Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial

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Summary

Background Daily oral triple therapy is effective at halting HIV disease progression, but can have toxic effects and is costly. We investigated whether dual therapy with lopinavir and ritonavir plus lamivudine is non-inferior to standard triple therapy.

Methods The GARDEL study (Global AntiRetroviral Design Encompassing Lopinavir/r and Lamivudine *vs* LPV/r based standard therapy) is a 48 week, phase 3, randomised, controlled, open-label, non-inferiority trial in antiretroviral-therapy-naive adults (age ≥18 years) with documented HIV-1 RNA viral load of at least 1000 copies per mL. The study was done at 19 centres in six countries. Patients were randomly assigned (1:1) to dual therapy or triple therapy by sealed envelopes, in blocks of four, stratified by baseline viral load (<100 000 *vs* ≥100 000 copies per mL). Dual therapy consisted of lopinavir 400 mg and ritonavir 100 mg plus lamivudine 150 mg, both twice daily. Triple therapy consisted of lopinavir 400 mg and ritonavir 100 mg twice daily and lamivudine or emtricitabine plus another nucleoside reverse transcriptase inhibitor (NRTI) in fixed-dose combination. Efficacy was analysed in all participants who received at least one dose of study drug. The primary endpoint was virological response rate, defined as the proportion of patients with HIV RNA less than 50 copies per mL at 48 weeks. Dual therapy was classed as non-inferior to triple therapy if the lower bound of the 95% CI for the difference between groups was no lower than –12%. Patients and investigators were unmasked to treatment allocation. This study is registered with ClinicalTrials.gov, number NCT01237444.

Findings Between Dec 10, 2010, and May 15, 2012, 217 patients were randomly assigned to the dual-therapy group and 209 to the triple-therapy group. 198 patients in the dual-therapy group and 175 in the triple-therapy group completed 48 weeks of treatment. At week 48, 189 patients (88·3%) in the dual-therapy group and 169 (83·7%) in the triple-therapy group had viral response (difference 4·6%, 95% CI –2·2 to 11·8; p=0·171). Patients with baseline viral load of at least 100 000 copies per mL showed similar results (87·2% *vs* 77·9%, respectively; difference 9·3%, 95% CI –2·8 to 21·5; p=0·145). Toxicity-related or tolerability-related discontinuations were more common in the triple-therapy group (n=10 [4·9%]) than in the dual-therapy group (n=1 [0·4%]; difference 4·5%, 95% CI –8·1 to –0·9; p=0·011). 65 adverse events in the dual-therapy group and 88 in the triple-therapy group were possibly or probably drug related (p=0·007). Two serious adverse events occurred, both in the dual-therapy arm, one of which (a case of gastritis) was reported as possibly or probably related to drug treatment.

Interpretation Dual therapy with lopinavir and ritonavir plus lamivudine regimen warrants further clinical research and consideration as a potential therapeutic option for antiretroviral-therapy-naive patients.

Funding Fundación Huésped and AbbVie.

Introduction

The present standard of antiretroviral therapy (ART) consists of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third active drug, which effectively controls viral replication.[1–4] NRTI exposure is associated with tolerability and toxicity issues, such as anaemia, gastric disturbances, and lipoatrophy (zidovudine); hypersensitivity reaction (abacavir); and renal and bone impairment (tenofovir).[5,6] Mitochondrial toxicity and lactic acidosis have also been reported, mainly with drugs that are no longer recommended, such as stavudine and didanosine.[7] Lamivudine is an NRTI without major side-effects.[7] There has been interest in using boosted protease inhibitor monotherapies as part of initial and switch strategies, on the basis of their high barrier to resistance and to reduce costs and toxicity. Data show that this treatment is not as effective as triple therapy, because it is associated

with reduction in viral suppression and increased intermittent viraemia and leads to higher rates of protease inhibitor resistance compared with triple therapy in treatment-naive patients.[8]

The coformulation of lopinavir and ritonavir is a potent HIV-1 protease inhibitor with a high barrier to resistance.[9–11] Lamivudine is a potent cytidine nucleoside analogue; however, as a monotherapy it quickly selects for resistance, because of a low-barrier single point mutation that reduces antiviral activity.[12] In the context of triple therapy that includes lopinavir and ritonavir, the selection of lamivudine resistance mutations is rare.[11]

Findings from a small pilot study of dual therapy with lopinavir and ritonavir plus lamivudine for treatment of ART-naive HIV-infected patients[13] prompted us to do a fully powered, non-inferiority, randomised clinical trial to assess the efficacy of lopinavir and ritonavir plus lamivudine (dual therapy) compared with lopinavir and ritonavir plus two NRTIs (triple therapy).

Methods

Study design and patients

The GARDEL study (Global AntiRetroviral Design Encompassing Lopinavir/r and Lamivudine *vs* LPV/r based standard therapy) is a 48 week, phase 3, randomised, controlled, open-label, non-inferiority, multicentre, international trial comparing the safety, tolerability, antiviral activity, and emergence of resistance with a dual-therapy regimen of lopinavir and ritonavir plus lamivudine versus a triple-therapy regimen of lopinavir and ritonavir plus lamivudine or emtricitabine plus one other, investigator selected, NRTI among ART-naive, HIV-1-infected patients. The study was done at 19 centres in six countries: Argentina, Chile, Mexico, Peru, Spain, and the USA.

