0.25, p=0.69). Recurrence rate under indefinite combination of HP NAs and HBIG was lower than that under HP NAs monotherapy (p=0.0003), and similar to that under NAs plus finite course of HBIG (p=0.53). Pooled HCC recurrence rate was 5.34% (95% CI 0.78%-12.48%). HBV-recurrence related mortality and all-cause mortality were 0.17% (95% CI 0.00%-1.51%) and 7.29% (95% CI 4.42%-10.71%) respectively.

Conclusion: Our study suggests HP NAs-based regimens provide satisfactory HBV antiviral prophylaxis and improved long-term outcome for LT recipients. Finite combination of HP NAs and HBIG is an alternative to lifelong dual therapy.

1. Background

For patients with chronic hepatitis B virus (HBV) infection, the prognosis after liver transplantation (LT) has been improved markedly, largely attributable to prophylaxis against HBV recurrence¹⁻³. The first milestone of preventive therapy was long-term hepatitis B immune globulin (HBIG), which tremendously decreased the risk of graft infection (from 75% to 33%) and increased 3-year survival (from 54% to 83%)^{4,5}. Despite of the advances, HBIG monotherapy was far from satisfactory. The efficacy was compromised among patients with high risk of HBV reactivation or those developed immune escape⁶⁻⁸. Other problems such as supply limitation and high cost were difficult to ignore⁹. The second breakthrough for HBV recurrence prophylaxis was antiviral agents. Lamivudine (LAM) and/or adefovir (ADV) proved synergistic activity with HBIG by further lowering the HBV recurrence rate to less than 10%¹⁰⁻¹². Nevertheless, the emerging issues such as YMDD mutants and renal impairment were major obstacles to long-term application of these low potent nucleos(t)ide analogues (LP NAs)¹³⁻¹⁶.

A new era came with the development of high potent and high genetic barrier nucleos(t)ide analogues (HP NAs, i.e. entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide). As the safety and efficacy being proved in registrational and real-world studies, HP NAs have been substituted for LP NAs as the preferred antiviral prophylaxis¹⁷⁻²¹. Although there have been numerous clinical studies relevant to this topic, the only systematic review focusing on HP NAs-based prophylaxis was issued in 2013²². In that review, Cholongitas E and Papatheodoridis GV included 519 patients treated by combination of HP NAs and HBIG, and they found HBV recurrence incidence under indefinite combination of HP NAs and HBIG was 1.0%, significantly lower than that under LAM plus HBIG. Since HP NAs-based regimens have become standard care for LT recipients in recent years¹⁹⁻²¹, the critical issues are not their rationale of usage anymore, but rather their clinical outcomes and treatment strategy. The HBV reinfection and recipients' mortality under HP NAs-based therapies is not clear. In terms of treatment strategy, there are still many questions need to be answered, for example what the risk factors of HBV recurrence for HP NAs-based therapies are, whether HP NAs monoprophyllaxis is equally effective as combination of HP NAs and HBIG. Therefore, we conducted this meta-analysis to probe these two issues and hope to provide evidence for clinical practice.

2. Methods

2.1 Literature search strategy

We followed PRISMA (Preferred reporting items for systematic review and meta-analyses) statement to conduct this study (23). A comprehensive literature search was performed via PubMed, EMBAES, MEDLINE, Web of Science, and Google Scholar under the terms of "liver transplantation", "HBV recurrence", "entecavir" and "tenofovir". For example, the search algorithm in PubMed was: ((liver transplantation) AND ((HBV recurrence) OR HBV reactivation)) AND ((entecavir) OR tenofovir). Abstract books from the major international transplantation conferences and hepatology meetings were also reviewed. Literature search was last updated on February 2020.

