Reviewer No. 2

APPLICATION FOR ADDITION OF ZIDOVUDINE/LAMIVUDINE/ABACAVIR FIXED DOSE COMBINATION FOR THE TREATMENT OF HIV-1 INFECTION

(1) Have all important studies that you are aware of been included?

Yes □ No □

If "No", add missing references with brief summary of key findings.

(2) Is there adequate evidence of efficacy for the proposed use?

Yes □ No X

The mainly available randomized clinical trials are of moderate or low methodological quality, with small number of enrolled patients, open-label design, 48-weeks follow-up, intention-to-treat analysis. Among the studies found there are few focused on the specific fixed dose combination (1 of 8 trials for first-line treatment and 3 of 5 for second-line treatment). There are conflicting results from clinical trials and systematic reviews. Some important clinical guidelines stated that this combination is generally not recommended. It should be only used as an alternative for first-line ART in situations of intolerance or resistance to NNRTIs when PI-based regimens are unavailable or should be preserved for the treatment of HIV-2 infection or HIV/TB co-infected individuals when the simultaneous treatment of both conditions is indicated. In other international documents the FDC is considered a high priority missing in the WHO EML. In consequence, the existing evidence is not sufficient to generate a robust recommendation.

(3) Is there evidence of efficacy in diverse settings and/or populations?

Yes □ No X

The available evidence has come from a small number of non-inferiority trials that compare the triple NRTI fixed dose combination with multiple preferred regimens for HAART in naïve-treated patients or second-line treatments. The evidence neither covers diverse settings nor ascertains populations with the specified conditions or co-morbidities that indicate the alternative use of this medicine.

(4) Are there adverse effects of concern?

Yes X No □

The safety profile is acceptable, except for serious or even fatal hypersensitivity reactions that have been associated with abacavir in few patients. Side effects are more severe in naïve-treated people. A recent paper reported an excess incidence of myocardial infarction in patients treated with isolated abacavir.
(5) Are there special requirements or training needed for safe/effective use?

Yes X No ☐

Requirements of HIV services where facilities are available to perform confirmation tests of HIV infection status, co-morbidities and opportunistic infections, measurement of virologic and immunologic efficacy and safety. Health personnel should be trained for monitoring adherence and therapy results.

(6) Is this product needed to meet the majority health needs of the population?

Yes ☐ No X

HIV-infection is a pandemic disease, with a wide global distribution, and the availability of its adequate treatment is an issue of public health relevance. Even so there is no reason for accepting every ARV and every FDC as “essential”.

(7) Is the proposed dosage form registered by a stringent regulatory authority?

Yes X No ☐

If "No", give details.

(8) What action do you propose for the Committee to take?

The selection of essential medicines should be based on hierarchical criteria. The first one is efficacy. There is lack of specific and qualified evidence on AZT+3TC+ABC fixed-dose combination as well as contradictory trial results. The same conflicting or inconclusive data are provided by systematic reviews and clinical guidelines. Additionally, despite acceptable safety in the majority of patients, there is concern about hypersensitivity reactions and increased rate of myocardial infarction associated with abacavir use. The simplified administration, low pill burden and increased adherence do not correlate to its real use in resource-limited settings probably due to its higher comparative cost that accounts for reduced access or to the restricted conditions in which the FDC is needed. Considering the FDC as an alternative in HAART or in second-line ARV therapy that could be substituted by the combination of the three separate products or the addition of ABC to the double FDC of ZDV/3TC, both still existent in the list, I recommend that this fixed-dose combination formulation of zidovudine/lamivudine/abacavir not be added to the EML.

(9) Additional comment, if any.

References in the short review (see below)
BACKGROUND

Fixed-dose combinations (FDCs) have been formulated to increase efficacy (by reduction of viral resistance development or lengthening of viral suppression time), tolerability (different toxicity profile), convenience (reduced number of tablets to be swallowed each day, once or twice daily dosing, no cold chain requirement) and corresponding compliance. Furthermore, they should have widespread availability and be comparatively inexpensive. Disadvantages of FDCs include different medicine half-lives which complicate ART stopping procedures, the fact that a single mutation is associated with resistance to some agents (3TC and the NNRTIs), and cross-resistance within the NNRTI class.

