Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study

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Background: Switching to raltegravir in selected patients treated with ritonavir-boosted protease inhibitors may result in similar efficacy and lower plasma lipids.

Methods: SPIRAL is a 48-week multicentre, open-label trial in which HIV-infected adults with less than 50 copies/ml of plasma HIV RNA for at least the previous 6 months on ritonavir-boosted protease inhibitor-based therapy were randomized (1 : 1) to switch from the ritonavir-boosted protease inhibitor to raltegravir or to continue on ritonavir-boosted protease inhibitor-based therapy. Primary endpoint was the proportion of patients free of treatment failure (noncompleter = failure) at 48 weeks. SPIRAL study was powered to show noninferior efficacy of raltegravir-based therapy with a margin of −12.5%.

Results: Two hundred and seventy-three patients assigned to switch to raltegravir ($n = 139$) or to continue ritonavir-boosted protease inhibitor ($n = 134$) were included in the efficacy analysis. At 48 weeks, 89.2% (raltegravir-based therapy) and 86.6% (ritonavir-boosted protease inhibitor-based therapy) of the patients remained free of treatment failure [difference 2.6%; 95% confidence interval (CI) −5.2 to 10.6]. A total of 96.9% (raltegravir-based therapy) and 95.1% (ritonavir-boosted protease inhibitor-based therapy) of the patients remained free of virological failure (difference 1.8%; 95% CI −3.5 to 7.5). Switching to raltegravir was associated with significant decreases in plasma lipids and total-to-HDL cholesterol ratio relative to continuing ritonavir-boosted protease inhibitor. Severe adverse events and study drug discontinuations due to any adverse event occurred in 4 and 2% of the patients in each group.

Conclusion: In patients with sustained virological suppression on ritonavir-boosted protease inhibitor-based therapy, switching from ritonavir-boosted protease inhibitor to raltegravir demonstrated noninferior efficacy and resulted in a better lipid profile at 48 weeks than continuing ritonavir-boosted protease inhibitor.

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Introduction

Antiretroviral therapy containing protease inhibitors changed HIV-1 infection from a fatal disease into a chronic condition [1]. Protease inhibitor are recommended agents for both antiretroviral-naive and antiretroviral-experienced patients because of their potency and high barrier to resistance [2,3]. The addition of low-dose ritonavir to currently available protease inhibitor acts as a pharmacokinetic booster increasing exposure to the active protease inhibitor and allowing for less dosing frequency, but it may also lead to a higher risk for adverse effects and drug interactions [4]. Protease inhibitor have been associated with a higher risk of cardiovascular disease due at least in part to their lipid effects [5]. Ritonavir at doses similar to those used for protease inhibitor boosting has been shown to increase plasma lipids [6,7].

Simplification of antiretroviral therapy has been commonly pursued through the replacement of a drug with potential long-term tolerability problems by another equally effective drug without such problems [2,3]. The efficacy of raltegravir in antiretroviral-naive [8,9] and antiretroviral-experienced [10,11] patients has been established and so far it has demonstrated a low impact on plasma lipids. Although raltegravir needs to be taken twice daily, and this schedule may be not as convenient as that of some the currently available protease inhibitors that are administered once daily, raltegravir might be an attractive option to simplify ritonavir-boosted protease inhibitor-containing antiretroviral therapy because of potential long-term metabolic concerns.

We hypothesized that switching from the ritonavir-boosted protease inhibitor component to raltegravir in selected HIV-infected adults treated with combination therapy containing ritonavir-boosted protease inhibitor and showing sustained plasma HIV-1 RNA below 50 copies/ml would result in similar efficacy and a better lipid profile.

Methods

Patients

This multicentre, randomized, open-label clinical trial was carried out in 17 centres in Spain. The protocol was approved by the Ethics Committee at each centre and by the Spanish Medicines Evaluation Agency. Eligible patients were otherwise clinically stable HIV-1-infected patients aged 18 years or more who were receiving combination antiretroviral therapy consisting of at least two antiretroviral agents other than protease inhibitor plus a ritonavir-boosted protease inhibitor including indinavir, fosamprenavir, saquinavir, lopinavir, atazanavir, tipranavir, or darunavir and showing plasma HIV-1 RNA below 50 copies/ml for at least the previous 6 months. Patients currently receiving prophylaxis or treatment for an opportunistic infection or malignancy were allowed as long as the above criteria were met. The following laboratory values were required within 1 month prior to randomization: haemoglobin higher than 8.0 g/dl, neutrophil count higher than 750/μl, platelet count higher than 50 000/μl, creatinine less than 2.0 mg/dl, and both alanine and aspartate aminotransferases less than 200 mg/dl.