Patients were eligible for enrolment if they were infected with HIV-1, were at least 18 years old, were naive to ART, had a plasma HIV RNA viral load of at least 1000 copies per mL at screening, were hepatitis B surface antigen negative, were in good general medical health, were not pregnant and were willing to use two contraceptive methods, did not have abnormal laboratory results (appendix), and did not have alcohol or substance misuse.

Patients were excluded if they were pregnant or breastfeeding; had HIV-2 infection; had moderate or severe hepatic impairment; had any clinically significant active disease; and had any medical history or physical examination findings (including active AIDS-associated opportunistic diseases within 30 days after screening) that, in the investigator's opinion, might risk the patient's safety, the results of the study, or protocol adherence. Additionally, patients were excluded if laboratory results at screening showed a haemoglobin concentration of 80 g/L or lower, absolute neutrophil count of $0{\cdot}75\times10^9$ cells per L or lower, platelet count of 50×10^9/L or lower, or creatinine concentration at least 1·5 times higher than the upper limit of normal. No eligibility restrictions were based on CD4 cell count. Patients who had evidence of resistance to lopinavir and ritonavir, lamivudine and emtricitabine, or other NRTIs at screening visit on the basis of the 2009 International Antiviral Society USA (IAS-USA) resistance list were deemed ineligible. Resistance to lopinavir and ritonavir was defined by the presence of two or more minor protease inhibitor mutations or any of the following major protease inhibitor mutations: Val32Ile, Ile47Val/Ala, Leu76Val, and Val82Ala/Phe/Thr/Ser.[14]

The protocol was designed by a protocol writing committee that included investigators and funders. The study was approved by the institutional review board at

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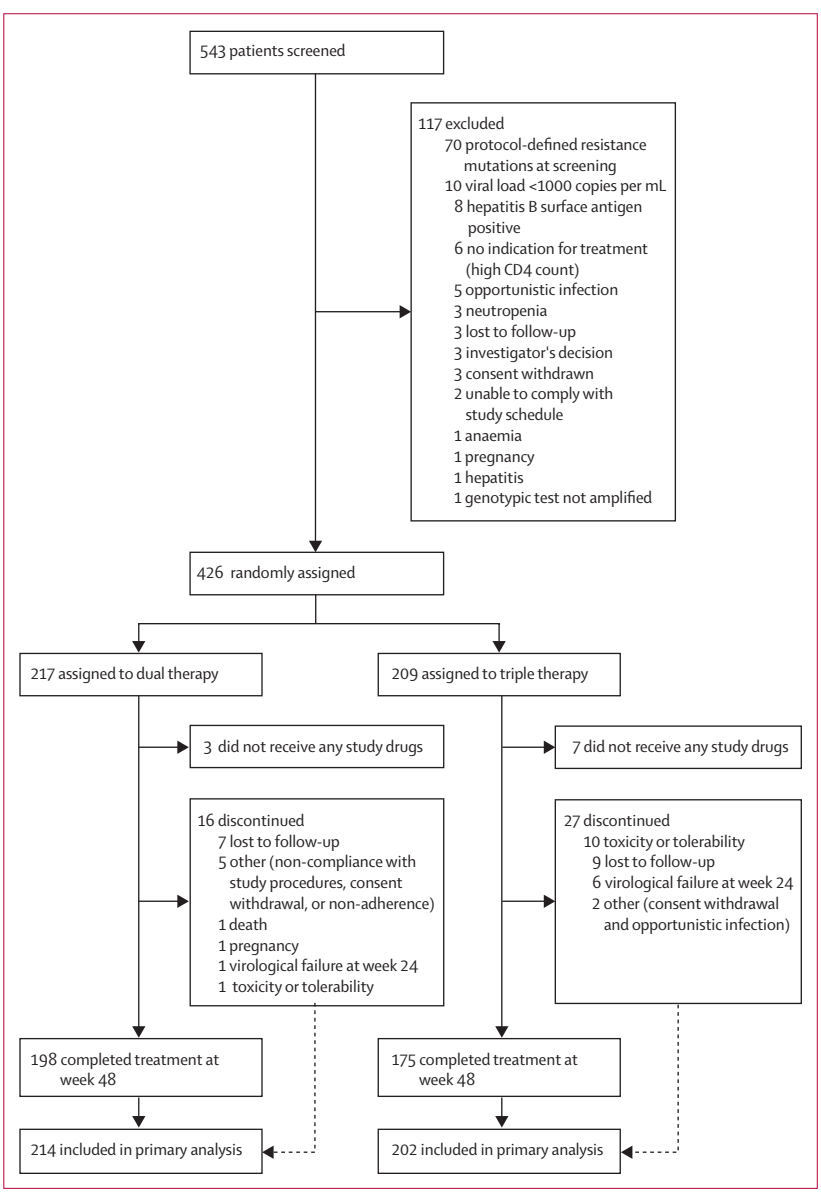

Figure 1: **Trial profile**

each participating centre. Ethics committee approval was obtained at all participating centres in accordance with the principles of the 2008 Declaration of Helsinki. Every patient gave written informed consent before undergoing study procedures.