First-line therapy currently includes two NRTIs and a NNRTI or PI. The effectiveness of these regimens decreases over time, requiring a switch to combinations that retain efficacy in the presence of viral resistance. Increasing access to second-line FDCs and new developments in first-line ARV therapy are cost challenges. In high-income countries the cost of ARV therapy is largely irrelevant. On the contrary, in resource-poor settings cost is a huge factor that limits drug access, resulting in high rates of new infection and subsequent mortality.

The WHO Guidelines of Antiretroviral Therapy for HIV infection in Adults and Adolescents (2006) identify a triple NRTI regimen (zidovudine- AZT, lamivudine - 3TC and abacavir-ABC) as a recommended alternative for first-line ART in situations of intolerance or resistance to NNRTIs when PI-based regimens were unavailable or should be preserved for the treatment of HIV-2 infection and of HIV/TB co-infected individuals when the treatment of both conditions was simultaneously indicated. On the other hand, another document posted on the WHO website “UNITAID and WHO Secretariat proposal: the priority missing essential medicines for HIV” proposed those medicines as a triple FDC as a priority missing in the WHO Model List of Essential Medicines. The document emphasizes that the combination regimen would be recommended for adult first line ART. All components are on the EML as individual agents. For children, the document recommends zidovudine + lamivudine + abacavir (60/30/60 mg tablet) as a high priority.

In 2008 Brazilian Health Ministry guidelines the preferred option is to start with co-administrated zidovudine + lamivudine plus efavirenz or nevirapine (in pregnancy). In the initial therapy, abacavir is only recommended in patients with zidovudine intolerance, since its higher cost does not have a proportional benefit in comparison to other options. The triple FDC is not mentioned.

The International AIDS Society-USA recommendations for adult ART stated that the initial regimen must be individualized, particularly in the presence of co-morbid conditions. The panel members pointed the results of a randomised, open-label study that evidenced similar antiretroviral activity between 4 NRTIs (zidovudine, lamivudine, abacavir, and tenofovir) and efavirenz plus zidovudine + lamivudine (1 NNRTI and 2 NRTI). Nevertheless, the quadruple NRTI combination may be only considered in special circumstances, such as co-administration with tuberculosis.
therapy or when co-morbid conditions mandate treatment with other medications that have substantial drug interactions with NNRTIs and PIs.

The British HIV Association Guidelines do not recommend currently use of triple NRTI regimen7.

A systematic review8 that included all trials focused on the presented application compared the effectiveness of three drug combination antiretroviral therapy (ART) in treatment-naive HIV-infected adults. The review identified the responses to variable combinations added to two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTI): (1) a protease inhibitor (PI); (2) a non-nucleoside RTI (NNRTI); (3) a third NRTI; or (4) a ritonavir-boosted PI (BPI). NNRTI and BPI-containing regimens offer superior virologic suppression over 48 weeks.

Confirmation of the apparently inferior virologic control of triple NRTI therapy was demonstrated in the AIDS Clinical Trials Group A5095 study9 with zidovudine/lamivudine/abacavir combination in adults. Such a combination should only be considered in special situations. Examples cited include informed patient choice based on anticipated poor adherence on other treatment regimens, or if concomitant drugs such as tuberculosis medication are prescribed.

APPLICATION

Dr Patti Whyte from the Department of HIV proposed the inclusion of zidovudine/lamivudine/abacavir fixed dose combination (tablet: 300 mg + 150 mg + 300 mg) for the treatment of HIV-1 infection on the WHO Model List of Essential Medicines.

EFFICACY

Treatment-naive patients

There are various HAART options for naive patients with proved efficacy, favourable long-term tolerability profiles, wide availability and low pill burden10.

In 2001, a 48-week, multicenter, phase 3, randomised, double-blind trial (n=562)11 evaluated antiretroviral equivalence and safety of two triple combination regimens: zidovudine + lamivudine + abacavir (triple nucleoside regimen) twice daily versus zidovudine + lamivudine + indinavir (2 nucleoside + 1 PI) twice daily for initial antiretroviral treatment. At week 48 the proportion of patients who met virologic suppression (400 copies/ml or less) was equivalent in the abacavir group and in the indinavir group (51% vs. 51%; difference:-0.6%; CI95%:-9% - 8%). The proportion of patients achieving less than 50 copies/ml was 45% in the indinavir group and 31% in the abacavir group (treatment difference: -14%; CI95%: 27% - 0%). The effects on CD4 cell count were comparable in both treatments. There was no difference between groups in the frequency of treatment-limiting adverse events or laboratory abnormalities. So, in this study the abacavir-containing regimen was inferior to indinavir containing regimen in achieving a plasma HIV RNA level of less than 50 copies/ml at week 48.