Exclusion criteria were pregnancy or a wish to become pregnant during the study period, lack of expectation to maintain assigned study medication during study period, prior treatment with raltegravir, therapy with investigational drugs in the previous 3 months, alcohol or substance abuse, visceral Kaposi sarcoma, acute hepatitis in the previous 6 months, and any condition or history of any illness which, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering study drugs to the patient. Written informed consent was obtained from all eligible patients before randomization.

Procedures

Patients were randomly assigned in a 1 : 1 ratio to switch to raltegravir or to continue on the ritonavir-boosted protease inhibitor while maintaining the same background therapy. A random sequence was generated by a computer stratifying by current use of lipid-lowering therapy. Patients were assessed at baseline, 4, 16, 32, and 48 weeks. At each visit, clinical data were collected and blood samples were obtained after at least 8-h overnight fast. Complete blood and CD4 cell counts, measurement of plasma HIV-1 RNA, triglycerides, total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterols, and liver (alanine and aspartate aminotransferases) and kidney (creatinine) tests were performed at each site throughout follow-up. LDL cholesterol was measured indirectly, whenever triglycerides were lower than 400 mg/dl [12]; otherwise, it was measured directly. Specific metabolic, body composition, and cardiovascular biomarkers substudies were planned, but their results are not reported here. Safety was assessed through the reporting of clinical adverse events and laboratory abnormalities. The severity of adverse events was evaluated according to the Division of AIDS toxicity table [13].

Definitions

Virological failure was defined as the first of two consecutive measurements of plasma HIV-1 RNA equal to or higher than 50 copies/ml separated by at least 2 weeks. In such cases, therapy could be maintained or changed at the discretion of the physician and the patient could continue in the study at least until he or she completed the 48-week follow-up period. In cases of virological failure in the raltegravir group, serum samples were stored and tested for resistance by integrase

genotyping of virus from patients who had more than 400 copies/ml at virological failure [14]. Other resistance testing in virological failures from both groups was done with the use of ViroSeq HIV-1 genotyping system according to the manufacturer's instructions (Applied Biosystems, Foster City, California, USA). Treatment failure was defined as any of the following events: virological failure, discontinuation of study therapy, withdrawal of consent, lost to follow-up, progression to AIDS, or death. Progression to AIDS was defined by the occurrence of any new clinical event included in category C of the 1993 classification of the Centers for Disease Control and Prevention [15].

End points

The primary end point of the study was the proportion of patients who were free of treatment failure at 48 weeks ('noncompleter = failure' intent-to-treat analysis). According to the protocol, events occurring within 2 weeks after the 48-week follow-up period were also included in the analysis of end points. Secondary end points were the proportion of patients who were free of virological failure, time to treatment or virological failure, changes in CD4 and CD8 cell counts and in fasting plasma lipids, and incidence of adverse effects at 48 weeks.

Sample size calculation

The sample size was computed to detect noninferiority between the treatment groups in the proportion of patients with treatment failure at the end of the study, because very few virological failures, clinical events and deaths were expected. For this purpose, we took into account the expectations of failure with antiretroviral therapy containing ritonavir-boosted protease inhibitor [16,17]. A total of 130 patients per group were required for the noninferiority assessment with a two-sided alpha level of 0.05 and a statistical power of 80%, assuming that treatment failure was less than 15% in the worst arm and that losses to follow-up were less than 5%. Noninferiority for raltegravir was considered proven if the lower limit of the 95% confidence interval (CI) of the difference between the proportions (raltegravir − ritonavir-boosted protease inhibitor) of patients with treatment failure in each group was less than 12.5%.

Statistical analysis

Patients were followed for the entire trial period regardless of whether they prematurely discontinued assigned study medication. All randomized patients, except those who were found to have violated the entry criteria and those who never started the study medication, were included in the analysis. Additional analyses according to prior virological failure or suboptimal therapy and a sensitivity analysis including all randomized patients were also planned. In the intention-to-treat or 'treatment failure' analysis, failure was considered in all patients who had progression to AIDS, died, had virological failure, discontinued the study medication, withdrew consent or were lost to follow-up. In the on-treatment or 'virological failure' analysis, failure was defined by progression to AIDS, death, or virological failure during treatment, whereas patients who withdrew consent, were lost, or switched or stopped study medication were censored. Switches in the background regimen were not considered treatment failure as long as plasma HIV-1 RNA remained less than 50 copies/ml. Changes from baseline in plasma lipids and in total-to-HDL cholesterol ratio were primarily analysed by intention-to-treat and their results are reported here; a posthoc on-treatment analysis reproduced identical results (data not shown).

