Non AIDS complications and treatment optimizations for HIV-1 infected Thai adult patients with and without TB or hepatitis
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Citation for published version (APA):
Avihingsanon, A. (2013). Non AIDS complications and treatment optimizations for HIV-1 infected Thai adult patients with and without TB or hepatitis
CHAPTER 3

Efficacy of tenofovir plus emtricitabine compared to emtricitabine in HIV/HBV coinfected antiretroviral naïve individuals in Thailand

Antiviral Therapy 2010; 15 (6):917-22

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Short communication

Efficacy of tenofovir disoproxil fumarate/emtricitabine compared with emtricitabine alone in antiretroviral-naive HIV–HBV coinfection in Thailand

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Background: Therapy for chronic hepatitis B with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) or emtricitabine (FTC) is currently recommended for HIV–HBV coinfection. However, there is limited randomized data on the efficacy of combined therapy with TDF and FTC, especially in antiretroviral (ARV)-naive patients.

Methods: This was a prospective randomized clinical trial comparing the efficacy of HBV monotherapy with FTC versus TDF/FTC combination therapy in ARV-naive HIV–HBV coinfection. HIV–HBV-coinfected patients initiating ARV were randomized to either FTC/zidovudine/efavirenz (EFV; n=6) or TDF/FTC/EFV (n=10). The primary end point was the time-weighted area under the curve (TWAUC) of HBV DNA at 48 weeks.

Results: The median baseline CD4+ T-cell count was 64 cells/µl (interquartile range [IQR] 36–172), plasma HIV type-1 RNA was 4.90 log_{10} copies/ml (IQR 4.58–5.44) and plasma HBV DNA was 8.76 log_{10} copies/ml (IQR 8.45–8.82). A total of 11/16 (69%) patients were hepatitis B e antigen (HBeAg)-positive. The median TWAUC decrease in HBV DNA was -5.32 log_{10} copies/ml in the TDF/FTC group compared with -3.25 log_{10} copies/ml in the FTC group (P=0.03). At week 48, 90% of the TDF/FTC group and 33% of the FTC group had plasma HBV DNA <170 copies/ml (P=0.036, intention-to-treat analysis). HBeAg loss was observed in 4/11 (36%) HBeAg-positive patients. Hepatic flares were observed in 3/16 (19%) of patients.

Conclusions: TDF/FTC combination therapy resulted in a significantly greater decrease in HBV DNA than FTC monotherapy, with a greater proportion of patients with undetectable HBV DNA at week 48. Our study supports the current recommendation of ARV containing TDF/FTC as the treatment of choice for patients with HIV–HBV coinfection.

Introduction

Chronic HBV is a major coinfection in HIV-infected patients in Africa and Asia, where both HIV and HBV are prevalent. HIV infection modifies the natural course of HBV leading to accelerated liver disease progression, increased liver-related morbidity [1] and increased rates of antiretroviral (ARV)-related hepatotoxicity [2]. Treatment for both HIV and HBV are usually initiated simultaneously and treatment is generally life-long. Current HIV treatment guidelines recommend the use of combination therapy, including two HBV-active nucleoside/nucleotide analogues for any HIV–HBV-coinfected patient initiating antiretroviral therapy (ART). The most commonly used HBV-active nucleoside/nucleotide analogues that are also active against...
HIV include lamivudine (3TC), emtricitabine (FTC) or tenofovir disoproxil fumarate (TDF).

FTC is structurally similar to 3TC, but has a longer half-life [3], and selects the YMDD mutation less often and less rapidly [4]. Although FTC is currently not approved for the treatment of HBV, it induces a rapid and sharp reduction in HBV DNA, and more than one-half of HBV-monoinfected patients treated with FTC maintained suppression of HBV DNA at 48 weeks [4]. There is limited randomized data on the efficacy of FTC or TDF plus FTC in ARV-naive, HIV–HBV-coinfected patients. In this trial, we examined the efficacy and safety of FTC alone or in combination with TDF in treatment-naive HIV–HBV-coinfected patients starting ART and found that patients who received TDF/FTC combination therapy were significantly more likely to have an undetectable HBV DNA at week 48.