In 2003, an open-label, randomised, 48-week study12 compared the efficacy and safety of a triple nucleoside regimen (lamivudine + zidovudine, twice daily and abacavir, twice daily) to a protease inhibitor-containing triple regimen (lamivudine + zidovudine, twice daily and nelfinavir 750 mg, every 8 h) in 195 HIV-1-infected ART-naive adults. At week
48, plasma HIV-1 RNA was <50 copies/ml in 57% and 58% of subjects, respectively. Median CD4 increase was +110 and +120 cells/mm³, respectively. This study demonstrated equivalence between triple nucleoside combination and nelfinavir-containing regimen at week 48.

In 2004, a randomised, double-blind, phase III trial¹³ compared the relative effectiveness of three antiretroviral regimens for the initial treatment of 1147 subjects infected with HIV-1:

- zidovudine-lamivudine-abacavir, zidovudine-lamivudine plus efavirenz, and zidovudine-lamivudine-abacavir plus efavirenz. A scheduled review by the data and safety monitoring board with the use of prespecified stopping boundaries led to a recommendation to stop the triple-nucleoside group and to present the results in the triple-nucleoside group in comparison with pooled data from the efavirenz groups. After a median follow-up of 32 weeks the virologic failure was 21% vs. 11% in the triple-nucleoside group and the combined efavirenz groups, respectively; the time to virologic failure was significantly shorter in the triple-nucleoside group (P<0.001). Changes in the CD4 cell count and the incidence of grade 3 or grade 4 adverse events did not differ significantly between groups.

An open-label, randomised, 48-weeks trial (n=342)¹⁴ compared antiviral response, tolerability, and adherence with a triple nucleoside regimen (abacavir [ABC] plus a lamivudine/zidovudine combination tablet [COM] twice daily) vs. a regimen containing a protease inhibitor (indinavir [IDV] 800 mg three times daily plus COM twice daily [IDV/COM]). At week 48, 66% of ABC/COM-treated patients vs. 50% of IDV/COM-treated patients (difference: 16.6%; CI95%: 6.0-27.2; P = 0.002) achieved HIV-1 RNA < 400 copies/ml; for HIV-1 RNA < 50 copies/ml the results were 60% vs. 50% (difference: 9.6% (CI95%:-1.1-20.2) in ABC/COM group and IDV/COM group, respectively. Median increases from baseline in CD4+ cell counts were similar in the two treatment groups. The authors concluded by the equivalence of the two treatments over 48 weeks, but admitted that the study was not powered to determine equivalence of treatments, and bias could not be ruled out due to the open-label study design.

In 2005, a small study¹⁵ randomised 53 antiretroviral-naïve individuals to receive zidovudine + lamivudine (combined tablet) plus efavirenz or zidovudine + lamivudine + abacavir (combined tablet) plus efavirenz (quad regimen). At week 48 the fall in viral load and increase in CD4 count showed no significant differences between regimens. In an intent-to-treat analysis, 77% of patients in the triple therapy group reached an undetectable viral load (<50 copies/ml) compared with 84.2% of the quadruple therapy group.

