Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial

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Summary

Background Our objective was to assess therapeutic non-inferiority of dual treatment with lopinavir–ritonavir and lamivudine to triple treatment with lopinavir–ritonavir plus two nucleos(t)ides for maintenance of HIV-1 viral suppression.

Methods In this randomised, open-label, non-inferiority trial, we recruited patients from 32 HIV units in hospitals in Spain and France. Eligible patients were HIV-infected adults (aged ≥18 years) with HIV-1 RNA of less than 50 copies per mL, for at least 6 months on triple treatment with lopinavir–ritonavir (twice daily) plus lamivudine or emtricitabine and a second nucleos(t)ide, with no resistance or virological failure to these drugs, and no positive hepatitis B surface antigen. Investigators at each centre randomly assigned patients (1:1; block size of four; stratified by time to suppression [<1 year or >1 year] and nadir CD4 cell count [<100 cells per μL or >100 cells per μL]; computer-generated random sequence) to continue triple treatment or switch to dual treatment (oral lopinavir 400 mg and oral ritonavir 100 mg twice daily plus oral lamivudine 300 mg once daily). The primary endpoint was response to treatment in the intention-to-treatment population (all randomised patients) at 48 weeks. The non-inferiority margin was 12%. This study is registered with ClinicalTrials.gov, number NCT01471821.

Findings Between Oct 1, 2011, and April 1, 2013, we randomly assigned 250 participants to continue triple treatment (127 [51%) patients) or switch to dual treatment (123 [49%] patients). In the intention-to-treatment population, 110 (86·6%) of 123 in the dual-treatment group responded to treatment versus 108 (87·8%) of 127 in the triple-treatment group (127 [51%] patients) or switch to dual treatment (123 [49%] patients). In the intention-to-treat population, 110 (86·6%) of 123 in the dual-treatment group (p=0·223).

Interpretation Dual treatment with lopinavir–ritonavir plus lamivudine has non-inferior therapeutic efficacy and is similarly tolerated to triple treatment.

Funding AbbVie and Red Temática Cooperativa de Investigación en Sida.

Introduction Expert guidelines recommend several treatment switch strategies in HIV-infected patients who have achieved virological suppression with triple drug treatment to prevent or resolve toxic effects of drugs or to simplify the antiretroviral regimen.1–3 Most guidelines recommend changing of the triple drug regimen to another triple drug regimen. Findings from the GARDEL trial4 have convincingly shown that in patients who are antiretroviral naive, a dual-treatment regimen consisting of lopinavir–ritonavir plus lamivudine twice daily was non-inferior to a triple drug regimen of lopinavir–ritonavir plus two nucleos(t)ides reverse transcriptase inhibitors in achieving and maintaining virological suppression during 48 weeks of treatment, irrespective of baseline viral load. This result contrasts with that of the dual-treatment regimen of darunavir–ritonavir plus raltegravir in the NEAT001-ANRS143 trial,5 which has not shown non-inferiority to triple treatment in patients with a high baseline viral load, or with the regimen of darunavir–ritonavir plus maraviroc in the MODERN trial,6 which showed inferior virological efficacy to a triple drug regimen, irrespective of baseline viral load. The dual-treatment strategy of atazanavir–ritonavir plus lamivudine as a switch strategy has been tested in a single-arm small pilot clinical trial (ATLAS),7 with positive but inconclusive results, and in two ongoing randomised clinical trials.8,9 No findings from prospective, randomised, controlled clinical trials have shown the

Published Online June 8, 2015
http://dx.doi.org/10.1016/ S1473-3099(15)00096-1
This online publication has been corrected.
The corrected version first appeared at thanlancet.com/specialty on June 22, 2015
See Comment page 748
See Articles page 775
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Evidence before this study