Randomisation and masking

Randomisation was stratified according to baseline viral load (<100 000 *vs* ≥100 000 copies per mL). Participants were randomly assigned (1:1) by the study statistician to receive either the double or triple treatment regimen, in blocks of four, by centre, by a central computer-generated randomisation table, with allocation distributed in consecutive sealed opaque envelopes. Dual therapy consisted of lopinavir 400 mg and ritonavir 100 mg plus lamivudine 150 mg, both twice daily. Triple therapy consisted of lopinavir 400 mg and ritonavir 100 mg twice daily and lamivudine or emtricitabine plus another NRTI in fixed-dose combination, including zidovudine and lamivudine, abacavir and lamivudine, or tenofovir and emtricitabine. The NRTI backbone in the triple-therapy group was selected by each site investigator, on the basis of local guidelines and practices during the enrolment period (2010–12).

The study was open label; thus, patients and investigators were unmasked to treatment allocation. The study statistician and the data safety and monitoring board (DSMB) members were masked to treatment allocation throughout the study.

	Dual therapy (n=214)	Triple therapy (n=202)
Age (years)	34 (19–67)	35 (18–68)
Sex		
Men	179 (84%)	168 (83%)
Women	35 (16%)	34 (17%)
Ethnic origin		
Hispanic or Latino	152 (71%)	149 (74%)
Not Hispanic or Latino	62 (29%)	53 (26%)
Region		
Europe	18 (8%)	13 (6%)
USA	22 (10%)	24 (12%)
Latin American	174 (81%)	165 (82%)
Mode of transmission		
Men who have sex with men	132 (62%)	119 (59%)
Heterosexual	74 (35%)	75 (37%)
Other	8 (4%)	8 (4%)
HIV RNA (log 10 copies per mL)	4·87 (IQR 4·30–5·35)	4·87 (IQR 4·34–5·33)
HIV RNA count (copies per mL)		
≥100 000	94 (44%)	86 (43%)
<100 000	120 (56%)	116 (57%)
Baseline CD4 count (cells per μL)*	319 (IQR 215–422)	329 (IQR 226–414)
CD4 count (cells per μL)		
≤100	12 (6%)	12 (6%)
>100 to ≤200	33 (15%)	26 (13%)
>200 to <500	139 (65%)	136 (67%)
≥500	29 (14%)	26 (13%)
Missing	1 (<1%)	2 (1%)
HIV subtype		
B	145 (68%)	130 (64%)
BF	27 (13%)	25 (12%)
Other	42 (20%)	47 (23%)
Previous AIDS-defining illnesses	6 (3%)	6 (3%)
Background nucleoside reverse transcriptase inhibitors		
Abacavir and lamivudine	NA	19 (9%)
Tenofovir and emtricitabine	NA	74 (37%)
Zidovudine and lamivudine†	NA	109 (54%)

Data are median (range), n (%), or median (IQR). Some percentages do not total 100 because of rounding. NA=not applicable. *Data missing for one patient in the dual therapy group and two patients in the triple-therapy group. †Two patients changed zidovudine and lamivudine to tenofovir and emtricitabine because of anaemia and continued on the study.

Table 1: **Demographics and baseline disease characteristic**

Procedures

Patients were assessed at screening, day 1 (baseline), and weeks 4, 8, 12, 24, 36, and 48, or at early termination. HLA-B*5701 screening was done if abacavir use was planned in patients assigned to the triple-therapy group; a positive result was classed as an exclusion criterion. Clinical assessments were done, and blood or urine samples, or both, were collected at every assessment visit except week 8. Adherence was assessed by pill count and by self-administered adherence questionnaires at every assessment visit except the final or follow-up visit. Resistance testing was done at screening and upon the development of confirmed protocol-defined virological failure.

Virological failure was defined as two consecutive quantitative viral loads (≥7 days and not >30 days apart) greater than 400 copies per mL at week 24 or thereafter or 50 copies per mL or higher at week 48. Viral load tests that were done by the Roche Taqman assay (Indianapolis, IN, USA) and results between 50 copies per mL and 400 copies per mL needed confirmation by another viral load assay to be regarded as true virological failure. Patients with confirmed virological failure were discontinued from the study. In the triple-therapy group, changes in the NRTI backbone (except lamivudine or emtricitabine) because of toxicity were allowed and patients remained on study and were not counted as treatment failures.

All laboratory tests 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. Plasma HIV-RNA concentrations were measured using either the Abbott RealTime HIV-1 assay (Abbott Molecular, Des Plaines, IL, USA), Roche Amplicor assay (Roche Molecular Systems, Branchburg, NJ, USA), or COBAS-TaqMan Assay (HIV-1 Test, version 2.0, Indianapolis, IN, USA), according to availability at each

site. Each site used the same assay across the study period. Samples have been stored on site and will be shipped to the coordinating centre after the end of the extension study at 96 weeks.