Methods

Patients

Patients were recruited from the HIV Netherlands Australia Thailand (HIV-NAT) Research Collaboration, Thai Red Cross AIDS Research Centre (Bangkok, Thailand) and the Chulalongkorn King Memorial Hospital, Chulalongkorn University (Bangkok, Thailand). HIV-infected men and women with chronic hepatitis B (hepatitis B surface antigen [HBsAg] detected on two occasions 6 months apart) and aged between 18 and 70 years were enrolled if they were ARV-naive, had HBV DNA>100,000 copies/ml, creatinine ≤2.0 mg/dl and platelet count ≥50,000 cells/mm³. Exclusion criteria were positivity for HCV RNA, immunoglobulin M antibody to hepatitis A virus and other causes of chronic liver disease (autoimmune, α-antitrypsin deficiency and haemochromatosis), serum alanine aminotransferase (ALT) levels >1,000 U/l, decompensated cirrhosis or α-fetoprotein >3× the upper limit normal (ULN).

Study design

This was a prospective two-arm non-blinded randomized clinical trial to compare the efficacy of FTC or FTC plus TDF over 48 weeks in ARV-naive HIV–HBV-coinfected individuals. The study was originally conducted at three sites in the Netherlands and one site in Thailand. Because of a limited number of eligible participants in the Netherlands, the Netherlands sites were terminated prematurely and only patients enrolled in Thailand were included in this analysis. Patients were enrolled between April 2005 and December 2006. The patients were randomized on a 1:1 basis to one of the following arms: arm 1, zidovudine (AZT; 250 mg twice daily) plus FTC (200 mg once daily) plus efavirenz (EFV; 600 mg once daily); and arm 2, FTC (200 mg once daily) plus TDF (300 mg once daily) plus EFV (600 mg once daily).

Patients randomized to the combination of TDF plus FTC could take Truvada (TDF/FTC fixed combination tablet) once daily. Patients were allowed to switch or modify the dose of AZT and EFV for toxicity or intolerance. All patients gave informed written consent and the study was approved by the relevant institutional review boards in Thailand. Liver biopsies were optional and were collected at week 0 and week 48.

Statistical analyses

The primary end point of the study was a median log_{10} copies/ml change in HBV DNA from baseline to week 48 using time-weighted area under the curve (TWAUC) analysis. Secondary end points included proportion of patients with undetectable HBV DNA at weeks 12, 24 and 48, hepatitis B e antigen (HBeAg) and HBsAg loss/seroconversion rates, median change from baseline in HIV type-1 (HIV-1) RNA and CD4+ T-cell count (cells/mm³), median change in ALT and time to ALT normalization over 48 weeks, development of HBV resistance mutations at week 48 and rate of hepatic flares. All analyses were performed on an intention-to-treat (ITT) basis. Hepatic flares were defined as an increase in ALT or aspartate aminotransferase levels from a baseline of >5×ULN or >100 U/l from baseline if abnormal at entry. Treatment arms were compared using the Wilcoxon signed-rank test for continuous variables and Fisher’s exact test for dichotomous variables. All tests were two-sided and P<0.05 was considered statistically significant.

Laboratory methods

Safety bloods (haematology, biochemistry and clotting), HBV serology, T-cell subsets and HIV-1 RNA were performed at the local laboratory (HIV-NAT; Bangkok, Thailand).

HBV DNA quantification was performed at a central laboratory (Victorian Infectious Diseases Laboratory, Melbourne, Australia). HBV DNA measurement was performed on all samples using the Versant HBV DNA 3.0 bDNA assay (Bayer HealthCare, Tarrytown, NY, USA). The linear dynamic range of the assay was from 2×10^3 to 1×10^8 copies/ml (3.6×10^2–1.8×10^7 IU/ml). For samples below the lower limit of detection on the bDNA assay, repeat testing was performed using the COBAS® TaqMan® HBV Test (Roche Diagnostics, Branchburg, NJ, USA). Using a manual extraction procedure, the lower limit of quantification of this assay was approximately 170 copies/ml (30 IU/ml). Liver biopsy was not mandated by the study protocol, but was recommended for HBV disease assessment. Histological scoring was performed initially by a Thai pathologist and then subsequently by an independent pathologist in Australia who was blinded to the results. Where histological scores differed between the two pathologists by more than two fibrosis stages,
the biopsies were scored again by a third independent pathologist in Australia.

