First, the aim of our study, as is stated in the introduction, was to assess the cost-effectiveness of various antiviral drugs [1]. The "no therapy" strategy was included because a considerable number of patients with chronic hepatitis B have their treatment deferred for different reasons. Secondly, as direct comparisons between antiviral treatments are not available then indirect comparison remains the only approach to evaluate cost-effectiveness of any anti-HBV therapy. The limitations of indirect treatment comparisons in cost assessment are well recognized. For this reason, modeling techniques are especially appropriate and indicated to compare the data from different sources [2]. Indeed, modeling techniques allow extrapolation of short/medium-term results from clinical trials to long-term effectiveness outcomes, which is what we did in our model, in line with previous studies [3,4]. In addition, the probabilistic sensitivity analysis helps the reader to better understand eventual differences between the compared options even if the primary data, virological response rates, do not derive from head-to-head studies comparing different antiviral options, as occurs in chronic hepatitis B treatment. The robustness of our model was exhaustively tested in the probabilistic analysis, and the expected variability was analysed within the Monte Carlo simulation. Finally, the basic cost-effectiveness results depicted in Figures 1 and 2 of the manuscript [1] clearly show that a number of treatment options are dominated by others (in some cases by more than one option) [1]. Thus, the only incremental cost-effectiveness ratios (ICERs) to be calculated are those of the more effective options relative to immediately less effective options, performing a standard incremental cost-effectiveness analysis. In our study, ICERs are shown for tenofovir *vs.* lamivudine and no treatment (Table 5 of the manuscript [1]), and the only ICERs omitted are those of lamivudine *vs.* no treatment in both HBeAg-positive and HBeAg-negative patients.

In our opinion, the only real contribution of the letter by Mantovani and de Portu is when they point out that lamivudine is a cost-effective option in relation to "no treatment". This is a well-known fact that has little current relevance, since lamivudine is not a recommended first-line option in the treatment of chronic hepatitis B infection.

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Antiviral therapy for chronic hepatitis B: Challenges in Hong Kong ☆

To the Editor:

I read with great interest the review article by Prof. Liaw published in a recent issue of this journal [1]. The article highlighted the reality and difficulties many patients and clinicians in Asian countries are now facing in the treatment of chronic hepatitis B. Although the more recent antiviral agents (entecavir and tenofovir) have strong antiviral potency and very low risk of drug resistance, these drugs may not be available to all patients in need. This is due to the restricted reimbursement criteria in place in different countries as well as the low income of the population in some areas.

In 2008, the gross national income per capita in Hong Kong was approximately USD 30,380, which was comparable to that of Singapore, Japan, Australia and Europe [1]. Instead of full reimbursement for antiviral drugs, Hong Kong has very restricted criteria of reimbursement. Before July 2008, lamivudine was the only drug reimbursable to patients with significant disease activity while adefovir could only be reimbursed for patients with lamivudine resistance and significant disease activity. After July 2008, lamivudine was not reimbursable to treat new patients. Instead, entecavir could be

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reimbursed for patients with alanine aminotransferase (ALT) higher than 5 times the upper limit of normal (ULN) and patients with decompensated liver cirrhosis. Use of these antiviral drugs outside the listed indications as well as other antiviral agents (peginterferon, telbivudine, tenofovir) was at the patients' own expense.

We performed a drug expenditure audit over 4 weeks between November and December 2008. Four hundred and forty-four chronic hepatitis B patients attended the outpatient clinic during the audit period. One hundred and sixty-three (37%) patients had received antiviral therapy, 121 (27%) were indicated for antiviral treatment but not treated while the remaining 160 (36%) were not indicated for treatment. As hepatitis B virus (HBV) DNA and liver biopsy were not routine tests, we arbitrarily defined patients who had evidence of liver cirrhosis and those who had elevated ALT were indicated for antiviral treatment. This would be an underestimate as a significant proportion of patients who had high normal ALT might already have advanced liver fibrosis, particularly the older patients with elevated HBV DNA [2,3]. The exact reasons why some patients did not receive antiviral treatment were not explored in this audit. One obvious reason was that a significant proportion of untreated patients did not meet the criteria for reimbursement and could not afford the high cost of the antiviral medications.