The ESS40013 study¹⁶ tested abacavir/lamivudine/zidovudine (ABC/3TC/ZDV) and efavirenz (EFV) for the 48-week induction phase in 448 antiretroviral-naive adult patients, followed by 3-drug maintenance therapy. Two hundred eighty-two patients were randomised in a 1:1 ratio to continue ABC/3TC/ZDV+EFV or to simplify to ABC/3TC/ZDV for the 48-week maintenance phase. No significant differences were noted between the two regimens for an HIV RNA level <50 copies/ml (79% vs. 77%; P = 0.70) or time to treatment failure (P = 0.75) at week 96. Virologic failure occurred in 22 patients during induction and in 24 patients (11% in ABC/3TC/ZDV group and 6% in ABC/3TC/ZDV+EFV group; P = 0.134) during maintenance.
In 2006, the AIDS Clinical Trials Group performed a randomised, double-blind, placebo-controlled, long-term study in 765 patients with HIV-1 RNA levels of 400 copies/ml or greater and CD4 cell count of 240 cells/mm³. The patients were randomly assigned to receive zidovudine/ lamivudine plus efavirenz (3-drug regimen) or zidovudine/lamivudine/ abacavir plus efavirenz (4-drug regimen). After a median 3-year follow-up, 26% vs. 25% of patients receiving the 3-drug and 4-drug regimens, respectively, reached protocol-defined virologic failure; time to virologic failure was not significantly different. At 3 years, the HIV-1 RNA level < 200 copies/ml was 90% vs. 92% (P = 0.59) and < 50 copies/ml was 85% vs. 88% (P = 0.39) in patients receiving the 3-drug and 4-drug regimens, respectively. CD4 cell count increase and grade 3 or 4 adverse events were not significantly different. These results support current guidelines recommending 2 nucleosides plus efavirenz for initial treatment of HIV-1 infection; adding abacavir as a fourth drug provided no additional benefit\textsuperscript{17}.

A randomised, open-label comparative pilot study\textsuperscript{6} compared zidovudine/ lamivudine/ efavirenz (triple) versus abacavir/lamivudine/zidovudine/tenofovir (quadruple) therapy in HIV-1-infected, treatment-naive individuals. Both regimens were taken without regard to food and consisted of a twice-daily regimen and three pills per day. The two regimens performed similarly with regards to all endpoints. At week 48, by intention-to-treat, missing=failure analysis, 68% of triple- and 67% of quadruple-drug treated patients had an HIV-1 RNA <50 copies/ml (P>0.05). On-treatment analysis showed 40/40 (100%) of triple- and 39/40 (97.5%) of quadruple-drug treated patients (P=0.996) had responded to < 50 copies/ml. This pilot study suggests the equivalence between a quadruple NRTI-based regimen and a 2-class triple therapy regimen with the same administrative characteristics.

In 2007, an analysis of viral evolution based on genotypic resistance tests (GRT) from samples collected during non-suppressive first-line therapy with zidovudine + lamivudine + abacavir fixed-dose combination was performed in patients from the Frankfurt HIV cohort with at least 3 months uninterrupted first-line therapy with the triple combination. Patients continued (median of 87 weeks) treatment with the FDC triple combination even with detectable viraemia. After 54 weeks, continuous treatment in the presence of viral replication was associated with a stepwise accumulation of resistance mutations. In the majority of patients selection of M184V was associated with accumulation of thymidine analogue mutations at different rates leading to a substantial loss of active nucleoside analogues, despite continuous virological and immunological benefit when compared with baseline\textsuperscript{18}.

**Treatment-experienced patients**

A Cochrane systematic review\textsuperscript{19} included randomised controlled trials of HIV-infected adult patients administered second-line ART after virologic failure of a first-line regimen. There was insufficient evidence to evaluate second-line therapies for the HIV-1 infected patients who fail first-line treatment with d4T+3TC+NVP, d4T+3TC+ EFV, ZDV+3TC+NVP and ZDV+3TC+EFV. For the authors, current recommendations are based on available resources and results from individualized treatment decisions based on resistance testing and clinician choice.

Another randomised, open-label study\textsuperscript{20} of the AIDS Clinical Trials Group assigned 170 subjects receiving zidovudine/lamivudine/abacavir on ACTG 5095 with HIV-1 RNA < 200 copies/ml to intensify either with tenofovir or efavirenz. Treatment
failure occurred in 31 subjects: 18 (21%) in quadruple nucleosides regimen and 13 (15%) in efavirenz-containing regimen. In more than 88% of subjects HIV-1 RNA remained suppressed to <200 copies/ml and in more than 78% to <50 copies/ml at week 72, without differences by treatment arm. There were no significant differences between the regimens in CD4 cell increases, time to new grade 3/4 adverse events, or adherence.