Results

Demographics

A total of 19 Thai patients participated in this study. Three patients had HBV DNA < 100,000 copies/ml at baseline; therefore, only 16 patients were included in this analysis. Baseline characteristics of enrolled patients are given in Table 1. Six patients were treated with AZT/FTC/EFV (arm 1) and 10 patients were treated with TDF/FTC/EFV (arm 2). The study group was predominantly male (75%), the majority of patients identified heterosexual exposure (73%) as the most likely route of HIV-1 infection and 50% had a history of chronic HBV infection in their family. The median age of the patients was 34 years (interquartile range [IQR] 30–39) with a median body weight of 55 kg (IQR 51–62). The median baseline CD4+ T-cell count was 64 cells/µl (IQR 36–172) and the median HIV-1 RNA was 4.90 log_{10} copies/ml (4.58–5.44). Of the cohort, 16% had a prior AIDS-defining illness (CDC classification C) and 63% had CDC classification B, with 58% and 53% of the group on cotrimoxazole and fluconazole treatment, respectively.

Baseline HBV DNA levels were high at a median of 8.76 log_{10} copies/ml (IQR 8.45–8.82) and 11 (69%) patients were HBeAg-positive. There was no significant difference in baseline HBV DNA levels between HBeAg-positive and HBeAg-negative patients (8.0 log_{10} copies/ml versus 7.1 log_{10} copies/ml; P = 0.09). Despite high HBV DNA levels at baseline, the median ALT was only 42 U/l (IQR 32–76) and almost one-half (44%) of patients had normal ALT levels at baseline. A total of 12 (81%) patients underwent liver biopsy at study entry and overall liver disease was mild. The median inflammatory activity (A) score was 1 (range 0–3) and the fibrosis score (F) was 1.5 (range 0–4). Only three patients had an F-score of 3/4, consistent with advanced fibrosis. Of our patients, 15 (94%) were coinfected with hepatitis B genotype C and only 1 patient had genotype B.

HBV DNA and serological response

There was a significantly greater reduction in time-weighted median change in HBV DNA over 48 weeks of study in the TDF/FTC group (-5.32 log_{10} copies/ml [IQR -6.19–5.13]) compared with the FTC group (-3.25 log_{10} copies/ml [IQR -5.43–2.66]; P = 0.03; Figure 1). The proportion of patients with HBV DNA < 170 copies/ml (30 IU/ml) at 48 weeks by ITT analysis was significantly higher in the TDF/FTC group than in the FTC group (90% versus 33%; P = 0.036). Of the five patients who had detectable HBV DNA at 48 weeks (HBV DNA 4.21–8.05 log_{10} copies/ml), none had experienced undetectable viral load