Genotypic assays used were PhenoSense HIV assay (Monogram Biosciences, San Francisco, CA, USA), ViroSeq HIV-1 (ViroSeq HIV-1 Genotyping System version 2.0; Celera, Alameda, CA, USA), and TRUGENE HIV-1 Genotyping Assay (Siemens Healthcare Diagnostics, Munich, Germany), according to availability at each site.

An independent DSMB reviewed the study results in real time every 6 months. Their assessment included safety and efficacy data comparisons between arms.

Outcomes

The primary endpoint was virological response rate, defined as proportion of participants with plasma viral load less than 50 copies per mL at 48 weeks. Virological efficacy was assessed with the US Food and Drug Administration snapshot algorithm (patients with missing data are classed as non-responders and are further classified on the basis of reasons for missing data).[15]

Secondary endpoints were safety; tolerability; change in CD4 cell count; lipid profile (not reported in this manuscript); proportion of patients with plasma HIV-1 RNA concentration less than 400 copies per mL at week 24 and week 48 and less than 50 copies per mL at week 24; emergence of resistance mutations at time of virological failure; treatment interruptions and duration (not reported in this manuscript); rationale for premature study withdrawal; frequency, type, and severity of adverse events; changes in quality of life (not reported in this manuscript); laboratory abnormalities (by the Division of AIDS grading scale); frequency of opportunistic infections; pharmocoeconomics (not reported in this manuscript); and disease progression and death.

Statistical analysis

Dual therapy was deemed non-inferior to triple therapy if the lower bound of the 95% CI for the difference between groups, those receiving dual therapy minus those receiving triple therapy, for the primary endpoint was no lower than –12%. Assuming a response rate of 75% at week 48 for the comparator regimen, and an α of 0·05, the planned sample size of 410 patients provided the study with 80% power to show the non-inferiority of the dual therapy regimen.

Efficacy was analysed in the intention-to-treat exposed population (ie, all participants who received at least one dose of study drug). We also did several sensitivity analyses: an observed data analysis, which excluded patients with missing data; an intention-to-treat analysis in which non-completers were classed as treatment failures; an intention-to-treat analysis in which missing data were classed as treatment failures; and an intention-to-treat and last-observation-carried-forward analysis. Also, patients with a baseline viral load greater than 100 000 copies per mL were assessed in an intention-to-treat analysis (appendix).

Between-group differences with respect to the primary outcome were assessed with the χ^2 statistic and the relative risk with 95% CIs. Multiple logistic regression models were used to adjust the between-group differences for potential confounders including patient's age and baseline characteristics. The student's *t* test for independent samples was used to assess between-group differences with respect to the mean change in viral load and CD4 cell counts between the baseline and final assessments.

This study is registered with ClinicalTrials.gov, number NCT01237444.

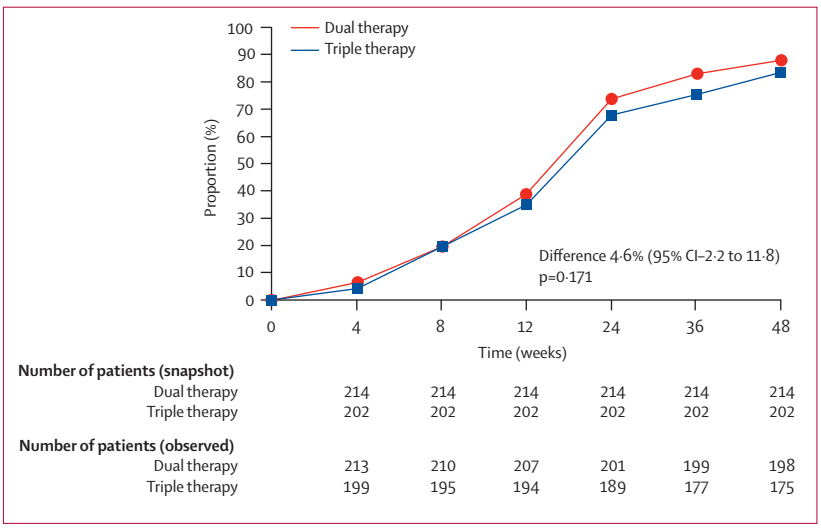

Figure 2: **Proportion of patients with plasma HIV-1 RNA less than 50 copies per mL**
Analysis included all participants randomly assigned to treatment groups who received at least one dose of study drug.