A randomised, open-label, 24-week pilot study\(^2\) enrolled 36 patients currently receiving an initial regimen of abacavir/lamivudine/zidovudine, twice daily plus efavirenz once daily for at least 6 months with HIV-1 RNA <50 copies/ml for at least 3 months and a screening CD4+ cell count > or = 200 cells/mm\(^3\). Thirty-five patients (97%) completed the study. Participants were randomised to switch to 2 tablets of abacavir/ lamivudine/ zidovudine once daily plus EFV once daily (QD arm) or continue current treatment (BID arm) for 24 weeks. At week 24, HIV-1 RNA <50 copies/ml was achieved for 94% of participants in the QD arm and 89% in the BID arm. Median CD4+ cell count change from baseline was +26 cells/mm\(^3\) for the QD arm and -39 cells/mm\(^3\) for BID arm. So, both arms maintained virologic suppression.

A randomised, open-label, 48-week study\(^3\) was performed in subjects who have received two NRTIs plus a PI or a NNRT or three NTRIs for at least 6 months, with a history of undetectable plasma HIV-1 RNA since initiation of therapy and plasma viral load of <50 HIV-1 RNA copies/ml at screening. The patients were randomised 1:1 to continue their current treatment or to switch to a simplified treatment with a combined tablet containing zidovudine + lamivudine + abacavir (TZV) administered twice daily. At week 48, the proportion of treatment failures in TZV arm (22%) was non-inferior to that observed in continued arm (22%) with a treatment difference stratified by prior ART of 1.2% [CI95%: -10.1- 12.5].

A randomised, open-label, parallel-group, multicenter, formulation-switch study\(^4\) compared one tablet containing abacavir + lamivudine + zidovudine (TZV) versus one tablet containing lamivudine + zidovudine given with one abacavir tablet (COM-ABC) administered twice/day for 24 weeks. Both treatments were clinically equivalents. The intent-to-treat observed analysis at week 24 showed a similar rate of virologic success (83% and 77%, respectively). The intent-to-treat missing = failure analysis showed comparable results. Changes in CD4+ cell count from baseline, overall mean self-reported adherence, and adverse events did not differ significantly between treatments.

An open-label, randomised, non-inferiority study\(^5\) compared co-formulated zidovudine/ lamivudine/abacavir (group 1) vs. co-formulated zidovudine/lamivudine plus nevirapine (group 2) in 134 HIV-1-infected patients receiving successful first-line highly active antiretroviral therapy. By intention-to-treat analysis (switch equals failure), the percentage of virologic suppression <200 copies/ml (<50 copies/ml) at week 48 was 71.0% (65.1%) and 73.0% (63.3%) in groups 1 and 2, respectively (P=0.783).
SAFETY

In TRIZAL study\textsuperscript{22} the incidence of adverse events was similar in patients that continued their current regimens and those that switched to abacavir-lamivudine-zidovudine combination tablet. The incidence of possible hypersensitivity reaction with the tablet combination arm was 10%. Significant reductions in cholesterol and triglyceride plasma levels were observed in the same arm ($P < 0.001$ and $P = 0.006$, respectively).

Based on TRIZAL study, the evolution of clinical lipodystrophy and metabolic abnormalities in patients continuing to receive HAART (n=103) versus patients (n=106) switched to zidovudine + lamivudine + abacavir (TZV) was analyzed after 48 weeks\textsuperscript{23}. One or more symptoms of clinical lipodystrophy were present in 40% in the TZV arm and 50% in HAART arm (difference not significant). After 48 weeks, the prevalence was 28% and 42% respectively ($P =0.03$), and the median number of lipodystrophy symptoms per patient was 2 in the TZV arm and 4 in the continued HAART arm ($P =0.016$). Median decreases in cholesterol levels over the 48-week study period were greater in the TZV arm than in the continued HAART arm. Median triglyceride levels decreased in the TZV arm but increased in the continued HAART arm ($P =0.006$).

In an open-label, randomised, 48-week trial\textsuperscript{14} that compared abacavir plus lamivudine/ zidovudine combination tablet (ABC-COM) vs. indinavir + lamivudine/ zidovudine combination tablet (IDV-COM) in naive-treated HIV-infected patients, significantly more patients on IDV-COM reported drug-related adverse events (87% vs. 65% with ABC/COM; $P < 0.001$); similar proportions discontinued treatment due to adverse events (13% vs. 10%), and a slightly greater proportion in the ABC/COM group reported serious adverse events (13 vs. 8%). About half of the adverse events in the ABC/COM group comprised suspected ABC-related hypersensitivity reactions (overall rate, 6%). Most adverse events were gastrointestinal in nature in both groups.