2.2 Study selection and data extraction

Studies which published in English and fulfilled all of the following criteria were included: 1. Subject: adult patients received HBV-related LT. 2. Intervention: Entecavir or tenofovir disoproxil fumarate or tenofovir alafenamide (with or without HBIG). 3. Study design: RCT or observational cohort studies. We excluded the studies if they met any following criterion: 1. The number of patients who used HP NAs was less than 10. 2. Median/mean follow-up period was less than 12 months, since we expect the episode of HBV recurrence may not be captured during short period of follow-up. 3. HBV recurrence rate was not mentioned for

HP NAs group. 4. Patients were exposed to LP NAs after LT. Two authors (Li MS, Hou ZH) conducted the literature search and screen independently, any disagreement was resolved by consensus or consulting to corresponding author.

2.3 Data Extraction

Data from manuscript and abstract were extracted manually (Li MS), in aspect of patient characteristics, therapeutic regimen and clinical outcome. To describe patient characteristics, the proportion of patients with pre-LT HCC, quantifiable HBV DNA and HDV coinfection was pulled. Drugs, treatment duration and administrative route were recorded. In terms of clinical outcomes, events of HBV reactivation, HCC recurrence, HBV recurrence-related mortality and all-cause mortality were calculated. Parameters related to renal function were also extracted to review the impact of HP NAs on renal safety.

2.4 Assessment of quality (risk of bias)

Newcastle-Ottawa scale (NOS) and Cochrane Collaboration's tool for assessing risk of bias (RoB) were used to evaluate the study quality/risk of bias for observational studies and RCT 24, 25. In the NOS system, quality of observational study was rated as high, moderate or low based on total score i.e. score 7-9 indicated high study quality, 4-6 fair quality, and 0-3 low quality. According to RoB, the risk of bias of each RCT was graded as high, unclear or low by 6 domains.

2.5 Data analysis

The primary study outcome was HBV recurrence, which was defined by original studies or as reappearance of HBsAg and/or HBV DNA if there was no definition in original studies. The secondary outcome included HCC recurrence, HBV recurrence-related mortality and all-cause mortality. Heterogeneity across studies was assessed by I-square index, which indicated substantial heterogeneity with a value over 50% (26). Random effect model was applied in case of significant heterogeneity, and fixed effect model was used in the absence or minor heterogeneity (27). Subgroup analysis was conducted by risk factors, HP NAs, combination approaches and administration of HBIG. We made sensitivity analysis to examine the robustness of primary finding. Meta-analysis was conducted with the R software program (version 3.6.2) and the R-package meta.

3. Results

3.1 Studies and patient characteristics

A total of 419 citations were identified by initial search, 348 duplicated or irrelevant records were later removed. According to the inclusion/exclusion criteria, 45 literature was further excluded, and final 26 studies (n= 2374) were included for our analysis (Figure 1).

The study and patient characteristics were summarized in Table 1. 24 observational studies and 2 RCT were included. 21 of them were presented in manuscript, and 5 in conference abstract. 18 studies were conducted in Asia, 3 in Europe, 3 in North America, 1 in Australia, and 1 across continents. 15 studies enrolled patients with HBV viremia and 5 included patients with HDV superinfection. HCC was a major indication for LT, responsible for 13.6% to 80% of the surgical cases. Considerable follow-up period was ensured across the studies, with 84.6% (22/26) over 24 months and 30.7% (8/26) over 48 months.