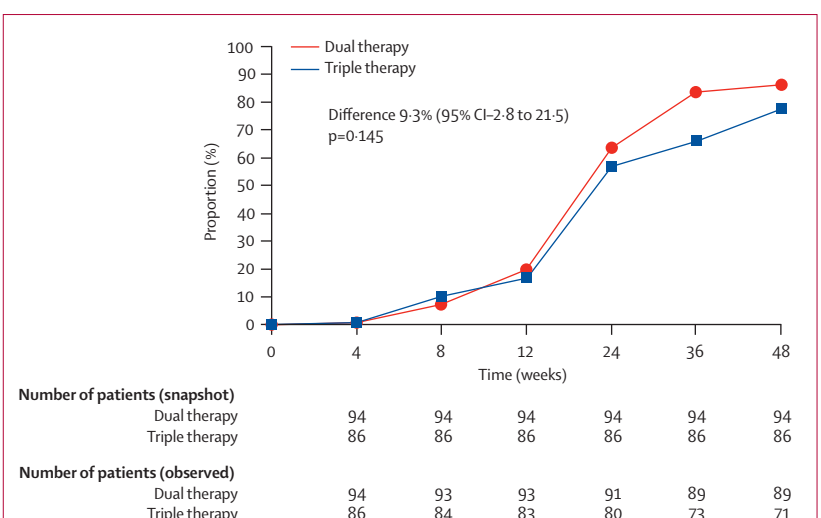

Figure 3: **Proportion of patients with plasma HIV-1 RNA less than 50 copies per mL and with a baseline viral load of at least 100 000 copies per mL**
Analysis included all participants randomly assigned to treatment groups who received at least one dose of study drug.

	Viral load <50 copies per mL at week 48(%)		Difference (95% CI)	p value
	Dual therapy (n=214)	Triple therapy (n=202)		
ITT, exposed, snapshot (n=416)	189 (88·3%)	169 (83·7%)	4·6% (–2·2 to 11·8)	0·171
ITT, exposed, snapshot, baseline viral load ≥100 000 copies per mL (n=180)	82/94 (87·2%)	67/86 (77·9%)	9·3% (–2·8 to 21·5)	0·145
Last observation carried forward, exposed (n=416)	195/214 (91·1%)	176/202 (87·1%)	4·0% (–2·5 to 10·5)	0·245
Observed (n=373)*	189/198 (95·5%)	169/175 (96·6%)	–1·1% (–5·6 to 3·4)	0·777

ITT=intention to treat. *Excludes patients with missing data.

Table 2: **Proportion of patients with HIV-1 RNA viral load less than 50 copies per mL at 48 weeks using different analyses**

Role of the funding source

The study was sponsored by Fundación Huésped. Trial funding was provided by AbbVie. AbbVie participated in the study design and writing of the report. All operational aspects of the study, including study design, monitoring, data collection, data analysis, and writing of the report were managed by Fundación Huésped. All authors had full access to all the data in the study and are responsible for the veracity and completeness of the data reported. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Dec 10, 2010, and May 15, 2012, 543 patients were screened, and 426 were randomly assigned: 217 to dual therapy and 209 to triple therapy (figure 1). 416 patients received at least one dose of study drug: 214 in the dual-therapy group and 202 in the triple-therapy group. Baseline characteristics were balanced between treatment groups (table 1). NRTIs used in the triple-therapy arm in order of frequency were zidovudine and lamivudine (54%), tenofovir and emtricitabine (37%), and abacavir and lamivudine (9%).

The proportion of patients in the dual-therapy group who reached the primary efficacy endpoint at 48 weeks was non-inferior to that in the triple-therapy group (figure 2): 189 patients (88·3%) in the dual-therapy group and 169 (83·7%) in the triple-therapy group had viral loads less than 50 copies per mL at 48 weeks (difference 4·6%, 95% CI –2·2 to 11·8; p=0·171). Patients with a baseline viral load of at least 100 000 copies per mL showed similar results (dual therapy 87·2% *vs* triple therapy 77·9%; difference 9·3%, 95% CI –2·8 to 21·5; p=0·145; figure 3). Planned sensitivity analyses confirmed these findings (table 2). There was a higher rate of discontinuations in the triple-therapy arm than in the dual-therapy arm (table 3). When the comparison was limited to the patients treated with tenofovir-based or abacavir-based NRTIs, 189 (88·3%) of 214 patients in the dual-therapy group and 83 of 93 (89·2%) in the triple-therapy group had viral load less than 50 copies per mL at week 48 (difference –0·9 [95% CI –9·3 to 7·5; p=0·968]). Median increases in CD4 count from baseline to week 48 were 227 cells per µL (IQR 115–330) in the dual-therapy group and 217 cells per µL (87–316) in the triple-therapy group (p=0·625).

22 participants had protocol-defined virological failure: ten (4·7%) in the dual-therapy group and 12 (5·9%) in the triple-therapy group (difference –1·3 [95% CI –6·1% to 3·5; p=0·720]). Seven virological failures were confirmed at week 24 (one in the dual-therapy group and six in the triple-therapy group) and 15 at week 48 (nine in the dual-therapy group and six in the triple-therapy group). Of these 22 patients, viral replication was never suppressed in ten (two in the dual-therapy group and eight in the triple-therapy group) and 12 were rebounders (eight in the dual-therapy group and four in the triple-therapy group; appendix).