Table 1. Baseline characteristics by study arm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm 1, FTC/AZT/EFV (n=6)</th>
<th>Arm 2, FTC/TDF/EFV (n=10)</th>
<th>Overall (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>34 (27–34)</td>
<td>33 (30–41)</td>
<td>34 (30–39)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>5 (83)</td>
<td>7 (70)</td>
<td>12 (75)</td>
</tr>
<tr>
<td>Risk for HIV acquisition, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM, n (%)</td>
<td>1 (17)</td>
<td>2 (20)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Heterosexual, n (%)</td>
<td>4 (66)</td>
<td>8 (80)</td>
<td>12 (75)</td>
</tr>
<tr>
<td>Risks for HBV acquisition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertical, n (%)</td>
<td>3 (50)</td>
<td>5 (50)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>MSM, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heterosexual, n (%)</td>
<td>0</td>
<td>1 (10)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>3 (50)</td>
<td>4 (40)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>CD4+ T-cell count, cells/µl</td>
<td>46 (15–67)</td>
<td>69 (46–214)</td>
<td>55 (36–172)</td>
</tr>
<tr>
<td>HIV-1 RNA, log_{10} copies/ml</td>
<td>4.91 (4.56–5.70)</td>
<td>4.90 (4.60–5.30)</td>
<td>4.90 (4.58–5.44)</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>36 (30–39)</td>
<td>81 (56–157)</td>
<td>42 (52–760)</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>4.25 (3.9–4.6)</td>
<td>4.1 (3.4–4.3)</td>
<td></td>
</tr>
<tr>
<td>HBV DNA, log_{10} copies/ml</td>
<td>8.82 (8.76–8.82)</td>
<td>8.54 (8.16–8.81)</td>
<td>8.76 (8.45–8.82)</td>
</tr>
<tr>
<td>HBeAg-positive status, n/total n (%)</td>
<td>5/6 (83)</td>
<td>6/10 (60)</td>
<td>11/16 (69)</td>
</tr>
<tr>
<td>Anti-HBe-positive status, n/total n (%)</td>
<td>0/69 (0)</td>
<td>4/10 (40)</td>
<td>4/16 (25)</td>
</tr>
<tr>
<td>Fibrosis score‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0, n</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>F1/F2, n</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>F3/F4, n</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) unless indicated otherwise. *Liver biopsies were performed in 13 patients. ALT, alanine aminotransferase; AZT, zidovudine; anti-HBe, antibody against hepatitis B e antigen; EFV, efavirenz; FTC, emtricitabine; HBeAg, hepatitis B e antigen; HIV-1, HIV type-1; MSM, men who have sex with men; TDF, tenofovir disoproxil fumarate.
The median (IQR) decrease in HIV-1 \( \mu \)FTC arm and 192 cells/l (71–170) in the

Only one patient, who was randomized to FTC, lost HBeAg (one by

Evidence of wild-type virus with no mutations detected in

Median reduction in HBV DNA according to

AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

or viral rebound and four were receiving FTC only. The median HBV DNA reduction in these five patients was -3.66 log\(_{10}\) copies/ml (range -5.43– -0.76). All patients had evidence of wild-type virus with no mutations detected in HBV polymerase. Each of these five patients had HIV-1 RNA<50 copies/ml at week 48, which was consistent with these patients being compliant with ART.

Of the study group, 11/16 (69%) were HBeAg-positive at baseline and 3/6 (50%) of HBeAg-positive patients randomized to TDF/FTC lost HBsAg (one by week 12 and two by week 24). Two of these patients developed antibody against HBsAg (anti-HBe) at the same time points. One patient randomized to FTC (1/5; 20%) lost HBsAg and developed anti-HBe at week 48. Only one patient, who was randomized to FTC, lost HBsAg at week 48.

HIV-related outcomes

The median (IQR) change in CD4+ T-cell count from baseline to week 48 was 120 cells/\mu l (71–170) in the FTC arm and 192 cells/\mu l (119–271) in the TDF/FTC arm (P=0.14). The median (IQR) decrease in HIV-1 RNA to week 48 was -3.21 log\(_{10}\) copies/ml (-3.76– -2.86) for FTC and -3.20 log\(_{10}\) copies/ml (-3.60– -2.90) for TDF/FTC (P=0.87). Five (83%) of the six patients in the FTC arm and all patients in the TDF/FTC arm had HIV-1 RNA<50 copies/ml at week 48 (P=1.00).