Table 1
Identified studies for systematic review and meta-analysis

First Author	Year	Study design	NOS score/ RoB	Pre-transplant HBV DNA positivity (%)	Pre-transplant HDV superinfection (%)	HCC before LT (%)	HP NAs-based regimen	Median/mean Follow-up period (month)	Definition of HBV recurrence	HBV recurrence	HE rec rel mo
Xi ZF ^[28]	2009	RC	6	60.0	NA	41.6	ETV + HBIG	34	reappearance of both HBsAg and HBV DNA	0/30	NA
Cai CJ ^[29]	2012	RC	6	Mean level 8.74×10 ⁶ cp/ml	NA	29.9	ETV+HBIG	41.2	reappearance of HBsAg	0/63	NA
Teperman LW ^[30]	2013	RCT	Unclear risk of bias	NA	0	NA	FTC/TDF±HBIG	18	HBV viremia	0/37	0/
Yi NJ ^[31]	2013	PC	5	NA	0	72.4	Sequential ETV following HBIG+ETV	32.6	reappearance of HBsAg	1/29	0/
Kim YK ^[32]	2013	RC	4	26.0	0.6	NA	ETV+HBIG	28	reappearance of HBsAg	5/154	0/
Perrillo R ^[33]	2013	PC	6	0	NA	36.9	ETV+HBIG	18	HBV viremia	0/61	NA
Ueda Y ^[34]	2013	RC	5	46.0	NA	53.9	ETV+HBIG	25.1	reappearance of HBsAg and/or HBV DNA	0/26	0/
Elsiesy H ^[35]	2013	RC	4	40.0	NA	NA	ETV+HBIG, TDF+HBIG	32	reappearance of HBsAg or HBV DNA	0/15	NA
Cholongitas E ^[36]	2014	PC	5	0	28.0	50.0	Sequential ETV, TDF following HBIG+ETV or HBIG+TDF	18	reappearance of HBsAg and/or HBV DNA	0/28	0/
Na GH ^[37]	2014	RC	5	74.9	NA	54.0	ETV+HBIG	49	reappearance of HBsAg	4/262	NA
Hu TH ^[38]	2014	PC	6	NA	NA	NA	ETV+HBIG	36	reappearance of HBsAg	2/145	NA
Gao Y ^[39]	2014	RC	6	69.1	NA	39.1	ETV+HBIG	57.1	reappearance of both HBsAg and HBV DNA	0/84	NA
Fernández J ^[40]	2015	PC	5	26.0	17.0	38.0	Sequential ETV, TDF following HBIG+ETV or HBIG+TDF	28	reappearance of HBsAg and/or HBV DNA	0/58	0/
Choudhary NS ^[41]	2015	PC	5	76.0	0	22.7	Sequential ETV, TDF following HBIG+ETV or HBIG+TDF	43	reappearance of HBsAg and/or HBV DNA	1/175	NA
Shen S ^[42]	2015	RC	5	34.2	NA	46.4	ETV + HBIG	45.8	reappearance of HBsAg or HBV DNA	5/491	NA
Chen G ^[43]	2015	PC	6	NA	NA	21.5	ETV+HBIG	36	reappearance of both HBsAg and HBV DNA	5/102	NA
Idilman R ^[44]	2016	PC	6	29.0	29.2	41.9	ETV+HBIG, TDF+HBIG	46	reappearance of HBsAg	1/89	NA
Togashi J ^[45]	2016	RC	4	30.0	NA	NA	ETV+HBIG	64	reappearance of HBsAg or HBV DNA	0/12	NA
Nolan A ^[46]	2016	RC	4	51.7	NA	NA	Sequential ETV, TDF following HBIG+ETV or HBIG+TDF	28	NA	0/17	0/

Fung J ^[47]	2017	PC	5	61.0	NA	36.6	ETV	59	reappearance of HBsAg or HBV DNA	14/242	9/
Gane E ^[48]	2018	RCT	Unclear risk of bias	NA	NA	NA	TDF, sequential TAF following TDF	12	HBV viremia	0/48	NA
Saab S ^[49]	2019	RC	5	37.0	NA	80.0	Sequential TAF following HBIG	57.4	reappearance of HBsAg	0/32	NA
Lee WC ^[50]	2019	RC	4	NA	NA	54.7	Sequential ETV following HBIG+ETV	42.2	reappearance of HBsAg	8/80	NA
Teegen EM ^[51]	2019	RC	5	NA	12.2	20.5	ETV+HBIG, TDF+HBIG	166.8	reappearance of HBsAg or HBV DNA	0/22	NA
Darweesh SK ^[52]	2019	RC	6	NA	NA	13.6	ETV± HBIG	72	reappearance of both HBsAg and HBV DNA	0/34	NA
Muthiah MD ^[53]	2020	RC	5	50.0	NA	62.0	ETV± HBIG, TDF±HBIG	79	HBV viremia	2/38	NA

PC: prospective cohort; RC: retrospective cohort; RCT: randomized controlled trial; HP NAs: high potent nucleot(s)ide analogues; ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; HBIG: hepatitis B immune globulin

No observational studies scored under 4 or above 6, indicating all of them having fair quality. Both RCT had unclear risk of bias because the process of random sequence generation or blinding outcome assessment was not described.