Median quantitative plasma viral load at the time of virological failure was 236 copies per mL (IQR 183–17 687) in the dual-therapy group and 1027 copies per mL (IQR 123–4880) in the triple-therapy group. 12 of 22 samples from study participants were successfully amplified (five in the dual-therapy group and seven in the triple-therapy group). In two patients in the dual-therapy group the Met184Val mutation was present at treatment failure. None of the amplified samples at treatment failure in the triple-therapy group showed any resistance mutations. Mutations associated with protease inhibitors were not identified in either arm.

Most patients experienced at least one adverse event over the 48-week study period. 1376 adverse events were

	Dual therapy (n=214)	Triple therapy (n=202)
Virological non-response	25 (12%)	33 (16%)
Data in window not <50 copies per mL (virological failure at week 48)	9 (4 %)	6 (3%)*
Discontinued because of insufficient viral load response (virological failure at week 24)	1 (<1%)	6 (3%)†
Discontinued for other reason while not <50 copies per mL	15 (7%)	21 (10%)
No virological data at week 48	16 (7%)	27 (13%)
Discontinued because of adverse events or death	3 (1%)	11 (5%)
Discontinued for other reasons	13 (6%)	16 (8%)

Data are number of participants (%) by US Food and Drug Administration snapshot analysis, unless otherwise stated. *Two patients on zidovudine and lamivudine, three patients on tenofovir and emtricitabine, and one patient on abacavir and lamivudine. †Four patients on zidovudine and lamivudine and two patients on tenofovir and emtricitabine.

Table 3: **Proportion of patients with virological non-response or no virological data at week 4**

reported: 676 in the dual-therapy arm and 700 in the triple-therapy arm. 153 adverse events were possibly or probably drug related: 65 in the dual-therapy group and 88 in the triple-therapy group (p=0·007). The most common adverse events were hyperlipidaemia, diarrhoea, nausea, and dyspepsia (table 4 and appendix). Toxicity-related or tolerability-related discontinuations (n=11) were more frequent in the triple-therapy arm (n=10 [4·9%]) than in the dual-therapy arm (n=1 [0·4%]; difference 4·5%, 95% CI –8·1 to –0·9; p=0·01). Two serious adverse events occurred, both in the dual-therapy arm, one of which (a case of gastritis) was reported as possibly or probably related to drug treatment. One death occurred (in the dual-therapy group) as a result of bacterial sepsis and was reported as probably not related to the drug treatment.

	Dual therapy (n=214)	Triple therapy (n=202)	p value
Total number of grade 2–3 AEs (possibly or probably drug related)*	65 (30%)	88 (44%)	0·007
Total number of patients with grade 2–3 AEs (possibly or probably drug related)*	43 (20%)	48 (24%)	0·43
Drug-related AEs (≥2% of patients in either group)			
Hyperlipidaemia	23 (11%)	16 (8%)	0·41
Diarrhoea†	14 (7%)	14 (7%)	0·97
Nausea†	2 (1%)	9 (4%)	0·05
Dyspepsia†	2 (1%)	6 (3%)	0·02
Serious AEs possibly or probably drug related‡	1 (<1%)	0 (0%)	..
Death	1 (<1%)	0 (0%)	..
Safety events leading to discontinuation (primary reason)	2 (1%)	11 (5%)§	..
Selected grade 3–4 laboratory abnormalities¶			
Haemoglobin	2 (1%)	2 (1%)	..
White blood cell	0 (0%)	0 (0%)	..
Platelet count	4 (2%)	3 (1%)	..
Alanine aminotransferase	0 (0%)	0 (0%)	..
Aspartate aminotransferase	1 (<1%)	0 (0%)	..
Creatinine	0 (0%)	0 (0%)	..
Glucose	0 (0%)	3 (1%)	..
Total cholesterol	18 (8%)	14 (7%)	..
Triglycerides	8 (4%)	17 (8%)	..
LDL cholesterol	21 (10%)	13 (6%)	..

Data are number (%), unless otherwise stated. AE=adverse event. *Investigator defined. †Multiple occurrences of the same adverse event in one individual counted only once. ‡Gastritis. §Zidovudine related: gastrointestinal intolerance in six patients, anaemia in three patients, and rash in one patient. Tenofovir related: rash in one patient. ¶Based on the Division of AIDS adverse event grading table.

Table 4: **Clinical adverse events and laboratory abnormalities at week 48**

Discussion

A dual-therapy regimen for HIV consisting of lopinavir and ritonavir plus lamivudine is non-inferior to a standard triple-therapy regimen of lopinavir and ritonavir plus two NRTIs in ART-naive patients in term of rates of viral suppression. Non-inferiority of the dual therapy was shown irrespective of baseline viral load and sensitivity analysis used to assess results. Emergent HIV drug resistance was uncommon in both arms, with no protease inhibitor resistance in any of the arms and the Met184Val mutation being present in two patients at virological failure in the dual-therapy group. Viral resistance emerges almost inevitably when combination ART fails. Should Met184Val be confirmed as the only resistance mutation selected by this strategy, various second-line options would still be preserved. After 48 weeks, the dual-therapy strategy showed similar efficacy to triple therapy but had the advantage of fewer side-effects and a lower discontinuation rate. The efficacy of the dual-therapy combination tested in GARDEL might be explained by the high antiviral potency of lopinavir and ritonavir, which nevertheless was not enough when this ritonavir-boosted protease inhibitor was tested as monotherapy in ART-naive patients,[8] and the higher rate of side-effects and discontinuations in the triple-therapy group. Our results suggest that the addition of lamivudine was enough to increase the overall potency of this combination. The lower rate of side-effects and discontinuation reported in the dual-therapy group is attributable to the avoidance of the second NRTI.