Statistical analysis was performed with the use of Stata (release 9.2) and StatXact (version 6). χ^2 or Fisher's exact tests were used to compare proportions between treatment groups. Mann–Whitney *U*-test or ANOVA tests were used for comparisons of continuous variables between groups. For testing noninferiority of raltegravir relative to ritonavir-boosted protease inhibitor, 95% confidence intervals for the treatment difference were calculated by Newcombe's method [18]. The time to treatment or virological failure was estimated with the Kaplan–Meier product-limit method. The equality of the distributions of times to an event between groups was estimated with the generalized log–rank test. Simple comparisons were made with use of a two-sided alpha level of 0.05.

The data safety monitoring board periodically reviewed safety and efficacy results in a planned manner. Due to early cessation of SWITCHMRK studies, an unplanned futility analysis with conditional power approach [19] was done in April 2009 when all patients had at least 16 weeks of follow-up. The data safety monitoring board recommended continuing SPIRAL study because conditional power obtained was superior to the prespecified value of 60%. The SPIRAL trial is registered with ClinicalTrials.gov, number NCT00528892.

Results

Population

Between 4 April 2008 and 31 December 2008, 339 patients were assessed for eligibility, 282 underwent randomization and were included in the safety analysis and 273 (raltegravir, $n = 139$; boosted protease inhibitor, $n = 134$) received at least one dose of study drugs and were included in the efficacy analysis (Fig. 1). Baseline characteristics are shown in Table 1. Twenty-three percent were women and median CD4 cell count was 516 cells/μl. Most common protease inhibitors at entry were lopinavir ($n = 120$, 44%) and atazanavir ($n = 96$, 35%). One hundred and four (38%) patients had received prior suboptimal therapy with one or two nucleoside

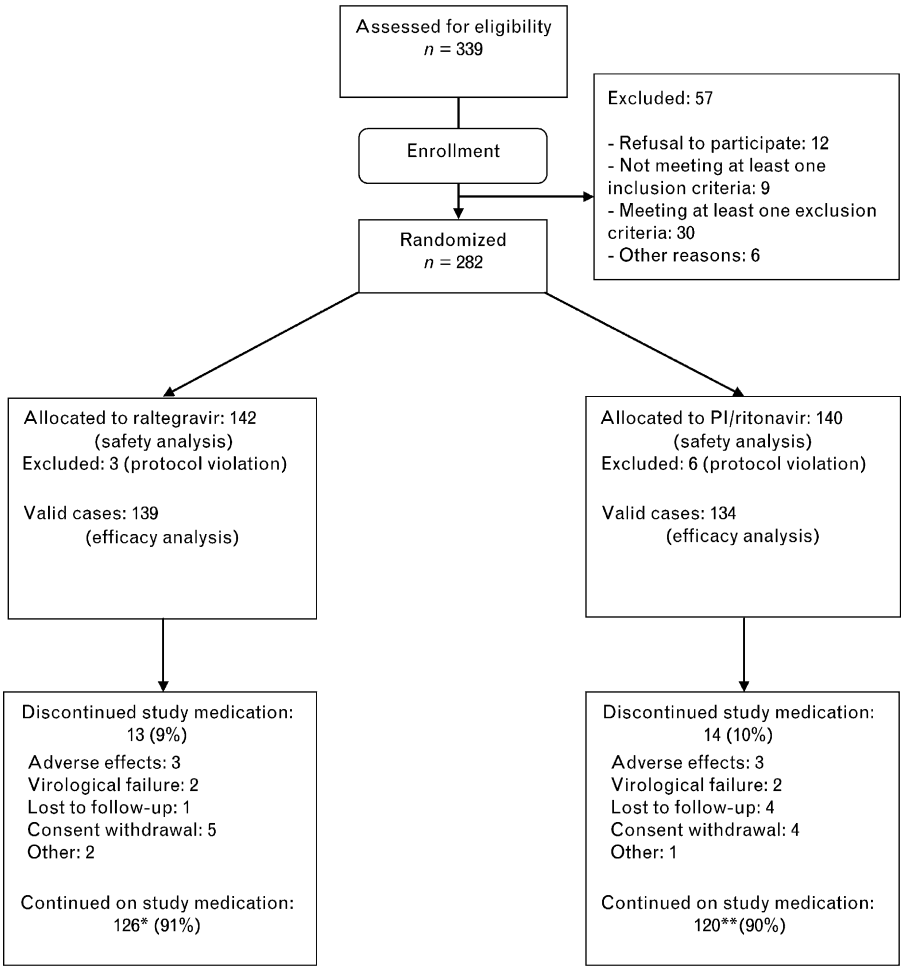


Fig. 1. Trial profile for the SPIRAL study up to week 48. PI/ritonavir, ritonavir-boosted protease inhibitor. *, two patients with virological failure. **, four patients with virological failure.

reverse transcriptase inhibitors (NRTIs) exclusively, but all of them had this therapy prescribed before 1997. Although 103 (38%) patients had experienced a prior virological failure, HIV-1 RNA had been maintained below detection level for a median (interquartile range) of 73 (39–106) months before randomization.