Overall, only 27 of 444 (6.1%) patients in our clinic were treated under the hospital reimbursement scheme. One hundred and thirty-six (83%) of the 163 treated patients were purchasing their antiviral medications without reimbursement. These numbers again reflect the inadequacy of the highly restricted reimbursement policy in force in Hong Kong. In our previously conducted cross-sectional studies including over 1500 chronic hepatitis B patients, approximately 3.5% of hepatitis B e antigen (HBeAg)-positive patients and 2% of HBeAg-negative patients had ALT levels higher than 5 times ULN [2,3]. The prevalence of clinical liver cirrhosis was approximately 16% among HBeAg-negative patients in our clinic, and the prevalence of decompensated cirrhosis was expected to be lower [4]. In other words, the number of patients eligible for reimbursement under the current policy would only be a minority of all those who should be indicated for antiviral treatment according to the Asian-Pacific recommendations [5].

The most commonly used antiviral medication was entecavir (Fig. 1). Seventy-two (44% of the treated) patients were on entecavir but only one of them was reimbursed. This was partly related to a very recent change in reimbursement policy and the restricted criteria for reimbursement. Adefovir was used in 32 (20% of the treated) patients and 7 of them were reimbursed. Thirteen of the 32 patients on adefovir were using combination treatment with lamivudine or entecavir for lamivudine resistance. Although adefovir was used primarily as a salvage therapy for lamivudine resistance, patients who had adefovir started on virological breakthrough with normal ALT did not meet the criteria for reimbursement due to the lack of disease activity. The financial restrictions inevitably delayed the commencement of adefovir for the best treatment outcome [6]. In a recent report, 14 of the 26 patients with lamivudine resistance had ALT higher than 2 times ULN when adefovir was started in our clinic, and this was translated to a suboptimal viral suppression in the long term [7].

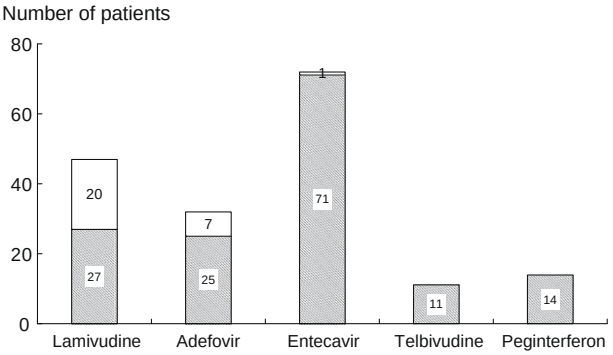

Fig. 1. Number of patients on different antiviral treatments during the audit period. Thirteen patients on adefovir were also on lamivudine or entecavir as combination therapy. The shaded area indicated patients who were on self-paid treatment and the clear area indicated patients on reimbursed treatment from the hospital.

I agree with Prof. Liaw that application of the roadmap approach by starting with a cheaper antiviral agent and switching to other agent(s) if HBV DNA is still detectable at 24 weeks of treatment should be explored [1]. In a recent cost-effectiveness analysis in Hong Kong, the roadmap approach starting with telbivudine or lamivudine and switching to entecavir if HBV DNA suppression is detectable at week 24 may be a cost-effective alternative to monotherapy with entecavir to all patients [8]. At present, tenofovir is not registered for the indication of chronic hepatitis B in Hong Kong and can only be prescribed after application for off-label use. The cost of tenofovir is currently higher than that of entecavir, but it will be an attractive alternative if its cost can be lowered as in the case of Europe. To facilitate the use of the limited resources to treat the large number of chronic hepatitis B patients in Asia, proper local cost-effective analysis should be performed before a reimbursement policy is reinforced.

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