3.2 HBV recurrence rate

The overall HBV recurrence rate was 0.92% (95% CI 0.47%-1.48%, $I^2 = 44\%$) (Figure 2). HBV recurrence rate did not differ significantly between studies with and without detectable HBV DNA patients (0.87% vs 0.00%, $p = 0.25$), or studies with and without HDV superinfected patients (1.00% vs 0.63%, $p = 0.69$) (Figure S1, S2).

Subgroup analysis demonstrated the preventive effect of ETV-based, TDF-based and TAF-based therapies were comparable, and in this analysis episode of transient recurrence was counted as recurrence event ($p = 0.27$) (Figure S3). The frequency of HBV reactivation was inconsistent among patients receiving indefinite combination (0.48%, 95% CI 0.10%–1.06%), NAs plus finite course of HBIG (1.05%, 95% CI 0.00%–4.38%) and HP NAs alone (5.00%, 95% CI 2.57%-8.07%) ($p = 0.001$) (Figure 3). Further comparison suggested that the reactivation rate under indefinite combination was lower than that under HP NAs monotherapy ($p = 0.0003$) and similar to that under NAs plus finite course of HBIG ($p = 0.53$). For studies which enrolled viremia or HDV superinfected patients, HBV recurrence were comparable between indefinite and finite combination subgroups ($p = 0.65$, $p = 0.16$) (Figure S4, S5). For patients received finite combination, the risk of reinfection didn't change significantly regardless of combination period (i.e. $\leq 6m$ vs $> 6m$) ($p = 0.31$) or the administration route of HBIG (i.e. IM vs change from IV to IM) ($p = 0.26$). There was no difference between studies under finite combination and monophylaxis ($p = 0.101$).

3.3 All-cause mortality and HBV-recurrence related mortality

Patient survival was reported in 16 studies, and the pooled death rate was 7.29% (95% CI 4.42%–10.71%, $I^2 = 73\%$) (Figure S6). Based on detailed information of death from 8 studies, HBV-recurrence related death was 0.17% (95% CI 0.00%-1.51%, $I^2 = 37\%$) (Figure 4).

3.4 HCC recurrence rate

19 studies included patients with pre-transplant HCC, and 5 reported information relevant to HCC recurrence. The aggregated HCC recurrence rate was 5.34% (95% CI 0.78%–12.48%, $I^2 = 52\%$) (Figure 5).

3.5 Renal function

10 trials measured renal function, among which 3 observed significant eGFR/creatinine clearance deterioration (1 TDF based, 2 ETV based)^{30,33,47}. Another 2 studies demonstrated a trend toward improved eGFR/CKD stage under sequential TAF treatment following TDF or HBIG+NAs^{48,49}. The renal function remained at a stable level in other trials^{35,36,40,41,52}.

3.6 Sensitivity analysis

After ruling out the abstracts and studies with follow-up period less than 24 months, the aggregated HBV recurrence was 1.37% (95%CI 0.46-2.60%). A proportion of original studies defined HBV recurrence by reappearance of HBsAg, and others defined by detectable HBV DNA. We compared the HBV recurrence under abovementioned two standards (i.e. HBsAg (or HBV DNA) vs HBV DNA (and HBsAg)) and found no significant difference between them ($p=0.49$).