In the ESS40013 study\textsuperscript{16} drug-related adverse events were more commonly reported for ABC/3TC/ZDV+EFV group than for ABC/3TC/ZDV group (15% vs. 6%). Improvements in total cholesterol, LDL-cholesterol, and triglycerides were observed in the later group.

A study\textsuperscript{24} performed in patients receiving successful first-line HAART therapy showed that 13 and 14 patients in groups 1 (68) and 2 (66), respectively, discontinued therapy due to adverse events. Dyslipidemia improved in both groups, with a higher improvement in LDL-cholesterol ($P= 0.049$) in group 1. Both strategies improved lipid profile.

An international, phase 4, open-label trial\textsuperscript{25} was conducted in 254 antiretroviral-naive HIV-infected out-patients that were randomised to abacavir + lamivudine + zidovudine (TZV) twice daily, lamivudine + zidovudine combination tablet plus nelfinavir twice daily (COM/NFV) and stavudine + lamivudine + nelfinavir twice daily (d4T/3TC/NFV) for 96 weeks to compare the lipid and metabolic effects, efficacy, and safety. Virological and CD4 responses to the treatments were similar in the total population and in the subgroups. At week 96, fasting LDL-cholesterol changed minimally in the TZV group, especially in women and black patients, but increased with d4T/3TC/ FV and COM/NFV ($P < 0.001$ versus TZV). Total cholesterol >200 mg/dl occurred in a smaller proportion of
patients receiving TZV (30%) compared with COM/NFV (50%) or d4T/3TC/NFV (60%; /P/ = 0.005 vs. TZV). High-density lipoprotein (HDL) cholesterol did not change markedly with any treatment. Although triglycerides increased, they changed least in women and Hispanic

patients receiving TZV. Diarrhoea was reported more often in the NFV arms and nausea in the ZDV arms.

A retrospective observational cohort study (n=730) analyzed the safety and effectiveness of abacavir, lamivudine, and zidovudine (ABC/3TC/ZDV) in antiretroviral therapy-naive HIV-infected patients. After a median follow-up of 50.5 weeks, 14.25% patients discontinued therapy because of adverse events and 4.93% had a suspected hypersensitivity reaction to ABC.

A study explored whether exposure to NRTIs (zidovudine, didanosine, stavudine, lamivudine, and abacavir) increases the risk of myocardial infarction in 33,347 HIV-infected individuals enrolled in a large, prospective observational cohort. Using Poisson regression models

the authors quantified the relation between cumulative, recent (currently or within the preceding 6 months), and past use of and development of myocardial infarction in patients enrolled in the D:A:D study. Over 157,912 person-years, 517 patients had a myocardial infarction. The study found no associations between the rate of myocardial infarction and cumulative or recent use of zidovudine, stavudine, or lamivudine. By contrast, recent-but not cumulative-use of abacavir or didanosine was associated with an increased rate of myocardial infarction (compared with those with no recent use of the drugs): relative rate 1.90 (95% CI: 1.47-2.45; /P/=.0001) with abacavir and 1.49 (95%CI: 1.14-1.95; /P/=0.003) with didanosine. Rates were not significantly increased in those who stopped these drugs more than 6 months previously compared with those who had never received these drugs. After adjustment for predicted 10-year risk of coronary heart disease, recent use of both didanosine and abacavir remained associated with increased rates of myocardial infarction. Thus, there exists an increased risk of myocardial infarction in patients exposed to abacavir and didanosine within the preceding 6 months.

In Keiser and Nassar’s opinion the use of alternative regimens, such as triple nucleoside-based regimens, can improve adherence and decrease toxicities associated with protease inhibitor therapy in HIV-infected patients. Administration of abacavir sulfate/lamivudine/ zidovudine also avoids side effects of antiretroviral therapy, such as hyperlipidemia, but its use is associated with a hypersensitivity reaction in a small number of patients.

