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Incorporated antivirals for chronic hepatitis B in Brazil: a cost-effectiveness analysis

ABSTRACT

OBJECTIVE: To evaluate the cost-effectiveness of different drug therapies for chronic hepatitis B in adult patients.

METHODS: Using a Markov model, a hypothetical cohort of 40 years for HBeAg-positive or HBeAg-negative patients was constructed. Adefovir, entecavir, tenofovir and lamivudine (with rescue therapy in cases of viral resistance) were compared for treating adult patients with chronic hepatitis B undergoing treatment for the first time, with high levels of alanine aminotransferase, no evidence of cirrhosis and without HIV co-infection. Values for cost and effect were obtained from the literature, and expressed in effect on life years (LY). A discount rate of 5% was applied. Univariate sensitivity analysis was conducted to assess model uncertainties.

RESULTS: Initial treatment with entecavir or tenofovir showed better clinical outcomes. The lowest cost-effectiveness ratio was for entecavir in HBeAg-positive patients (R$ 4,010.84/LY) and lamivudine for HBeAg-negative patients (R$ 6,205.08/LY). For HBeAg-negative patients, the incremental cost-effectiveness ratio of entecavir (R$ 14,101.05/LY) is below the threshold recommended by the World Health Organization. Sensitivity analysis showed that variation in the cost of drugs may make tenofovir a cost-effective alternative for both HBeAg-positive and HBeAg-negative patients.

CONCLUSIONS: Entecavir is the recommended alternative to start treating patients with chronic hepatitis B in Brazil. However, if there is a reduction in the cost of tenofovir, it can become a cost-effective alternative.

DESCRIPTORS: Hepatitis B, Chronic, drug therapy. Antiviral Agents, supply & distribution. Cost-Effectiveness Evaluation. Unified Health System, economics.

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INTRODUCTION

Chronic hepatitis B (CHB) is a highly prevalent disease, with an estimated 350 million cases worldwide.[13] According to the Information System for Notifiable Diseases (SINAN), between 1999 and 2010 there were 104,454 confirmed cases in Brazil. In 2009 alone there were 14,468 confirmed cases, giving a detection rate of 7.6 per 100,000 inhabitants.[a] Patients with CHB may develop progressive liver disease, which can result in cirrhosis and hepatocellular carcinoma. These stages of the disease are linked to an increased risk of morbidity and mortality, as well as involving considerable health care costs.[21]

CHB is caused by the hepatitis B virus (HBV) and diagnosis is confirmed if the patient has HBV surface antigens (HBsAg) for at least six months, as well as increased liver enzymes and histological findings. These patients can then be further subdivided, based on the presence of the "e" hepatitis B antigen (HBeAg) in the serum, either HBeAg-positive or HBeAg-negative. These groups differ in their natural history and response to antiviral treatment, with HBeAg-negative often associated with worse prognoses and response to treatment.[25] CHB treatment aims for the sustained repression of HBV replication, remission from liver disease and preventing cirrhosis, liver failure and hepatocellular carcinoma. In HBeAg-positive patients, durable HBeAg seroconversion to anti-HBe is a significant marker, associated with better prognostics.[11]

Before 2009, in Brazil, interferon and lamivudine were the only CHB treatments covered by the Brazilian Unified Health System (SUS). Adefovir dipivoxil, entecavir, pegylated interferon and tenofovir were then included in the treatment guidelines for this disease. Interferon was established as the first choice for treating HBeAg-positive patients and tenofovir for those who were HBeAg-negative.[b] These six drugs were part of the Specialized Component of Pharmaceutical Care (SCPC) and were made available through the Ministério da Saúde National Policy for Pharmaceutical Care.[c]

SUS spending on SCPC medications has shown an uninterrupted tendency to increase, going from R$ 685 million in 2000 (R$ 4.01 *per capita*) to 1.41 billion in 2007 (R$ 7.40 *per capita*).[2,d] This situation means that financial resources aimed at health care need to be optimized.

There is little evidence focusing on the use of tenofovir in Brazil. To renew or reject the option set in the treatment guidelines, it is important to carry out studies to better understand the economic impact and the public health results.

This study aims to assess the cost-effectiveness of different drug therapies for adults with chronic hepatitis B.

METHODS

Using the Markov model,[29] and the TreeAge Pro Suite 2009 program (TreeAge Software, Inc), a hypothetical cohort of HBeAg positive and another of HBeAg negative patients were created. Both contained four groups using adefovir dipivoxil (ADV), entecavir (ETV), lamivudina (LAM) or tenofovir (TDF). The treatments considered were those appropriate for adults with chronic hepatitis B, treatment-naïve, had high alanine aminotransferase levels, no evidence of cirrhosis and no HIV co-infection. The model had a time horizon of 40 years. Life years (LY) per patient treated were used as a measure of effectiveness. Only direct costs were considered, and these were shown in Brazilian currency (R$). The analysis was from the SUS perspective, in other words, the results of the cost-effectiveness of the treatment were analyzed considering the direct costs of treatment.

The model was made up of seven mutually exclusive transition states, corresponding to the six possible stages of the disease (CHB without complications, efficacy of treatment, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and death) and HBV resistance to the respective drug. For HBeAg positive patients, seroconversion HBeAg/Anti-HBe was considered to be the outcome of efficacy. For HBeAg negative patients, the outcome analyzed was undetectable serum HBV DNA (< 400 copies/mL).