Dual-therapy strategies have been tested in many clinical trials. In particular, there has been an interest in investigation of dual-therapy regimens as a means to preserve effectiveness with reduced toxicity and potential cost-saving implications.[16–19] However, those regimens have had lower effectiveness than standard triple-therapy regimens (panel).[17,20] Two randomised clinical trials have shown comparable results of a ritonavir-boosted protease inhibitor based dual therapy among treatment-naive patients.[23,24] The AIDS Clinical Trials Group Study A5142[19] found that the virological efficacy of the NRTI-sparing regimen (efavirenz plus lopinavir and ritonavir) was similar to that of the efavirenz regimen but was more likely to be associated with drug resistance. In the PROGRESS study,[23] patients were randomly assigned to lopinavir and ritonavir plus raltegravir or a standard triple-therapy regimen consisting of lopinavir and ritonavir plus emtricitabine and tenofovir. At 48 weeks, 83·2% of participants in the lopinavir and ritonavir plus raltegravir group and 84·6% of those in the lopinavir and ritonavir plus emtricitabine and tenofovir group achieved a plasma viral loads below 50 copies per mL, but this study did not enrol patients with advanced HIV disease.

Our study showed similar outcomes, with a larger sample size and a less costly drug, which is widely available as a generic. Raltegravir is an attractive alternative to lamivudine because it preserves the integrase inhibitor class, which is valuable as a therapeutic option in treatment-naive and treatment-experienced patients.[25–30]

In the GARDEL study, more patients in the dual-therapy group than in the triple-therapy group had

Panel: Research in context

Systematic review

The present standard of daily oral triple therapy is effective at halting HIV disease progression. However, challenges such as cumulative toxicity and cost have motivated research exploring alternative antiretroviral treatment (ART) strategies. One example of novel HIV-1 treatment research was the exploration of ritonavir-boosted protease inhibitors as monotherapy.[8,21,22] The boosted protease inhibitors are potent drugs and require the selection of multiple mutations before clinical resistance. However, so far, findings conclude that monotherapy in viraemic patients is associated with less suppression and more intermittent viraemia and leads to increased protease inhibitor resistance when compared with triple therapy.[8,21,22] Findings from the ritonavir-boosted protease inhibitor monotherapy trials[8,21,22] led us to surmise that dual therapy including a boosted protease inhibitor might be as effective as triple therapy. Dual therapy strategies have been tested in many clinical trials. In particular, there has been an interest to explore nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens as a means to preserve effectiveness with reduced toxicity and potential cost-saving implications. However, so far, class-sparing regimens have had lower effectiveness than standard triple-therapy regimens.[16,17,19,20,23] We did a systematic search of PubMed to address the question: has dual therapy in ART-naive HIV infected patients been studied in well powered randomised clinical trials? Search terms included "dual therapy" AND "naive AND phase 3". Searches were limited to articles published in English between 1997 and March, 2014. 30 articles were retrieved and hand searched; of those, only two showed non-inferiority of a ritonavir-boosted protease inhibitor-based dual therapy regimen among treatment-naive patients.[23,24]

Interpretation

This study is, to our knowledge, the first to show non-inferiority of a dual-therapy regimen consisting of lopinavir and ritonavir plus lamivudine compared with a standard triple-therapy regimen of lopinavir and ritonavir plus two NRTIs in ART-naive patients. Non-inferiority of the dual therapy was noted irrespective of baseline viral load and sensitivity analyses used to assess results. No resistance to protease inhibitor was reported at treatment failure. Two patients developed lamivudine resistance in the dual-therapy group. After 48 weeks, dual therapy resulted in similar efficacy to triple therapy but had fewer side-effects and a lower discontinuation rate, which was probably one of the drivers of the study results. Our results suggest that the addition of lamivudine was enough to increase the overall potency of this combination. The lower rate of side-effects and discontinuation reported in the dual therapy group is attributable to the avoidance of the second NRTI. Dual therapy with lopinavir and ritonavir plus lamivudine could be an effective, simple, and, in some settings, cost-effective first-line option for patients. In resource-limited settings, where non-nucleoside reverse transcriptase inhibitor based triple therapy is the first-line treatment, dual therapy with lopinavir and ritonavir plus lamivudine might be an option that needs less frequent safety monitoring than triple therapy. If our findings are confirmed in future studies, including also once-daily regimens, lamivudine plus ritonavir-boosted protease inhibitor dual therapy might challenge the value of a third nucleoside or nucleotide contribution to the outcomes of highly active ART in ART-naive patients.