We searched Medline, Embase, Biosis, and Current Contents for randomised controlled trials of dual treatment with ritonavir-boosted protease inhibitor combined with lamivudine in patients that have virologically suppressed HIV infections using the search terms “lopinavir” OR “atazanavir” OR “darunavir” OR “lamivudine” AND “simplification”. We only included reports published in English up to Dec 16, 2014. We identified two reports, the ATLAS and ATLAS-M studies. The ATLAS study is a single-arm pilot study that enrolled 40 patients who were receiving atazanavir–ritonavir plus two nucleos(t)ide reverse transcriptase inhibitors, without previous treatment non-response, with HIV RNA of less than 50 copies per mL for more than 3 months and CD4 of more than 200 cells per μL. Patients were switched to the combination of 300 mg of atazanavir and 100 mg of ritonavir, plus 300 mg of lamivudine, once daily. Results showed at 48 weeks that only one patient discontinued because of virological failure. Increases in total, HDL, and LDL cholesterol, and slight improvement of glomerular filtration rate occurred. ATLAS-M is an open-label, randomised study designed to show non-inferiority of efficacy of treatment simplification to atazanavir–ritonavir plus lamivudine versus maintenance of triple-drug treatment including atazanavir–ritonavir in 266 patients. An interim analysis at 24 weeks including 171 patients supports non-inferiority of the dual-treatment strategy. ATLAS and ATLAS-M results are inconclusive because of their small sample sizes and limited follow-up.

Methods

Study design and participants

In this randomised, open-label, non-inferiority, phase 3 trial that took place at 32 HIV units in hospitals in Spain and France, eligible participants were HIV-infected adults (aged 18 years or older) on a stable antiretroviral regimen consisting of lopinavir–ritonavir twice daily plus lamivudine or emtricitabine plus another nucleos(t)ide reverse transcriptase inhibitors, without previous treatment non-response, with HIV RNA of less than 200 cells per μL for at least the previous 6 consecutive months. Participants in any line of treatment could be enrolled if they did not have previous genotypic tests showing resistance mutations to lopinavir, ritonavir, lamivudine, or emtricitabine. We excluded patients with previous virological failures while receiving a regimen containing lopinavir–ritonavir, lamivudine, or emtricitabine. We also excluded patients with a positive hepatitis B serum surface antigen. Full inclusion and exclusion criteria are listed in the appendix.

We did the study in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the ethics committee of Hospital Universitario La Paz as the reference committee and by all committees from all participating hospitals. Every patient gave written informed consent before undergoing study procedures.

Randomisation and masking

Investigators at each centre randomly assigned eligible participants (1:1) to either switch to dual treatment or remain on triple treatment. We assigned patients to treatment groups by the electronic case report form on completion of the randomisation form. We generated a random sequence with a computer using concealed blocks (block size of four; Onmedic data tool, Onmedic Networks, Barcelona, Spain). We stratified randomisation by time to suppression (less than 1 year or more than 1 year) and nadir CD4 cell count (less than 100 cells per μL or more than 100 cells per μL). We assigned each patient’s identification number from the electronic case report form. The study design was open-label, so participants and investigators were not masked to group allocation.

Added value of this study

By contrast with previous trials, this study was adequately powered to show non-inferiority and patients were followed up for 1 year. This trial shows that in virologically suppressed patients, a dual-treatment regimen of lopinavir–ritonavir twice daily plus lamivudine once daily is non-inferior to a triple-treatment regimen of lopinavir–ritonavir plus two nucleos(t)ide reverse transcriptase inhibitors. Dual treatment was well tolerated and was not associated with an increased risk of resistance development.