Each cycle of the model corresponded to one year of treatment. In the first cycle, the population was composed of individuals with CHB, with no complications or drug resistance. Transition from the first to the second cycle, and so on, occurred according to the probabilities of transition from stage to stage. For those patients who showed viral resistance to the initial treatment, rescue therapy was modelled, representing the insertion of another nucleos(t)ide analogue to the treatment. The probabilities of transition were composed of data on progression of the disease (Table 1) and the efficacy of the drugs (Table 2) obtained, respectively, from randomized clinical studies and studies on the natural history of CHB.

[a] Ministério da Saúde. Bol Epidemiol Hepatites Virais. 2011;2(1):5-76. [cited 2011 Sept]. Available from: http://www.aids.gov.br/publicacao/2011/boletim_epidemiologico_hepatites_virais_2011

[b] Ministério da Saúde. Portaria nº 2.561, de 28 de outubro de 2009. Aprova Protocolo Clínico e Diretrizes Terapêuticas - Hepatite Viral Crônica B e Coinfecções. *Diario Oficial da Uniao*, Brasília, DF, 3 nov. 2009. Seção 1, p.59-71.

[c] Ministério da Saúde. Portaria nº 2.981, de 26 de novembro de 2009. Aprova o Componente Especializado da Assistência Farmacêutica. *Diario Oficial da Uniao*, Brasília, DF, 30 nov. 2009. Seção 1, p.725-771

[d] The exchange rate as of 29/12/2011 (US$ 1.00 = R$ 1.87) was used for the monetary values in this study.

Table 1. Annual rates of progression of the disease.

Annual rate of progression	Anual rate (%)	Reference No.
CHB to CC (HBeAg-positive)	6.00	12, 19, 20
CHB to CC (HBeAg-negative)	9.00	11
Seroconversion HBeAg to CC	1.00	9
Combined response to CC	1.30	19
CC to DC	5.00	9
CHB to HCC	0.50	10, 31
CC to HCC	2.50	8, 9, 10, 31
DC to CHC	2.50	9
CHB to death	0.35	30
CC to death	5.00	17, 28
DC to death	39.00	9, 31
HCC to death (HBeAg-positive)	56.00	31
HCC to death (HBeAg-negative)	37.20	27

CC: compensated cirrhosis; DC: decompensated cirrhosis. HCC: hepatocellular carcinoma. CHB: chronic hepatitis B

Literature on the natural history of the disease and the efficacy and effectiveness of treatment is scarce. The drugs examined in this economic assessment were recently approved by the regulatory body. Thus, studies were selected arbitrarily, based on economic assessments, clinical protocols (such as EASL and AASLD) and published clinical trials.

The modeling was carried out based on the following assumptions: patients who did not respond to treatment continued to receive the drug for the entire period of the cohort if no resistance developed; rescue therapy was given to patients who developed resistance to the initial treatments; resistance to rescue therapy was not included; patients at different stages of the disease followed the natural history of Chronic hepatitis B.

The monetary values of the drug treatments in the study were determined by the Drug Market Regulation Chamber – CMED for 2011, considering factory prices without tax, with the coefficient of price adjustment of 24.38% already discounted.[e]

Annual spending per patient, according to the stages of the disease, were obtained from a 2005 study evaluating the direct costs of CHB in Brazil.[3] The values were corrected sing the National Consumer Price Index (IPCA) for 2011. The costs included medical fees, laboratory tests, diagnostic and therapeutic procedures, hospitalizations and spending on non-anti-viral medicines. The estimates values were taken primarily from SUS payment tables.

When conducting economic assessments of health care technology, it is recommended to use a discount rate on the cost and the effectiveness. Bearing in mind that there is often a time lag between investment in health care service resources and the associated health care benefit, an arbitrary rate of 5%, recommended by the Ministry of Health when the time period under analysis lasts for more than a year, was used for costs and effectiveness.[f] Analyses were also carried out using discount rates of 0% and 10% in order to assess to what extent the arbitrary selection of a discount rate affected the study's conclusions.[g]

At the end of the hypothetical cohort, data on the patients' mean life expectancy and the proportion of patients at each stage of the disease was obtained for each group. Means for cost and effectiveness were calculated according to the intervention. For each intervention, the cost-effectiveness ratio (CER) which determined the mean spending for each LY was calculated. To compare between the alternatives, the incremental cost-effectiveness ratio (ICER) was calculated, which is the difference between the mean cost of two alternative treatments and the respective LY differences. The ICER represents the increment in financial resources necessary to obtain an addition LY in relation to a lower CER alternative. An intervention was deemed to be cost-effective if the value of the ICER was below R$ 57,048.00,[d] equivalent to triple the *per capita* Gross Domestic Product (GDP) in Brazil in 2011, adapted according to World Health Organization (WHO) guidelines.[h]

[e] Câmara de Regulação do Mercado de Medicamentos. Resolução nº 3, de 2 de março de 2011. *Diario Oficial da Uniao*, Brasília, DF, 9 mar. 2011. Seção 1, p.3

[f] Abbot T. Custo em saúde, qualidade e desfechos. São Paulo: ISPOR Brasil; 2009.

[g] Ministério da Saúde, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia. Diretrizes metodológicas: estudos de avaliação econômica de tecnologias em saúde. Brasília (DF); 2009. (Série A. Normas e Manuais Técnicos)

[h] World Health Organization. Cost-effectiveness thresholds. Geneva; 2005 [cited 2011 Nov 3]. Available from: http://www.who.int/choice/costs/CER_thresholds/en/index.htmlcosts/CER_thresholds/en/index.html.

Table 2. Annual probabilities associated with the treatments used in the model.