Biochemical and histological response

At week 48, median ALT decreased in the TDF/FTC group (from 81 U/l [IQR 56–157] to 52 U/l [IQR 43–57]), but increased in the FTC group (from 36 U/l [IQR 30–39] at baseline to 63 U/l [IQR 37–158]); however, the difference was not statistically significant (P=0.70). Four patients with normal ALT levels at baseline developed abnormal ALT levels by week 48 (FTC arm n=3 and FTC/TDF arm n=1; P=0.46). A total of 13 patients underwent liver biopsy prior to taking ARV, the median (range) A and F scores were 1 (0–3) and 1.5 (0–4), respectively. Only five patients had subsequent liver biopsy at study completion (48 weeks) for comparison. Of these, the activity and fibrosis scores were unchanged in two patients (both with A0 and F0 at baseline) and an improvement in activity and fibrosis scores were seen in three patients. For F3/4 patients, only one patient had available paired biopsies at week 48, which showed improvement from fibrosis stage F3 to F1.

Hepatic flares and other adverse events

Hepatic flares, defined as an increase in ALT to >5×ULN or a 100 U/l increase from baseline (if abnormal at entry) was observed in 3/16 (19%) patients. For two patients receiving TDF/FTC, the flare occurred at or before week 12, and for one patient receiving FTC, the flare occurred at week 48. Both patients with hepatic flare before week 12 were HBeAg-positive at baseline, and subsequently developed anti-HBe. The patient with hepatic flare at week 48 was in the FTC arm and had an HBV DNA level of 16,267 copies/ml. There was no significant change in serum creatinine from baseline for patients in either arm. Median change in creatinine from baseline to week 48 was -0.03 mg/dl (IQR -0.14–0.05) and -0.27 mg/dl (IQR -0.67– -0.12) for the FTC and TDF/FTC arms, respectively.

Discussion

In this randomized clinical trial comparing TDF/ FTC- to FTC-containing ART in HIV–HBV-coinfected patients in Thailand, we found that TDF/FTC led to significantly better control of HBV replication compared with FTC monotherapy. The median decrease in serum HBV DNA from the baseline and the number of patients reaching an undetectable HBV DNA at week 48 was significantly greater in patients receiving TDF/ FTC than FTC alone (90% and 33%, respectively).

The proportion of patients with undetectable HBV DNA in the combination TDF/FTC arm in this cohort was high (90%), higher than that seen in a previous study of TDF only (75%) or TDF/3TC-containing (64%) ARV in HIV–HBV-coinfected Thai patients [5]. Although we did not directly compare TDF/3TC to TDF/FTC in this study, enhanced potency of TDF/FTC in vivo is supported by in vitro studies, which showed greater reduction in HBV DNA following treatment with TDF/FTC compared with TDF/3TC for a hepatoja
cell line chronically infected with HBV (AD38 cell line) [6]. Using isobologram analyses, TDF/FTC was associated with a synergistic effect, whereas TDF/3TC had only an additive effect [6]. Interestingly, TDF/FTC, but not TDF/3TC, has also been shown to have synergistic anti-HIV activity in vitro [7]. Enhanced potency of TDF/FTC compared with TDF/3TC was also seen in chronic woodchuck hepatitis [8] with a greater antiviral response in vitro in woodchucks receiving TDF/FTC [8]. Whether TDF/FTC could be more efficacious than TDF/3TC in treating plasma HBV DNA needs to be determined in a further controlled trial.

In this study, the proportion of patients with undetectable HBV DNA (170 copies/ml) after 48 weeks with FTC (33%) and the TWAUC for HBV DNA decrease were both significantly less than that observed with TDF/FTC. In a previously randomized study (TICO) [3] of TDF/3TC versus 3TC versus TDF in HIV–HBV-coinfected Thai patients, although there was no difference in the TWAUC for HBV DNA decrease between the three arms, a lower proportion of patients that had a HBV DNA<1,000 copies/ml at 48 weeks with 3TC monotherapy (46%) compared with TDF/3TC (75%) was observed, which would be consistent with the findings in this current study.

FTC and 3TC have a similar chemical structure and both interfere with HBV DNA polymerase activity by chain termination. One possible explanation for the different efficacies of 3TC and FTC compared with combination treatment was the use of a higher dose of 3TC (300 mg/day) than the usual recommended dose for HBV (100 mg/day) in the TICO study [5]. The anti-HBV activity efficacy of FTC is also dependent on dosage [9], with the greatest reduction in HBV DNA (3.3 log10 copies/ml) following treatment of HBV monoinfection with a 300 mg dose. We used the currently recommended dose of 200 mg/day for FTC, which might not be the dose with maximal anti-HBV potency.