Implications of all the available evidence

We did this trial in parallel with SALT, a randomised, open-label, non-inferiority trial, to assess safety and efficacy of switching to dual treatment with a boosted protease inhibitor (atazanavir–ritonavir) plus lamivudine in adults with virologically suppressed HIV. In both studies, switching to dual treatment was non-inferior to continuation of the baseline regimen at maintenance of virological suppression at week 48. The results of these switch trials suggest that dual treatment with lopinavir–ritonavir or atazanavir–ritonavir plus lamivudine is a switch option that is effective and well tolerated for adults with virologically suppressed HIV infections on regimens containing a ritonavir-boosted protease inhibitor plus two reverse transcriptase inhibitors. Results of both trials challenge the need for use of a second nucleos(t)ide to maintain virological suppression if lopinavir–ritonavir (or atazanavir–ritonavir) plus lamivudine are fully active. Dual treatment would avoid the toxic effects associated with abacavir or tenofovir use.
Procedures
Patients who switched to dual treatment received the fixed dose combination of oral lopinavir 400 mg and ritonavir 100 mg twice daily plus lamivudine 300 mg once daily. Post-baseline study visits occurred at weeks 4, 12, 24, 36, and 48. Haematology, serum chemistry, urinalysis, CD4 cell count, and fasting lipid concentrations were done at a designated local laboratory for each study site. The local laboratories needed to meet Clinical Laboratory Improvement Amendments regulations or the country’s equivalent. We measured plasma HIV RNA concentrations using techniques available locally at each site, consisting of branched DNA, nucleic acid sequence-based amplification, and real-time PCR. We did resistance testing in patients with virological failures.

Outcomes
The primary endpoint was the proportion of participants responding to treatment at week 48 in the intention-to-treat population. This endpoint was centrally assessed by the protocol cochairs. Non-response was defined as any of the following: a confirmed (at least 2 weeks apart) plasma viral load of at least 50 copies per mL, death of any cause, progression to a new AIDS-defining disorder, loss to follow-up, or permanent change or interruption of randomised treatment. In secondary efficacy analyses, we assessed the proportion of participants responding to treatment at week 48 in the modified intention-to-treat population. We also analysed the proportion of patients with a virological response (a virological failure was defined as a confirmed [at least 2 weeks apart] plasma viral load of at least 50 copies per mL) or that died or progressed to a new AIDS-defining disorder. Additional secondary endpoints were the proportion of patients with blips (defined as unconfirmed episodes of detectable viral load) or a change in CD4 cell count, and safety and tolerability of the two regimens up to week 48. We assessed safety with laboratory tests, physical examinations, and reporting of adverse events.

Statistical analysis
All analyses were prespecified in the protocol and statistical analysis plan and were done with GraphPad Prism software version 6.01. We did interval estimation for the differences between proportions (triple minus dual treatment) and calculated 95% CIs using the Newcombe-Wilson hybrid score.10 Analyses included all data available after the last enrolled participant had completed the week 48 visit or prematurely discontinued the study drug. We did no interim analysis before week 48. For the primary endpoint, we analysed the intention-to-treat population, including all randomised patients. For a sensitivity analysis, we analysed the primary endpoint in the modified intention-to-treat population, which consisted of participants who were
randomly assigned and treated with at least one dose of study drug, excluding those with a documented prohibited resistance mutation on their historical genotypes or those who withdrew consent. We scrutinised participants in both groups equally and excluded those who violated these major eligibility criteria. We also analysed the proportion of patients with blips or blips and virological failures in those who completed treatment, censoring patients lost to follow-up and discontinuations due to non-virological reasons. For the primary efficacy analysis, non-inferiority would be established if the upper bound of a two-sided 95% CI for the difference in proportions (triple minus dual treatment) of participants responding to treatment at week 48 was lower than 12%. We chose a 12% non-inferiority margin on the basis of similar trials of switching antiretrovirals in aviraemic HIV-infected patients.11–14

The original sample size estimation was 336 patients. We calculated this sample size to provide 80% power to establish non-inferiority for the primary endpoint, with an assumed response of 85% in both groups, non-inferiority margin of –12%, and a 10% loss to follow-up. Recruitment was originally planned for 1 year. After we extended recruitment for an additional 6 months, we did not achieve the planned sample size. The trial Steering Committee recalculated sample size with a re-estimation of initial assumptions without assessing response rates during the trial. We took into account that the original sample size calculation had included 26 more patients than was necessary because original assumptions needed only 310 patients. We also considered efficacy results of other simplification trials11,12 and the fact that the noted rate of loss to follow-up during the trial was considerably lower than was expected. We backcalculated that 250 patients would still provide at least 80% power to establish non-inferiority for the proportion of participants without therapeutic failure at week 48, with an assumed response rate of 88% in both groups, and 8% losses to follow-up (StudySize; Creostat HB, Västra Frölunda, Sweden). The trial Steering Committee deemed these assumptions realistic and so we stopped recruitment after 250 patients were randomly allocated.