Treatment	HBeAg-positive		HBeAg-negative	
	Probability (%)	Reference No.	Probability (%)	Reference No.
Adefovir				
Response, year 1	12	22	51	14
Response, year 2-4	13	Assumed to be equal for all	15	14
Resistance, year 1	0	11	0	11
Resistance, year 2	3	11	3	11
Resistance, year 3	11	11	11	11
Resistance, year 4	18	11	18	11
Resistance, year 5	29	11	29	11
Entecavir				
Response, year 1	21	4	90	16
Response, year 2-4	13	Assumed to be equal for all	42	16
Resistance, year 1	0.2	11	0.2	11
Resistance, year 2	0.5	11	0.5	11
Resistance, year 3	1.2	11	1.2	11
Resistance, year 4	1.2	11	1.2	11
Resistance, year 5	1.2	11	1.2	11
Lamivudine				
Response, year 1	19	18	73	16
Response, year 2-4	13	Assumed to be equal for all	29	16
Resistance, year 1	24	11	24	11
Resistance, year 2	38	11	38	11
Resistance, year 3	49	11	49	11
Resistance, year 4	67	11	67	11
Resistance, year 5	70	11	70	11
Tenofovir				
Response, year 1	21	24	93	24
Response, year 2-4	13	Assumed to be equal for all	42	Assumed to be equal to entecavir
Resistance, year 1	0	11	0	11
Resistance, year 2	0	Assumed to be equal for all	0	Assumed to be equal to year 1
Resistance, year 3	0	Assumed to be equal for all	0	Assumed to be equal to year 1
Resistance, year 4	0	Assumed to be equal for all	0	Assumed to be equal to year 1
Resistance, year 5	0	Assumed to be equal for all	0	Assumed to be equal to year 1
Response durability				
Inicial treatment	80	Assumed to be equal for all	10	15, 16, 23
Rescue therapy				
Response, year 2	8	26	52	5

Univariate sensitivity analysis was carried out to assess the uncertainties of the model and assumed values due to the scarcity of data in the literature. To this end, the probabilities of transition and the costs varied between 10% less and 10% more.

RESULTS

At the end of the cohort, treatments which began with ETV and TDF had higher proportions of patients with the efficacy outcome. Respectively, 44.0% and 44.3% of the HBeAg-positive patients attained HBeAg seroconversion. For the HBeAg-negative patients, 17.7% of patients who started treatment with ETV and 18.3% of those who were initially treated with TDF had undetectable levels of HBV DNA (Table 3).

These treatments also offered more protection in terms of complications of the disease. For the group who started treatment with ETV, 44.1% of HBeAg-positive

and 18.2% of HBeAg-negative patients did not develop CC, DC or HC, die or develop viral resistance to treatment. In the group initially treated with TDF, 44.4% of HBeAg-positive and 19.0% of HBeAg-negative patients did not develop these complications.

Treatment with ADV resulted in higher costs and worse results. This alternative was, therefore, dominated by the other strategies. When a 5% discount rate for the costs and effects is considered, treatment with LAM was also dominated by ETV and TDF for HBeAg-positive patients. In these patients, a lower CER was observed for ETV (R$ 4,010.84/LY). The ICER for TDF, compared with ETV (R$ 162,735.04/LY) was more than treble *per capita* GDP in Brazil. For HBeAg-negative patients, treatment with LAM gave the lowest CER (R$ 6,205.08/LY), followed by ETV (R$ 6,532.04/LY) and TDF (R$ 6,651.64/LY). The ICER for ETV compared to that of LAM (R$ 18,065.14/LY) was lower than *per capita* GDP in Brazil. Compared with ETV, TDF had a CER of R$ 71,956.13 per LY, which is higher than the limit suggested by the WHO (Table 4).

When the situation is analyzed without applying discount rates, the CER of ETV (R$ 3,141.17/LY) for HBeAg-positive patients was lower than that of TDF (R$ 3,219.87/LY). The ICER for TDF in relation to ETV was R$ 52,966.58 per LY. For HBeAg-negative patients, treatment with LAM was dominated by ETV and TDF. The CER for ETV (R$ 5,894.36/LY) was lower than that of TDF (R$ 6,079.00/LY). The ICER for TDF compared to ETV was R$ 81,081.06 per LY.

When a discount rate of 10% was applied to costs and effects, the CER for ETV and TDF was R$ 4,665.08/LY and R$ 4,838.21/LY respectively for HBeAg-positive patients. The ICER for TDF compared to ETV was R$ 433,119.83 per LY. For HBeAg-negative patients, the lowest CER was for LAM (R$ 5,999.10/LY), followed by ETV (R$ 6,701.40/LY) and TDF (R$ 6,953.76/LY). The ICER for ETV compared to LAM was R$ 55,668.84 per LY. Considering TDF compared to ETV, the ICER was R$ 354,997.16 per LY.

According to sensitivity analysis, for HBeAg-positive patients, the variation of antiviral costs over the period of the cohort may make ICER lower than the threshold suggested by the WHO. For HBeAg-negative patients, the variation in the cost of antivirals, in the first year and in subsequent years, the ICER for TDF compared to ETV may also be less than triple Brazilian *per capita* GDP. Alteration in the variables considered in the model for HBeAg-negative patients did not make the ICER for ETV, compared to LAM, higher than three times Brazilian *per capita* GDP (Figure).

DISCUSSION

Considering the clinical evidence used and the cost defined by the CMED for nucleos(t)ide analogues, the most cost-effective alternative for HBeAg-positive patients was starting treatment with ETV and it is cost-effective, compared to LAM, for HBeAg-negative patients.

In HBeAg-positive patients, starting treatment with LAM produced higher costs and lower values for LY compared to ETV and TDF, characterizing it as a dominated alternative. For both subtypes of the disease, starting treatment with ADV was also dominated by ETV and TDF. These dominated options are not recommended for starting treatment.