An equivalence trial comparing abacavir, lamivudine and zidovudine regimen vs. indinavir-containing regimen showed no difference between groups in the frequency of treatment-limiting adverse events or laboratory abnormalities. The most common drug-related adverse events that were of moderate to severe intensity (grades 2-4) included nausea (with or without vomiting), malaise and fatigue, headache, and renal signs and symptoms. Nineteen patients (7%) in the abacavir-lamivudine-zidovudine group and 6 patients (2%) in the indinavir group were identified as having symptoms that were consistent with or similar to a possible abacavir hypersensitivity reaction. In the abacavir-lamivudine-zidovudine group, symptoms generally occurred within 6 weeks of initiating abacavir, and included fever and rash accompanied by gastrointestinal symptoms, such as nausea, vomiting,
and diarrhoea. In the indinavir group, symptoms were less severe, were gastrointestinal in nature, and included rash or fever but not both concurrently. One death in the abacavir group was attributed to hypersensitivity reaction, which occurred following recalling with abacavir, approximately 3 weeks after initiating study treatment.

In predominantly white populations, similar to the one in the PREDICT-1 study, 94% of patients do not carry the HLA-B*5701 allele and are at low risk for hypersensitivity reaction to abacavir.

In a pilot study the safety and tolerability of the four-nucleoside regimen zidovudine/ lamivudine/abacavir and tenofovir) were not significantly different from the efavirenz-containing regimen.

**CONVENIENCE**

The recommended dose of the examined FDC in adults is one tablet twice daily, giving a total daily dose of zidovudine 600 mg, lamivudine 300 mg and abacavir 600 mg. The tablets may be taken with or without food.

In a comparison between a triple nucleoside regimen (abacavir plus lamivudine + zidovudine combination tablet [ABC-COM] twice daily) and a regimen containing the protease inhibitor indinavir 800 mg three times daily plus COM twice daily (IDV-COM), a significantly greater proportion of patients taking ABC-COM were more adherent than those taking IDV-COM (72% vs. 45%; \( P<0.001 \)).

The ESS40013 study showed that a greater proportion of patients receiving ABC/3TC/ZDV in comparison to those receiving ABC/3TC/ZDV+EFV reported perfect adherence at week 96 (88.8% vs. 79.6%; \( P=0.057 \)).

In a pilot study that compared abacavir/lamivudine/zidovudine, twice daily plus efavirenz(EFV) once daily (BD arm) versus abacavir/lamivudine/zidovudine once daily plus EFV once daily (QD arm) the median adherence was slightly higher in the QD arm, although results in both arms showed a broad variability.

**COST, AVAILABILITY AND FEASIBILITY**

In spite of being regulated in a high number of countries in Europe, North America, South America, Caribbean, Asia and Africa, the fixed-dose combination containing AZT+3TC+ABC is scarcely used in resource-limited settings. The improved convenience (one tablet twice daily dosing) and the good results in adherence observed in comparative trials have seemed do not correlate with the real use.

A survey performed in 23 developing countries in 2006 reported that less than 1% of patients were receiving alternate first-line regimens. A second survey in 2007 found that in the 30 countries which responded, 3% of patients were using a first-line regimen. Given that it is estimated that up to 3 million individuals are taking antiretroviral therapy, this suggests that less than 100,000 will be using AZT/3TC/ABC.

Cost of the AZT + 3TC + ABC fixed-dose combination could be responsible for their little impact on ARV programmes in the developing world.
In Brazil abacavir is recommended in the initial therapy only in cases of zidovudine, tenofovir or enteric-coated didanosine intolerance since abacavir higher price does not correlate with proportional benefit in comparison with other options.\(^4\)

Despite substantial progress in 2007, most low- and middle-income countries are still far from achieving universal access goals. Obstacles include weak health care systems, a critical shortage of human resources and a lack of sustainable, long-term funding.\(^31\)

According to 2008 data from the Global Price Reporting Mechanism\(^32\), AZT/3TC/ABC fixed dose combination (300/150/300 mg), 2 tablets per day, costs US$ 852 per patient per year in low-income countries. Comparatively, 3TC+ZDV fixed dose combination (150/300 mg), 2 tablets per day, costs US$ 115 per patient per year. Abacavir 300 mg, 2 tablets per day, recommended as second line ARV medicines for adult treatment, costs US$ 335 per patient per year in low-income countries. If one considers the use of 3TC + ZDV in combined tablet more one tablet of abacavir, twice daily, the total cost will be US$ 450, i.e., almost half than the fixed dose triple combination price. In Brazilian Consensus for Adult and Adolescent ARV Treatment\(^4\) the prices per patient per year are: for abacavir 300 mg, US$ 1,095 and for the combined 3TC + ZDV, US$ 459 with a total of US$ 1,554.