We based safety analyses on count regression models. We estimated standard Poisson and negative binomial models, and the corresponding zero-inflated regression models. We used the Bayesian (Schwarz) information criteria and Vuong test to choose between models.

Figure 2: Outcomes at 48 weeks
(A) Proportion of responders in the ITT population and reasons for absence of response. (B) Therapeutic and virological response (triple treatment minus dual treatment) in the mITT and ITT populations, and in those who completed treatment. The dashed lines represent no difference and the 12% non-inferiority margin. (C) Patients with protocol-defined VF or blips. ITT=intention-to-treat. mITT=modified intention-to-treat. VF=virological failure.
Role of the funding source

Fundació Clinic per a la Recerca Biomèdica sponsored the trial. AbbVie and Red Temàtica Cooperativa de Investigacion en SIDA funded the trial. AbbVie participated in study design and writing of the report, but not in management of the trial. All operational aspects of the study, consisting of study design, monitoring, data collection, data analysis, and writing of the report, were managed by Fundació Clinic per a la Recerca Biomèdica. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Oct 1, 2011, and April 1, 2013, we screened 360 patients, randomly assigning 250 (69%)—123 (49%) to dual treatment and 127 (51%) to triple treatment (figure 1). 239 (96%) patients received at least one dose of study treatment—118 (49%) in the dual-treatment group and 121 (51%) in the triple-treatment group. Baseline characteristics were balanced between study groups (table 1).

At week 48, the proportion of patients in the triple-treatment group with treatment response in the intention-to-treat population was 110 (86·6%) of 127 compared with 106 (87·6%) of 121 in the triple-treatment group (difference 0·3% [95% CI –8·3 to 8·9]; p=0·90). The number of patients with protocol-defined virologic response in those who completed treatment was 108 (87·8%) of 123 in the dual-treatment group and 103 (87·3%) of 118 in the dual-treatment group (difference 0·5% [95% CI –5·1 to 5·3]; p=0·70; figure 2 and appendix). 12 (10%) of 113 in the triple-treatment group (difference <0·1% [95% CI –4·3 to 4·4]; p=0·90) had virological response in those who completed treatment—5 (4%) of 123 in the dual-treatment group and 40 cells per μL (SD 254) in the triple-treatment group. Resistance testing showed wild-type virus in three patients (two in the dual-treatment group and one in the triple-treatment group). In one patient in the dual-treatment group, we detected the 103Asn and 184Val resistance mutations in the reverse transcriptase gene. This patient had a previous history of non-adherence to antiretroviral treatment with tenofovir, lamivudine, and efavirenz. Before entering the study, the patient had remained suppressed for 7 months while receiving lopinavir–ritonavir plus tenofovir and lamivudine. Retrospective testing of a saved sample showed that the 103Asn, 181Cys, and 184Val mutations were present before treatment with tenofovir, lamivudine, and efavirenz was stopped.

Most patients had at least one adverse event—63 (53%) of 118 in the dual-treatment group and 70 (58%) of 121 in the triple-treatment group in the modified intention-to-treat population, of whom five (4%) in the dual-treatment group and eight (7%) in the triple-treatment group had serious adverse events (table 2). One (1%) patient in the dual-treatment group (Fanconi syndrome) had serious adverse events (table 2). One (1%) patient in the dual-treatment group (Fanconi syndrome) had serious adverse events (table 2).
and four (3%) in the triple-treatment group (increased bone metabolic markers, hip aseptic necrosis, osteopenia and renal tubulopathy, and worsening of renal function) discontinued the study drug because of adverse events. The most frequent adverse events occurring in at least 5% of patients were digestive, muscular or skeletal, respiratory, and dermatological, and were similar between groups. No deaths or AIDS-defining events occurred during the trial. Grade 3 or 4 laboratory adverse events were few and similar in both groups. We noted a small but significant increase of total and LDL cholesterol concentrations in the dual-treatment group at 48 weeks compared with the triple-treatment group (figure 3). We noted a small but significant increase in estimated glomerular filtration rate (Modification of Diet in Renal Disease equation) in the dual-treatment group compared with the triple-treatment group.