4. Discussion

Our meta-analysis demonstrated minimal risk of HBV reactivation under HP NAs-based regimens for LT recipients (0.92%). In subgroup analysis the risk of reactivation was similar between studies with and without HBV viremia/HDV coinfecting patients, suggesting that these elements might no longer affect the prophylaxis significantly in the era of HP NAs^{54,55}. The recurrent HCC remained an alarming signal. Its association with HBV reactivation was revealed by Idilman R, Lee WC et al who confirmed 21.4% to 100% cases of recurrence detected with concomitant HCC recurrence^{32,39,44,50}. For HP NAs, the recurrent HCC was supposed to present following challenges: HBV within tumor cells might be relatively inaccessible to drug because of the change in liver structure and blood supply. Beside the non-HCC tissues, closed circular DNA (ccc DNA) of HBV also existed in extrahepatic HCC micro-metastases and HCC cells, acting as potential reservoirs which couldn't be targeted by NAs. Furthermore, dysfunction of hepatic immune network induced by HCC might predispose to poorer response to antiviral treatment⁵⁶⁻⁵⁸. Although HCC was one of the major indications for LT, we found the HCC recurrence rate was not high (5.34%). Identifying the small population with high risk of HCC recurrence might help to further decrease HCC and HBV recurrence. All-cause mortality in our study was low, comparing previous studies which applied HBIG or LP NAs-based prophylaxis^{59,60}. Moreover, the HBV-flare related mortality was much lower than all-cause mortality. These results suggested effective antiviral prophylaxis have improved long-term clinical outcome for LT recipients notably.

In terms of the preventive strategy, whether HBIG is a necessity in the era of HP NAs remains controversial. Although HBIG has been the mainstay of prophylactic regimen, many investigators have been trying to reduce the usage of HBIG to overcome the disadvantages such as high cost and inconvenient administration. Although the preliminary research of lamivudine monoprophyllaxis demonstrated 90% of prevention by week 24⁶¹, later studies with longer follow-up resulted much lower effect (59%-80%) mainly because of drug resistance⁶²⁻⁶⁴. HP NAs (i.e. ETV, TDF, TAF) was an optimal choice for HBV prophylaxis due to superiority at efficacy and genetic barrier (65-68). Currently there were only two studies adopting HP NAs monoprophyllaxis to over 10 patients^{47,53}. These two studies both conducted long term follow-up (median follow-up period: 79m and 59m), while the HBV recurrence rate in Fung J's cohort (5.8%) was as twice as that in Muthiah MD's cohort (2.9%). One of the reasons for the disparity could be the HBV DNA level. In Fung J's trial, 26% of the patients had HBV DNA more than 4 log IU/ml at the time of transplant. And in Muthiah MD's cohort there were only 3% with more than 5 log copies/ml of HBV DNA. Subgroup analysis showed significant difference between HP NAs + HBIG and HP NAs monotherapy. These results suggested caution with HP NAs monoprophyllaxis, especially for patients with high level of HBV DNA at the time of LT. On the other hand, similar HBV reactivation was observed between lifelong dual therapy ($n=1607$) and HBIG withdrawal ($n=405$). We noticed this finding was different from that at Cholongitas E's systematic review, in which indefinite combination of HP NAs and HBIG ($n=303$), but not finite combination ($n=102$), presented superior prevention to LAM plus HBIG²². The inconsistency was reasonable considering Cholongitas E's study was publicized 7 years ago when there were fewer evidence for HP NAs-based therapies. There is no consensus at the timing to stop HBIG, and we didn't find significant difference between early and late withdrawal (i.e. $\leq 6m$ vs $>6m$). In this regard, individualized decision should be made based on kinetics of anti-HBs^{40,44,69}. We did not conduct stratification by dosage because most of the studies applied low-dose of HBIG (≤ 1000 IU) one week/month post-LT.