The preferred option for initial treatment AZT 300 mg + 3TC 150 mg (2 combined tablet/day) plus efavirenz 200 mg (3 tablets/day), costs US$ 115 + 207 that equals US$ 322 per patient per year in low-income countries. This is a median price lower than the corresponding price of triple combined fixed dose.

There are no available cost-effectiveness assessments of AZT/3TC/ABC to be applied in resource-poor settings. Given that AZT/3TC/ABC is, at best, non-inferior to comparator antiretroviral regimens, it may be difficult to demonstrate cost-effectiveness.\(^33\)

CONCLUSION

1. Efficacy: The available evidence concerning efficacy of the combination regimen AZT/3TC/ABC is contradictory, either through in clinical randomised trials (with moderate to low methodological quality) and systematic reviews or clinical guidelines. Regarding first-line treatment for naive-treated patients, this short review found one RCT with inferiority results and seven RCTs with non-inferiority results from 2001 to 2007. One of them was performed with the fixed-dose triple combination. The systematic review in naive-treated patient scenario found that AZT/3TC/ABC was virologically inferior to NNRTI and ritonavir-boosted PI-based regimens. Concerning second-line treatment in ARV-experienced adult patients, this short review found four RCTs with equivalence results. Three of them evaluated the fixed-dose triple combination. One of them compare the triple fixed dose combination (TZV) with the double fixed dose combination lamivudine + zidovudine given with one abacavir tablet (COM-ABC), the later option already included in WHO EML. Both treatments were clinically equivalents.

2. Safety: The fixed-dose combination AZT-3TC-ABC caused fewer symptoms of lipodystrophy and presented more favourable lipid profile, but higher incidence of hypersensitivity reaction in comparison to various regimens. Treatment-naive patients experienced more severe adverse events, including nausea, vomiting, malaise, fatigue and headache. A recent study reported an increased rate of
myocardial infarction in association with recent use (within the preceding 6 months) of abacavir but not with zidovudine, or lamivudine.

3. **Convenience:** The use of the triple fixed-dose combination (one tablet) taken twice daily with or without meals induced adherence in a significantly greater proportion of patients.

4. **Cost:** In low-income countries, median prices per patient per year of the fixed-dose triple combination AZT+ 3TC+ ABC (estimated as US$ 852) are higher than those corresponding to AZT+ 3TC (double combination) plus abacavir (estimated as US$ 450). In the same conditions, the price is also higher than the corresponding to the preferred option AZT/3TC/EVZ (US$ 322) for the initial treatment. In resource-poor settings cost is a huge factor that limits drug access, resulting in high rates of new infection and subsequent mortality. Probably the higher cost can account for the scarce use of this FDC in resource-limited settings.

**RECOMMENDATION**

The selection of essential medicines should be based on hierarchical criteria. The first one is efficacy. There is lack of specific and qualified evidence on AZT+3TC+ABC fixed-dose combination efficacy as well as contradictory trial results. The same conflicting or inconclusive data are provided by systematic reviews and clinical guidelines. Additionally, despite acceptable safety in the majority of patients, there is concern about hypersensitivity reactions and increased rate of myocardial infarction associated with abacavir use. The simplified administration, low pill burden and increased adherence do not correlate to its real use in resource-limited settings probably due to its higher comparative cost that accounts for reduced access or to the restricted conditions in which the FDC is needed. Considering the FDC as an alternative in HAART or in second-line ARV therapy that could be substituted by the combination of the three separate products or the addition of ABC to the double FDC of ZDV/3TC, both still existent in the list, I recommend that this fixed-dose combination formulation of zidovudine/lamivudine/abacavir not be added to the EML.
REFERENCES