Discussion

Dual treatment with lopinavir–ritonavir plus lamivudine seems to be an effective and tolerable simplification regimen for patients with virologically suppressed HIV infections receiving lopinavir–ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor when compared with continuation of this triple treatment. The patients in this trial had no history of virological failure to regimens containing the protease inhibitors lamivudine or emtricitabine, or previously recorded resistance mutations to lopinavir–ritonavir or lamivudine.

By contrast with protease inhibitor monotherapy studies,11,13,14 patients receiving dual treatment in this study did not have an increased incidence of low-level viraemia. Almost the same proportion of patients had pure virological failure, blips, or both events combined in both treatment groups, clearly showing non-inferiority of dual treatment to triple treatment. Addition of only lamivudine is able to get rid of the increased episodes of low-level viraemia noted with protease inhibitor monotherapy.

One of the concerns of use of dual treatment including lamivudine is a possible increased risk of resistance selection due to the low genetic barrier of lamivudine. In our study, the incidence of resistance development was very low, with lamivudine resistance developing in only one patient randomly assigned to the dual-treatment group. These results suggest that the risk of resistance development in patients who are aviraemic and switch to lopinavir–ritonavir plus lamivudine is not significantly increased by switching, at least during the first year of follow-up. An added advantage of use of coformulated lopinavir–ritonavir is that selective non-adherence (not taking ritonavir) is avoided, a fact that might decrease the risk of resistance development. We recognise that longer follow-up is needed than was done in our study before an increased risk of resistance development in patients receiving dual treatment is completely ruled out.

We noted small differences between treatment groups in safety variables. As expected, total and LDL cholesterol significantly increased in the dual-treatment group compared with the triple-treatment group. These results were because 60% of patients in the dual-treatment group switched away from a tenofovir-containing regimen. Tenofovir has a lipid-lowering effect,15 so patients randomly assigned to dual treatment who stopped tenofovir had an increase in their lipid concentrations. Although differences were small, we noted an increase in estimated glomerular filtration rate in patients who stopped tenofovir in the dual-treatment group. In terms of other adverse events, we noted no significant differences between groups. Because we enrolled patients who were already tolerating lopinavir–ritonavir, and patients in the dual-treatment group stopped two well tolerated nucleos(t)ides (abacavir or tenofovir), we did not expect substantial differences between groups.

Figure 3: Change from baseline at 48 weeks in (A) cholesterol, cholesterol fractions, and triglycerides, and (B) eGFR

Error bars are SDs. eGFR=estimated glomerular filtration rate. HDL-C+HDL cholesterol. LDL-C+LDL cholesterol. TG=triglyceride.
Our results extend findings of the GARDEL clinical trial 1 that showed that, in patients that are antiretroviral naive, dual treatment with lopinavir–ritonavir plus lamivudine was non-inferior to triple treatment with lopinavir–ritonavir plus two nucleos(t)ide reverse transcriptase inhibitors, irrespective of baseline viral load. By contrast with GARDEL, in which 54% of the patients received zidovudine in the triple-treatment group, most patients in the triple-treatment group in this trial received either tenofovir or abacavir. Therefore, our results are not skewed by a relatively poorer tolerance of the nucleos(t)ide reverse transcriptase inhibitors in the control group than in the treatment group. Our results are supported by similar findings in the SALT2 and ATLAS3 studies, which explored a dual-treatment combination—atazanavir–ritonavir plus lamivudine—as a switch strategy in patients who were virologically suppressed.

The other difference from GARDEL is that in our trial, lamivudine was given once daily instead of twice daily. Although the area under the curve at 24 h and maximum concentration of the once-daily and twice-daily regimens are bioequivalent to lamivudine triphosphate, lamivudine triphosphate trough concentration is slightly lower with the once-daily dosing than with the twice-daily dosing.6 Low trough concentrations could be theoretically more important in the context of a dual treatment than of a triple-treatment regimen. However, our results clearly support the use of once-daily lamivudine in the setting of suppressed viral replication.