The CER for ETV was lower compared to the other treatments for HBeAg-positive patients, with a cost of R$ 4,010.84 each LY. Treatment with TDF would

Table 3. Proportions of patients at each stage of the disease at the end of the cohort, by treatment.

Treatment	Proportion						
	Response[a]	No change	Resistence	CC	DC	HCC	Death
HBeAg-positive							
ADV	0.314	< 0.000	0.023	0.050	0.007	0.003	0.604
ETV	0.440	< 0.000	0.001	0.043	0.005	0.002	0.508
LAM	0.240	< 0.000	0.034	0.052	0.007	0.003	0.663
TDF	0.443	< 0.000	0.000	0.043	0.005	0.002	0.506
HBeAg-negative							
ADV	0.094	< 0.000	0.012	0.037	0.005	0.004	0.847
ETV	0.180	0.006	< 0.000	0.036	0.005	0.004	0.768
LAM	0.110	< 0.000	0.013	0.037	0.005	0.004	0.831
TDF	0.183	0.007	0.000	0.036	0.005	0.003	0.766

ADV: adefovir; CC: compensated cirrhosis; CD: decompensated cirrhosis, HCC: hepatocellular carcinoma; ETV: entecavir; LAM: lamivudine; TDF: tenofovir

[a] In HBeAg-positiv patients, response was defined as seroconversion HBeAg. In HBeAg-negative patients, response was defined as undetectable levels of hepatitis B virus DNA.

Table 4. Results for cost-effectiveness with a discount rate of 5% on the costs and effects.

Treatment[a]	Cost (R$)[b]	Incremental cost (R$)[c]	Effectiveness (LY)	Incremental effectiveness (LY)[c]	CER (R$/LY)	ICER (R$/LY)[c]
HBeAg-positive						
ETV	57,401.84		14.31		4,010.84	
TDF	59,307.01	1,905.17	14.32	0.01	4,140.57	162,735.04
LAM	66,937.69	7,630.69	13.59	-0.74	4,927.27	(Dominated)
ADV	80,484.43	21,177.42	13.85	-0.47	5,811.16	(Dominated)
HBeAg-negative						
LAM	74,900.36		12.07		6,205.08	
ETV	81,082.47	4,915.76	12.42	0.35	6,426.71	14,101.05
TDF	82,718.16	2,902.05	12.44	0.02	6,651.64	177,658.84
ADV	103,608.92	20,890.76	11.92	-0.52	8,693.69	(Dominated)

ADV: adefovir; LY: Life years gained; ETV: entecavir; LAM: lamivudine; CER: cost-effectiveness ratio; ICER: incremental cost-effectiveness ratio

[a] Treatments listed in order of increasing cost, according to the disease subtype.

[b] Exchange rate as of 29/12/2011: US$ 1.00 = R$ 1.87.

[c] Values regarding the non-dominated drug with the closest cost.

necessitate an incremental investment of R$ 162,735.04 per additional LY. Although this value is above the threshold set by the WHO, sensitivity analysis indicates that this situation may be reversed if the cost of the drug decreases, or if the cost of ETV increases. If these variations in cost are taken into account, starting treatment with TDF may also be considered the most cost-effective alternative.

In HBeAg-negative patients, the lowest CER was for treatment started with LAM. In order to reach one more LY with ETV compared to LAM, an incremental investment of R$ 18,065.14 is necessary. This value is lower than the threshold suggested by the WHO of three times national *per capita* GDP, which means ETV can be characterized as a cost-effective alternative. With regards treatment started with TDF, incremental investments of R$ 21,421.93 and R$ 71,956.13 for each LY would be necessary for treatment with LAM or ETV, respectively. Sensitivity analysis shows that, if variations in the costs of ETV and TDF are taken into account, this may also be a cost-effective alternative.

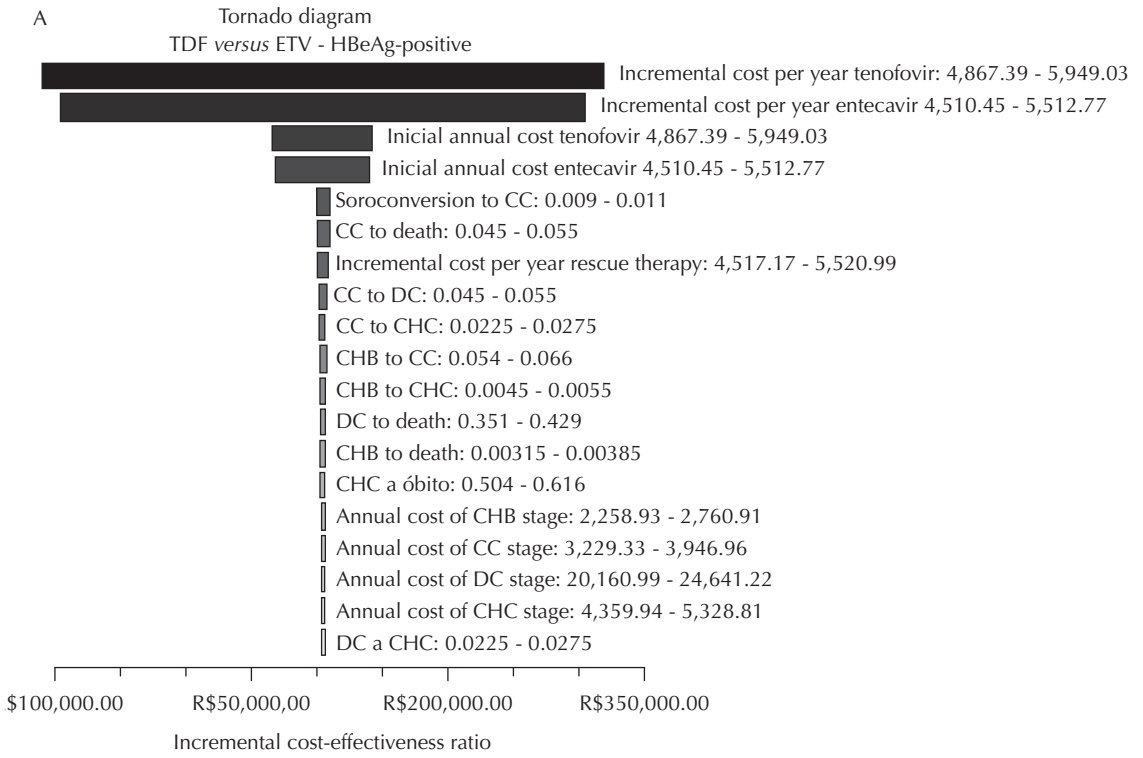
As it has a slight advantage over ETV, the model indicates that starting treatment with TDF gives better clinical results compared with the other treatments. With this treatment, there is a greater probability of obtaining efficacy as the outcome and a lower chance of progression to HBC complications.

