of fibrosis). Interestingly, in this carefully followed Spanish cohort, histological progression was clearly halted by UDCA treatment in comparison to placebo [6].

In contrast to this high-quality randomized, placebo-controlled trial, meta-analyses which include trials with a duration of up to two years for a disease with an estimated duration of up to two decades may be suited to analyze short-term biochemical effects of medical treatment, but certainly carry the risk of diluting the information needed for a well-based long-term survival analysis. The attempts of others [7,8] to provide meta-analyses which included long-term randomized, *placebo*-controlled trials for survival analysis only to avoid this dilutive effect may deserve mentioning here; these authors [7] concluded that long-term treatment with mid-dose UDCA can improve liver biochemistry, delay histological progression in early-stage disease and improve survival-free of liver transplantation. We have to keep in mind that meta-analyses are only as good as the trials they include and have to be judged with some caution [9].

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Oral antiviral therapies are cost-effective *vs.* no treatment but indirect comparisons should be avoided

To the Editor:

In their recent paper Buti and colleagues [1] claim to have performed a "cost-effectiveness analysis of different oral antiviral therapies in patients with chronic hepatitis B", but they did so presenting credible results in an inappropriate and potentially misleading manner.

By definition *incremental* cost-effectiveness ratio relates to *incremental* effectiveness put in relation to *incremental* cost. Therefore, the natural referent alternative for "oral antiviral therapies" is a therapy in which no antiviral therapy is used, what Buti and colleagues refer to as "no treatment". Indeed Buti and colleagues [1] conceptually appraised *decremental*, rather than *incremental*, cost-effectiveness ratio, by unconventionally taking as a reference the point estimate "most efficacious treatment". This is not a standard procedure in cost-effectiveness analyses. Consequently, the study would be much more informative presenting the incremental cost of (each) antiviral therapy compared to "no treatment" in relation to its incremental effectiveness. This is the standard approach widely adopted by public health technology assessment agencies. This approach has several advantages: (1) it informs decision makers on ICER (Incremental Cost-Effectiveness Ratio) of the various technologies, individually, that can be used compared to no treatment; (2) it does not require the use of a sophisticated model that would be needed to detect a meaningful and significant difference between active treatments; (3) it does not require problematic and sophisticated adjustments for differential characteristics of patients included in RCT's (Randomized Clinical Trial) of different active treatments (e.g. different baseline viral load, differences in tolerability profile), which are required when (indirect) comparisons between active treatments are made. A careful reading of the paper by Buti and colleagues [1] confirms that the model seems to make accurate and discriminating predictions of costs and outcomes when "no treatment" on one side and

Table 1
ICER of each active treatment *vs.* no treatment.

	Cost	QALY	Incremental cost	Incremental QALY	ICER[a]
HBeAg positive pts					
No treatment	83,406	13.69	Reference	Reference	
Telbivudine	90,721	14.96	7315	1.27	5760
Entecavir	90,273	15.21	6867	1.52	4518
Adefovir	91,199	14.68	7793	0.99	**7872**
Lamivudine	87,134	14.67	3728	0.98	3804
Tenofovir	87,615	15.43	4209	1.74	**2419**
HBeAg negative pts					
No treatment	90,866	12.48	Reference	Reference	
Telbivudine	111,097	15.47	20,231	2.99	6766
Entecavir	114,968	16.11	24,102	3.63	6640
Adefovir	103,916	14.21	13,050	1.73	**7543**
Lamivudine	95,547	14.30	4681	1.82	**2572**
Tenofovir	105,889	16.28	15,023	3.8	3953

Bold value represents the higher and lowest value in the group.
Abbreviations: RCT, Randomized Clinical Trial; QALY, Quality Adjusted Life Year; ICER, Incremental Cost-Effectiveness Ratio.
 [a] Incremental cost per incremental QALY. All costs are in Euro.

"oral antiviral treatment" on the other side are considered. Ultimately the authors evaluated the efficacy of tenofovir *vs.* all other drugs as the differences between response rates obtained from different trials. However when different treatments are studied in separate trials actual differences between response rates associated with the treatments (treatment effect) are confounded by the differences between the trials (trial effect), thus it is impossible to estimate the effects separately. Typically, trial effects are due to different patients characteristics (e.g. baseline, viral load). With regard to the cost of therapy used in the model it seems that only the cost of drugs was considered without considering the additional cost due to the administration cost, toxicity (e.g. monitoring of renal function for tenofovir) management of side-effects etc. Consequently, the model does not seem sensitive and precise enough for the purpose of comparing active treatments one against the other (see Table 1).

True and appropriate incremental cost per QALY (Quality Adjusted Life Year) gained of each individual oral antiviral therapy compared to "no treatment" can be computed, which are based on the very data of Buti and colleagues [1].

Once this standard approach for computing ICER is used, one can observe that all oral antiviral therapies are cost-effective compared to "no treatment", far below the commonly agreed threshold of 50.000 Euro per QALY. This is reassuring for the decision makers that oral antiviral therapies are value for money, so that the decision on appropriate therapy for the next patient can safely return in the sphere of clinical judgment and physician–patient interaction.

Reference

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Some oral antivirals are more cost-effective than others for the treatment of chronic hepatitis B

To the Editor:
In their letter referring to our study "Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B", Mantovani and de Portu claim that the presentation of our results is inappropriate. We beg to disagree.