Renal dysfunction is a major post-transplant morbidity, which negatively impacts the graft and patient survival⁷⁰. The prevalence of renal failure in LT recipients was the second highest among non-renal solid organ transplant patients, the 5-year cumulative incidence was 18-22%^{70,71}. Among the trials included in our analysis, there were 3 TDF/ETV-based studies reported deterioration in eGFR or creatinine clearance. It was difficult to conclude the impact of HP NAs on renal function in this meta-analysis since we could not rule out other important factors such as calcineurin inhibitors and surgery operation. While HP NAs with good renal safety profile are preferred since most of the patients require lifelong treatment. Minimal rates of renal function decline had been reported during long-term therapy with ETV and TDF in patients with CHB, while the nephrotoxic potential was higher for TDF^{20,72-74}. There had been several cases about TDF-associated Fanconi syndrome, including one LT recipient⁷⁵⁻⁷⁷. This issue might be mitigated by TAF, which has demonstrated a trend of improved renal function in CHB patients who were previously exposed to TDF^{78,79}. In Gane E and Sabb S' studies, we saw the same trend of TAF in LT recipients^{48,49}.

Our study has several strengths. To our knowledge this is the first meta-analysis for HP NAs-based prophylaxis in post-LT recipients. Comprehensive subgroup analysis was applied to examine different treatment strategies. However, the strengths of this meta-analysis should be weighed against some limitations. First, there were limited evidence of certain regimens (e.g. TAF-based regimen, HP NAs monoprophyllaxis). Second, there were only two RCT included in our analysis, and most of the original studies were observational with medium quality. Third, heterogeneity was moderate across studies which might attribute to varied sample size and preventive therapeutics. All of these issues may affect the robustness of the data and limit interpretation of the results.

5. Conclusions

Our systematic and meta-analysis suggested HP NAs-based regimens are highly effective at preventing HBV recurrence, and beneficial to long-term outcome for LT recipients. HBV recurrence prophylaxis was not affected by viremia or HDV coinfection. In terms of HP NAs options, ETV-based, TAF-based and TDF-based therapies demonstrated equivalent efficacy. HP NAS plus short-term HBIG serves an alternative to indefinite combination, and monotherapy of HP NAs might be appropriate for patients with low HBV DNA level before LT. To reduce risk of renal impairment, HP NAs with an optimized renal safety profile is preferred.

List Of Abbreviations

HBV, hepatitis B virus; LT, liver transplantation; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBeAg hepatitis B e-antigen; HBIG, hepatitis B immunoglobulin; HP NAs, high potent nucleos(t)ide analogues; ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; LP NAs, low potent nucleos(t)ide analogues; LAM: lamivudine; LdT: telbivudine; ADV: adefovir; PC: prospective cohort; RC: retrospective cohort; RCT: randomized controlled trial; OR, odds ratio; CI, confidence interval; IM, intramuscular; IV, intravenous.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and material

The datasets supporting the conclusions of this article is included within the article and its additional files.

Competing interests

MSL works for Gilead while concurrently enrolled in Ph.D.

Funding

This study was not supported by any commercial company or grants.

Authors' contributions

Deming Tan and Qian Lin designed the study and take responsibility for the entire process; Mingshu Li and Zhouhua Hou conducted literature search, data extraction and quality assessment; Guozhu Yao analyzed the data; Mingshu Li drafted the manuscript; All authors have read and approved the final paper.

Acknowledgements

The authors thank Ros Jia for providing statistical consult for this manuscript.

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Figures

Figure 1

Flowchart of literature search and screen

Figure 2

Forest plots showing the results of pooled HBV recurrence rate in LT recipients treated by HP NAs-based prophylaxis

Figure 3

Forest plots showing the results of meta-analysis comparing HBV recurrence rate in studies under indefinite combination of HP NAs +HBIG, finite combination of HP NAs +HBIG and HP NAs monotherapy

Figure 4

Forest plots showing the results of pooled HBV-recurrence related mortality in LT recipients treated by HP NAs-based prophylaxis

Figure 5

Forest plots showing the results of pooled HCC recurrence rate in LT recipients treated by HP NAs-based regimens

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