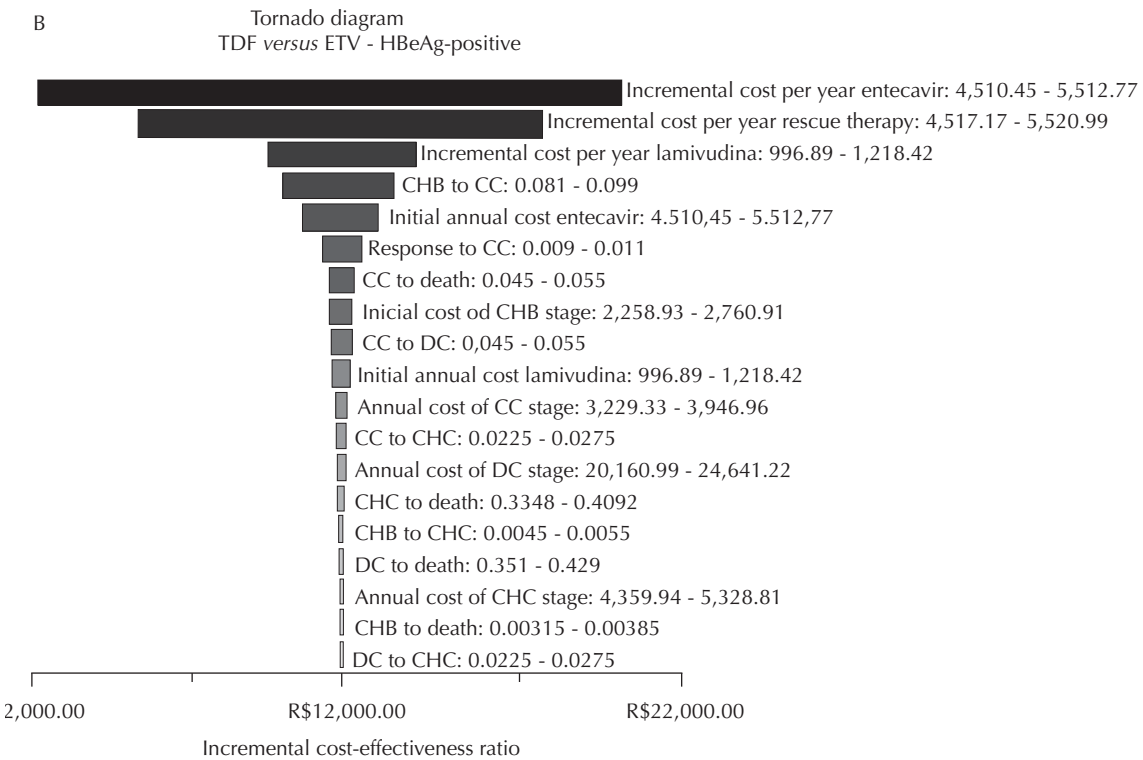
Economic models are simplifications of reality. The multifaceted complexity of treating a disease cannot be completely covered using this approach. Economic analyses support the decisions of those responsible for coordinating health care programs and services. These decisions should take into account factors and premises considered in the model, as well as others which are not modelled. Thus, some limitations to this study can be identified, such as obtaining costs from secondary sources, using data for efficacy and effectiveness obtained from studies of international populations, the arbitrary selection of studies to create the model and the extrapolation of clinical data, resistance rates and rescue therapy.

The perspective used for the cost-effectiveness analysis was that of the Brazilian Unified Health System. However, the data used were not obtained from national databases such as the Outpatient Information System – Sistema de Informações Ambulatoriais. Another limitation of this study concerns the data for efficacy and progression of the disease, which were taken from studies which did not deal with Brazilian patients. These data were used due to the lack of clinical studies on this disease in a national context. There are also few prospective studies for CHB, due to the long follow up period. Thus, the clinical data on response to treatment were extrapolated to the end of the hypothetical cohort.

Estimates of the effectiveness of rescue therapies after one year are few. Therefore, evaluating the data obtained for substituting a therapy due to viral resistance should be approached with caution.