Our study is limited by its open-label design, which could lead to bias. However, because both groups of patients were already receiving lopinavir–ritonavir at baseline, and the daily number of tablets in most patients did not change after randomisation, the open-label design should not majorly affect trial results. Masking would pose the added difficulty of having placebos for six different nucleos(t)ide combinations. Although the trial did not reach the original sample size target, the 250 enrolled patients provided enough power to prove non-inferiority of the dual-treatment group on the basis of more precise assumptions of efficacy and losses to follow-up. Differences between groups in the primary endpoint were small enough that in the main and supportive sensitivity analyses, we clearly demonstrated non-inferiority. Another limitation was that in two of the six patients who had virologic failure, virus could not be amplified.

Our results are important because the excellent efficacy achieved by the dual-treatment group challenges the need to use two nucleos(t)ides when a patient is receiving fully active lopinavir–ritonavir. Although we have not shown safety advantages of the dual-treatment strategy in the context of a 48 week trial, a strategy that avoids use of tenofovir and abacavir would be beneficial in the long term with respect to bone, renal, and possibly cardiovascular toxic effects. Additionally, because lamivudine is already generic, the dual-treatment strategy could be more cost-effective, and a coformulation would be attractive. The strategy of dual treatment is only applicable to settings with access to virological monitoring. Whether this strategy could lead to more resistance development in low-income countries without frequent access to virological monitoring remains unclear. The other remaining issue is the role of the dual combination of lopinavir–ritonavir plus lamivudine versus other nucleoside-sparing combinations, including drugs with an a-priori better safety profile, such as dual treatment with dolutegravir and rilpivirine.2

Contributors
JRA, JMG, and JP designed the study. JRA and JMG oversaw the study, reviewed and interpreted analyses of data, and wrote the first draft of the report. All authors enrolled patients, collected data, amended the report, and approved the final version.

OLE/IRIS-EST12 study team

Declaration of interests
JRA reports personal fees from Fundación Clinica per a la Recerca Biomèdica during the conduct of the study and from ViV, Tibotec, Janssen, AbbVie, Bristol-Myers Squibb, Gilead, and Merck Sharp and Dohme outside the submitted work. P-MG has received research grants from Bristol-Myers Squibb and Janssen, and consulting fees from Gilead and ViV. JM has received research grants from AbbVie, Bristol-Myers Squibb, Janssen, Merck Sharp and Dohme, and ViV. VE reports personal fees from Janssen, AbbVie, and Merck Sharp and Dohme, and grants from Bristol-Myers Squibb, and grants and personal fees from Gilead, outside the submitted work. JP reports grants from AbbVie during the conduct of this study and payments for lectures and educational programmes from AbbVie, Gilead, ViV, Merck Sharp and Dohme, and Janssen-Cilag outside the submitted work. FD has received personal fees and non-financial support from AbbVie, Gilead.
ViV, Merck Sharp and Dohme, and Bristol-Myers Squibb. FP has received a grant from Fundación Clínica per a la Recerca Biomèdica during the conduct of this study and personal fees from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp and Dohme, and ViV outside the submitted work. MM-R has received consulting fees from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp and Dohme, Pfizer, and ViV. HK has received personal fees and non-financial support from AbbVie, Gilead, ViV, Janssen, Merck Sharp and Dohme, and Bristol-Myers Squibb. LW has received personal fees from Bristol-Myers Squibb, Gilead, and Merck Sharp and Dome, and grants from ViV, Janssen-Cilag, GlaxoSmithKline, Bristol-Myers Squibb, and Gilead. JMG has received a research grant for his institution from AbbVie during the conduct of this study, personal fees from AbbVie, and grants and personal fees from Merck Sharp and Dohme, Gilead, Janssen, and Bristol-Myers Squibb. All other authors declare no competing interests.

Acknowledgments

This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie. This work was supported by research grants from Red Temática Cooperativa de Investigación en Sida G03/173 (RIS-EST13) and AbbVie.