Both FTC and 3TC have a low genetic barrier for HBV resistance and similar mutations are associated with resistance to both compounds. Consistent with these observations, we only observed inadequate virological suppression in patients receiving FTC alone. We noticed that at week 12, the HBV DNA of four out of six patients receiving FTC alone had decreased approximately by 2.72 log10 copies/ml (range 1.80–4.69) and after that, it plateaued. In contrast to FTC and 3TC, resistance to TDF has rarely been reported, although efficacy is reduced in individuals with prior exposure and resistance to adefovir [10–13]. We did not include a TDF-only arm in this study and therefore cannot definitively conclude whether the absence of drug resistance in the TDF/FTC arm was a consequence of patients receiving TDF or combination TDF/FTC therapy. Among all patients with detectable HBV DNA, none developed classical YMDD mutations, specifically rtM204I/V with or without the rtL180M and rtV173L [14]. Persistence of wild-type HBV DNA in patients who fail to control HBV DNA replication and/or experience virological rebound has been previously described for 3TC [5,15,16]. In this setting, detection of wild-type HBV DNA usually precedes the eventual detection of a YMMD mutation. We expect that a similar mechanism might occur with FTC. All of these patients are now receiving TDF in addition to FTC and thus we are unable to determine if these patients would have eventually developed a YMMD mutation with prolonged FTC monotherapy.

As reported previously in HIV–HBV coinfected patients [5,17], we also observed high rates of HBeAg loss, 36% in HBeAg-positive patients, which was higher than previous studies in HBV-monoinfected patients treated with TDF (21%) [18], entecavir (21%) [19] and 3TC (18%) [19]. This might be a consequence of robust immune reconstitution and acquisition of either enhanced pathogen-specific innate or adaptive immune responses following ARV. Indeed, the HIV-related virological and immunological responses to highly active antiretroviral therapy in this study were both excellent. The greater log10 copies/ml increase in CD4+ T-cell count in the TDF/FTC group probably reflects the effects of AZT on bone marrow function and lower baseline CD4+ T-cell in the FTC group.

This study is, however, limited by a small sample size, thus there was limited power to address the differences of some outcomes between the arms. Unlike our previous TICO study [5], we did not include a TDF HBV monotherapy arm, whether TDF is comparable to TDF/FTC in controlling HBV is therefore not known.

In conclusion, the combination of TDF/FTC had superior anti-HBV efficacy compared with FTC alone in HIV–HBV-coinfected patients. Our findings support the current recommended guidelines that combination therapy with TDF/FTC is an appropriate first-line option for HIV–HBV-coinfected patients.

Acknowledgements

This study was presented orally at the 12th European AIDS Conference (11–14 November 2009, Cologne, Germany; abstract PS2). The clinical trial registration number for this study is 00476463. The study was funded by Gilead Sciences, but the company had no role on the analysis and reporting of these results.

Disclosure statement

KR has received research grants/funding, honoraria and lecture sponsorships from, or is a consultant or advisor to, Abbott Laboratories, Boehringer–Ingelheim,
Bristol–Myers Squibb, Gilead Sciences, GlaxoSmithKline, and F Hoffmann–La Roche. JL has received consultancy fees and honoraria from GlaxoSmithKline, Boehringer–Ingelheim, Bristol–Myers Squibb, F Hoffmann–La Roche, Merck Sharp & Dohme, Schering–Plough, Bayer, Shire Pharmaceuticals, Agouron/ Pfizer and Virco/Tibotec. SRL has received research and travel grants from Gilead Sciences, Pfizer, Bristol–Myers Squibb, Merck, Sharp & Dohme and GlaxoSmithKline. All other authors declare no competing interests.

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Accepted for publication 11 March 2010

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