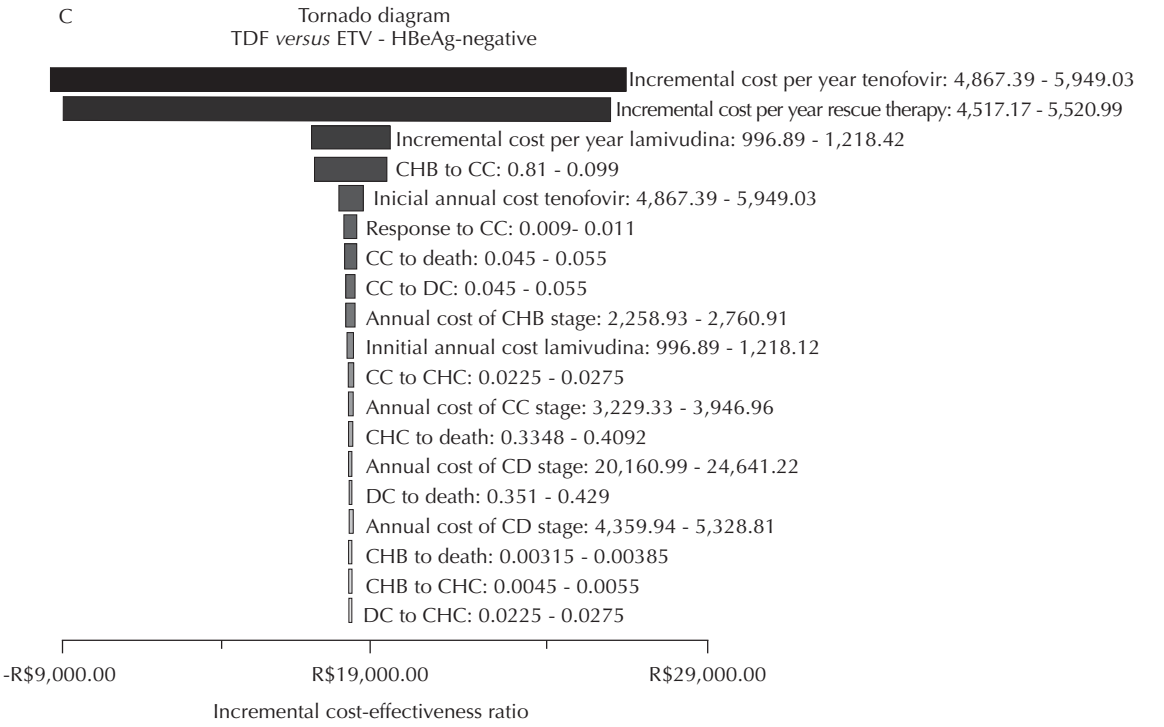
Cost-utility analysis from the perspective of health care services in other countries highlighted TDF as the most cost-effective option compared to ETV and LAM. A study from the Spanish perspective indicated TDF as responsible for higher life expectancy and lower costs compared to the other treatments.[1] A study carried out from the perspective of the Italian national health care system concluded that TDF was the most cost-effective alternative.[6] In both of these studies, the annual cost of this drug was lower than other nucleos(t)ide analogues,