hyperlipidaemia. The difference might have been driven by use of tenofovir by some patients in the triple-therapy group (appendix). Tenofovir is associated with a reduction in lipids whereas lopinavir and ritonavir is associated with an increase in lipids, especially triglycerides.[31] Similar findings have been described in other studies, in which tenofovir was not used in one of the study arms.[16,17,19,32–34] If independently confirmed, our results potentially have important global implications for the management of HIV-1 infection in adults. Avoiding NRTI-associated toxicities, the lopinavir and ritonavir plus lamivudine regimen might need less monitoring, making it a potentially attractive option for first-line therapy in resource-limited settings, and possibly allowing other NRTIs to be reserved for second-line therapy. Furthermore, our results pave the way for the exploration of other dual-therapy strategies and eventually coformulation of such regimens.

Limitations of our study include the open-label design and corresponding limitations associated with randomisation to a control arm of standard therapy, allowance of investigator-selected third NRTI, predominance of zidovudine as the third NRTI, and the 48 week duration of our trial. With respect to these limitations, the selection of zidovudine represents the clinical practice in some sites participating in this trial. When the analysis was limited to participants treated with abacavir or tenofovir as the third drug in the triple-therapy arm, the finding of no difference in efficacy remained. With respect to study duration, a roll-over study to provide 96 week follow-up is ongoing. Additionally, there are clinical questions with respect to this dual-therapy strategy that the GARDEL trial was not designed to address. Can one or both drugs be taken once daily? What would be the appropriate second-line regimen after first-line treatment with lopinavir and ritonavir plus lamivudine fails? Are these results limited to boosted lopinavir or can they be expected from other boosted protease inhibitors and lamivudine-based dual-therapy regimens?

Present ART guidelines recommend efavirenz-based fixed-dose combinations. Advantages such as once daily administration, low cost, few drug interactions, and generally few gastrointestinal side-effects need to be balanced with CNS tolerability issues and selection of two-class resistance at treatment failure, on top of the NRTI toxicity.[35] In resource-limited settings, where triple therapy based on non-nucleoside reverse transcriptase inhibitor is used as first-line therapy, dual therapy with lopinavir and ritonavir plus lamivudine might be an option that would need less frequent monitoring than triple therapy. Dual therapy with lopinavir and ritonavir plus lamivudine could be an effective, simple, and, in some settings, cost-effective first-line option for treatment-naive patients.

If our findings are confirmed in future studies, including for once-daily regimens, lamivudine plus dual therapy with a ritonavir-boosted protease inhibitor might challenge the value of a third nucleoside or nucleotide to the outcomes of highly active ART in ART-naive patients.

Contributors

PC and MN designed the study in consultation with the Steering Committee. The GARDEL investigators enrolled patients in the study and were involved in acquisition of data. PC, MJR, and MIF analysed data and clinically oversaw the study. PC, JA-V, JRA, JMG, JRL, MN, PP, JSM, OS, MIF, and MJR participated in data interpretation. The report was drafted by PC, JA-V, JRA, JMG, MN, JRL, PP, JSM, OS, MIF, and MJR. All authors provided input to the report and approved the final version.

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Declaration of interests

PC is a member of WHO Guidelines Panel and the IAS-USA Guidelines Panel. He has served on the advisory boards for GlaxoSmithKline (ViiV), Merck, Pfizer, Gilead Sciences, and Tibotec (Janssen) Therapeutics. He has served an investigator for Abbott, Avexa, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Pharmasset, Roche Laboratories, and Tibotec Therapeutics, and his institution has received honoraria for his speaking or chairing engagements from Abbott Laboratories, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Pfizer, and Tibotec Therapeutics. JA-V has been an investigator for Merck, GlaxoSmithKline, Abbott, Bristol-Myers Squibb, Gilead Sciences, Tibotec, Boehringer Ingelheim, and Janssen-Cilag and has served as a paid consultant and speaker for Merck, GlaxoSmithKline, Abbott, Bristol-Myers Squibb, Gilead Sciences, Boehringer Ingelheim, Janssen-Cilag, and Stendhal. JRA has received advisory fees, speaker fees, and grant support from ViiV, Tibotec (Janssen) Therapeutics, Abbott Laboratories, Bristol-Myers Squibb, Gilead, MSD, and Tobira. JMG has received honoraria for speaking or advisory boards or research grants from Gilead, Bristol-Myers Squibb, Boehringer Ingelheim, MSD, Janssen, Tobira, and AbbVie. MN holds an executive position at AbbVie Global Pharmaceutical Research and Development. JSM has been a speaker for Stendahl, MSD, and Jansen; has participated in advisory boards for MSD, Stendahl, and Jansen; has received grants for clinical trials from Pfizer, Bristol-Myers Squibb, Gilead, and MSD; has received travel support for meetings from Roche, Abbot, Stendahl, ViiV, and Jansen. OS has received honoraria for speaking or advisory boards from AbbVie and AstraZeneca and travel support from GlaxoSmithKline and Merck. JRL, PP, MIF, and MJR declare that they have no competing interests.

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