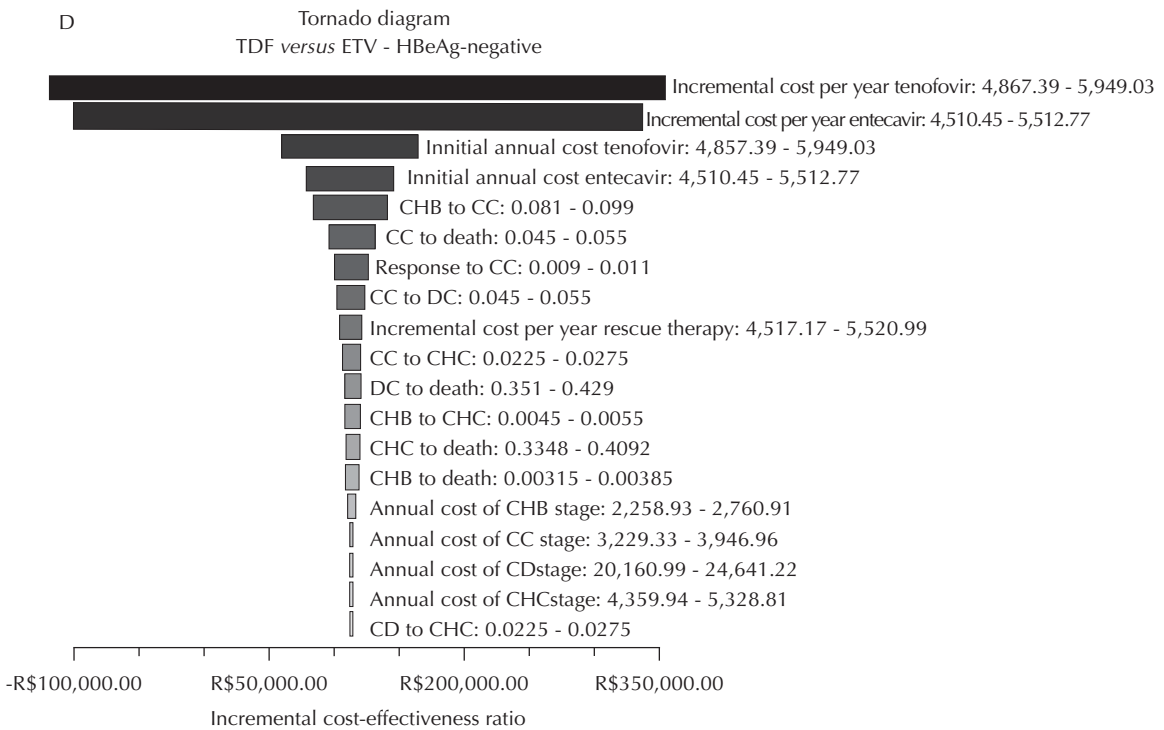

A
Tornado diagram
TDF *versus* ETV - HBeAg-positive
Incremental cost per year tenofovir: 4,867.39 - 5,949.03
Incremental cost per year entecavir 4,510.45 - 5,512.77
Inicial annual cost tenofovir 4,867.39 - 5,949.03
Inicial annual cost entecavir 4,510.45 - 5,512.77
Soroconversion to CC: 0.009 - 0.011
CC to death: 0.045 - 0.055
Incremental cost per year rescue therapy: 4,517.17 - 5,520.99
CC to DC: 0.045 - 0.055
CC to CHC: 0.0225 - 0.0275
CHB to CC: 0.054 - 0.066
CHB to CHC: 0.0045 - 0.0055
DC to death: 0.351 - 0.429
CHB to death: 0.00315 - 0.00385
CHC a óbito: 0.504 - 0.616
Annual cost of CHB stage: 2,258.93 - 2,760.91
Annual cost of CC stage: 3,229.33 - 3,946.96
Annual cost of DC stage: 20,160.99 - 24,641.22
Annual cost of CHC stage: 4,359.94 - 5,328.81
DC a CHC: 0.0225 - 0.0275
$100,000.00
R$50,000,00
R$200,000.00
R$350,000.00
Incremental cost-effectiveness ratio


B
Tornado diagram
TDF *versus* ETV - HBeAg-positive
Incremental cost per year entecavir: 4,510.45 - 5,512.77
Incremental cost per year rescue therapy: 4,517.17 - 5,520.99
Incremental cost per year lamivudina: 996.89 - 1,218.42
CHB to CC: 0.081 - 0.099
Initial annual cost entecavir: 4.510,45 - 5.512,77
Response to CC: 0.009 - 0.011
CC to death: 0.045 - 0.055
Inicial cost od CHB stage: 2,258.93 - 2,760.91
CC to DC: 0,045 - 0.055
Initial annual cost lamivudina: 996.89 - 1,218.42
Annual cost of CC stage: 3,229.33 - 3,946.96
CC to CHC: 0.0225 - 0.0275
Annual cost of DC stage: 20,160.99 - 24,641.22
CHC to death: 0.3348 - 0.4092
CHB to CHC: 0.0045 - 0.0055
DC to death: 0.351 - 0.429
Annual cost of CHC stage: 4,359.94 - 5,328.81
CHB to death: 0.00315 - 0.00385
DC to CHC: 0.0225 - 0.0275
2,000.00
R$12,000.00
R$22,000.00
Incremental cost-effectiveness ratio

Continue

Continuation





CC: compensated cirrhosis; CD: Incremental cost-effectiveness ratio decompensated cirrhosis, HCC: hepatocellular carcinoma; ETV: entecavir; CHB: Chronic Hepatitis B, no complications; LAM: lamivudine; TDF: tenofovir

Figure. Univariate sensitivity analysis between non-dominated treatment strategies. A) TDF *versus* ETV, HBeAg-positive; B) ETV *versus* LAM, HBeAg-negative; C) TDF *versus* LAM, HBeAg-negative; D) TDF *versus* ETV, HBeAg-negative.

ranging between 66.6% and 73.2% of the annual cost for ETV. In Brazil, according to the values set by the CMED, the annual cost of TDF is 107.9% that of ETV. In concordance with the results of this study, cost-effectiveness analysis comparing ETV and LAM from the perspective of the Brazilian Unified Health System concluded that treatment with ETV is the most cost-effective treatment.[7]

Sensitivity analysis makes it possible to assess the uncertainties, with a variation of 10% for each value used, allowing the robustness of the study's results in relation to the assumptions adopted to be considered. It was possible to define that the ICER is more sensitive to variations in the costs of the drugs. When the proposed variation is considered, situations in which ETV and TDF may be deemed to be cost-effective appear, with ICER below the threshold recommended for incorporating technologies in Brazil.

Bearing in mind the scientific output currently available, the assessment emphasizes incorporating and prioritizing ETV and TDF as nucleos(t)ide analogues in clinical protocol and treatment guideline for Chronic hepatitis B. There are some initiatives which may be important in reducing the prices of these drugs. One of these is incentivizing the use of official laboratories, rather than private, in producing low cost drugs. This would make treatment with TDF, which had the best clinical results, also produce better cost-effectiveness results compared with ETV. This action would lead to better treatment for the population affected by CHB.

Of the antivirals considered, ETV and TDF showed the best clinical results. For HBeAg-positive patients, they are the most cost-effective alternatives. For HBeAg-negative patients, they were reasonably cost-effective for use in Brazil. Thus, taking into account the perspective of the SUS and the data in the model, using ETV and TDF are the recommended options for starting CHB treatment in adult patients with no HIV co-infection. In order to reinforce these findings, more clinical studies – principally in Brazil – are necessary, as are budget impact studies.

REFERENCES

1. Buti M, Brosa M, Casado MA, Rueda M, Esteban R. Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B. *J Hepatol*. 2009;51(4):640-6. DOI:10.1016/j.jhep.2009.04.013.
2. Carias CM, Vieira FS, Giordano CV, Zucchi P. Exceptional circumstance drug dispensing: history and expenditures of the Brazilian Ministry of Health. *Rev Saude Publica*. 2011;45(2):233-40. DOI:10.1590/S0034-89102011000200001
3. Castelo A, Pessôa MG, Barreto TCBB, Alves MRD, Araújo DV. Estimativas de custo da hepatite crônica B no Sistema Único de Saúde brasileiro em 2005. *Rev Assoc Med Bras*. 2007;53(6):486-91. DOI:10.1590/S0104-42302007000600013
4. Chang TT, Gish RG, Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2006;354(10):1001-10. DOI:10.1056/NEJMoa051285
5. Chen EQ, Wang LC, Lei J, Xu L, Tang H. Meta-analysis: adefovir dipivoxil in combination with lamivudine in patients with lamivudine-resistant hepatitis B virus. *Virol J*. 2009;6:163. DOI:10.1186/1743-422X-6-163
6. Colombo GL, Gaeta GB, Viganò M, Di Matteo S. A cost-effectiveness analysis of different therapies in patients with chronic hepatitis B in Italy. *Clinicoecon Outcomes Res*. 2011;3:37-46. DOI:10.2147/CEOR.S16655
7. Costa AM, L'Italien G, Nita ME, Araujo ES. Cost-effectiveness of entecavir versus lamivudine for the suppression of viral replication in chronic hepatitis B patients in Brazil. *Braz J Infect Dis*. 2008;12(5):368-73. DOI:10.1590/S1413-86702008000500005
8. Crowley S, Tognarini D, Desmond P, Lees M, Saal G. Introduction of lamivudine for the treatment of chronic hepatitis B: expected clinical and economic outcomes based on 4-year clinical trial data. *J Gastroenterol Hepatol*. 2002;17(2):153-64. DOI:10.1046/j.1440-1746.2002.02673.x
9. Crowley SJ, Tognarini D, Desmond PV, Lees M. Cost-effectiveness analysis of lamivudine for the treatment of chronic hepatitis B. *Pharmacoeconomics*. 2000;17(5):409-27.
10. Di Bisceglie AM, Rustgi VK, Hoofnagle JH, Dusheiko GM, Lotze MT. NIH conference. Hepatocellular carcinoma. *Ann Intern Med*. 1988;108(3):390-401. DOI:10.7326/0003-4819-108-3-390
11. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol*. 2009;50(2):227-42. DOI:10.1016/j.jhep.2008.10.001
12. Fattovich G, Brollo L, Giustina G, Noventa F, Pontisso P, Alberti A, et al. Natural history and prognostic factors for chronic hepatitis type B. *Gut*. 1991;32(3):294-8.
13. Ganem D, Prince AM. Hepatitis B virus infection: natural history and clinical consequences. *N Engl J Med*. 2004;350(11):1118-29. DOI:10.1056/NEJMra031087
14. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med*. 2003;27;348(9):800-7. DOI:10.1056/NEJMoa021812
15. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2005;352(26):2673-81. DOI:10.1056/NEJMoa042957

16. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2006;354(10):1011-20. DOI:10.1056/NEJMoa051287

17. Lau DT, Everhart J, Kleiner DE, Park Y, Vergalla J, Schmid P, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology*. 1997;113(5):1660-7.

18. Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2005;352(26):2682-95. DOI:10.1056/NEJMoa043470

19. Liaw YF, Tai DI, Chu CM, Chen TJ. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Hepatology*. 1988;8(3):493-6.

20. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004;351(15):1521-31. DOI:10.1056/NEJMoa033364

21. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology*. 2007;45(2):507-39. DOI:10.1002/hep.21513

22. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med*. 2003;348(9):808-16. DOI:10.1056/NEJMoa020681

23. Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2004;351(12):1206-17. DOI:10.1056/NEJMoa040431

24. Marcellin P, Heathcote EJ, Buti M, Gane E, Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med*. 2008;359(23):2442-55. DOI:10.1056/NEJMoa0802878

25. Milich D, Liang TJ. Exploring the biological basis of hepatitis B e antigen in hepatitis B virus infection. *Hepatology*. 2003;38(5):1075-86. DOI:10.1053/jhep.2003.50453

26. Perrillo R, Hann HW, Mutimer D, Willems B, Leung N, Lee WM, et al. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology*. 2004;126(1):81-90.

27. Pwu RF, Chan KA. Cost-effectiveness analysis of interferon-alpha therapy in the treatment of chronic hepatitis B in Taiwan. *J Formos Med Assoc*. 2002;101(9):632-41.

28. Realdi G, Fattovich G, Hadziyannis S, Schalm SW, Almasio P, Sanchez-Tapias J, et al. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP). *J Hepatol*. 1994;21(4):656-66.

29. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13(4):322-38.

30. Takeda A, Jones J, Shepherd J, Davidson P, Price A. A systematic review and economic evaluation of adefovir dipivoxil and pegylated interferon-alpha-2a for the treatment of chronic hepatitis B. *J Viral Hepat*. 2007;14(2):75-88. DOI:10.1111/j.1365-2893.2006.00808.x

31. Wong JB, Koff RS, Tinè F, Pauker SG. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. *Ann Intern Med*. 1995;122(9):664-75. DOI:10.7326/0003-4819-122-9-199505010-00004

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HIGHLIGHTS

Considering the limited health care resources available, the increase in life expectancy, the increased mean age of the population, the higher prevalence of chronic compared with non-chronic health problems, and the growing appearance of pharmaceutical innovations, using pharma-economic knowledge and methods has become essential. Within the Brazilian Unified Health System (SUS), spending on medication from the Specialized Component of Pharmaceutical Care has grown without interruption, going from R$ 685 million in 2000 (R$ 4.01 *per capita*) to R$ 1.41 billion in 2007 (R$ 7.40 *per capita*). This situation calls for the rationalization and optimization of financial resources dedicated to pharmaceutical care.

Patients with chronic hepatitis B in Brazil have been treated with antivirals without pharma-economic studies being carried out in this context. This article uses a hypothetical cohort of patients with chronic hepatitis, both with and without positive HBeAg, in order to analyze the cost-effectiveness of the different drug therapies available. The outcome used was the life years gained in each of the alternatives.

At current prices, the most cost-effective treatments were Entecavir for HBeAg positive patients and Lamivudine for the HBeAg negative ones.

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