Efficacy

At 48 weeks, 124 out of 139 (89.2%) patients in the raltegravir group and 116 out of 134 (86.6%) patients in the ritonavir-boosted protease inhibitor group remained free of treatment failure (estimated difference 2.6%; 95% CI −5.2 to 10.6), thus demonstrating noninferiority of raltegravir relative to ritonavir-boosted protease inhibitor for the primary end point (Table 2). At 48 weeks, 124 out of 128 (96.9%) patients in the raltegravir group and 116 out of 122 (95.1%) patients in the ritonavir-boosted protease inhibitor group remained free of virological failure (estimated difference 1.8%; 95% CI −3.5 to 7.5), thus confirming noninferiority of raltegravir (Table 2). Additional efficacy analyses according to prior virological failure or suboptimal therapy and a sensitivity analysis including all randomized patients did not significantly affect the overall results (Table 2). There were no differences between treatment groups in time to either treatment ($P = 0.4775$, by log–rank test) (Fig. 2a) or virological ($P = 0.4602$, by log–rank test) failure (Fig. 2b).

Virological failure in patients from the raltegravir group developed at weeks 16 ($n = 3$) or 48 ($n = 1$), whereas that in those from the ritonavir-boosted protease inhibitor group developed at weeks 16 ($n = 3$) or 48 ($n = 3$). At the time of virological failure, HIV-1 RNA was 71, 260, 1278, and 10 000 copies/ml in patients assigned to raltegravir and 97, 111, 206, 870, 49 000, and 500 000 copies/ml in patients assigned to boosted protease inhibitor. Five plasma samples were available for resistance analysis and had HIV-1 RNA amplifiable. In the ritonavir-boosted protease inhibitor group ($n = 4$), genotypic analysis did not show any mutation associated with resistance to study drugs in one patient, whereas three patients showed multiple resistance mutations in the protease and/or nucleoside reverse transcriptase genes

Table 1. Baseline characteristics by treatment group.

	Raltegravir ($n=139$)	PI/r ($n=134$)
Age, years [median (IQR)]	44 (41–50)	45 (40–50)
Female sex [*n* (%)]	26 (19)	37 (28)
Risk group[a] [*n* (%)]		
Heterosexuals	42 (30)	46 (34)
Male homosexuals	46 (33)	44 (33)
Intravenous drug users	39 (28)	32 (24)
Other or unknown	12 (9)	12 (9)
Antiretroviral backbone at entry [*n* (%)]		
3TC/FTC + TDF	81 (58)	74 (55)
3TC/FTC + ABC	27 (19)	27 (20)
3TC/FTC + ZDV	10 (7)	11 (8)
TDF + ABC	6 (4)	6 (4)
TDF + ZDV	2 (1)	5 (4)
TDF + ddI	2 (1)	4 (3)
ABC + ddI	3 (2)	1 (1)
ZDV + ddI	1 (1)	3 (2)
ddI + 3TC	3 (2)	1 (1)
TDF + NNRTI	2 (1)	1 (1)
3TC/FTC + NNRTI	1 (1)	1 (1)
ABC + NNRTI	1 (1)	0 (0)
PI/r at entry [*n* (%)]		
Lopinavir/r	60 (43)	60 (45)
Atazanavir/r	52 (37)	44 (33)
Fosamprenavir/r	15 (11)	18 (13)
Saquinavir/r	9 (6)	12 (9)
Darunavir/r	1 (1)	0 (0)
Indinavir/r	1 (1)	0 (0)
Tipranavir/r	1 (1)	0 (0)
Patients on their first antiretroviral regimen [*n* (%)]	16 (12)	14 (10)
Exposure to antiretroviral therapy (years) [median (range)]	11 (5–13)	10 (6–12)
Exposure to protease inhibitor-based therapy (months) [median (range)]	31 (20–47)	31 (18–22)
Patients with previous suboptimal antiretroviral therapy[b] [*n* (%)]	57 (41)	47 (35)
Patients with previous virological failure [*n* (%)]	55 (40)	48 (36)
Patients with previous virological failure with protease inhibitors, n (%)	33 (24)	25 (19)
Patients with previous suboptimal antiretroviral therapy or virological failure [*n* (%)]	79 (57)	65 (49)
Number of previous antiretroviral regimens [median (IQR)]	5 (2–8)	5 (3–7)
Number of previous suboptimal antiretroviral regimens [median (IQR)]	2 (1–3)	2 (1–3)
Number of previous virological failures [median (IQR)]	2 (1–3)	2 (1–3)
Patients with AIDS [*n* (%)]	63 (38)	65 (39)
CD4 cell count (cells/μl) [median (IQR)]	529 (377–780)	509 (369–726)
CD8 cell count (cells/μl) [median (IQR)]	858 (651–1093)	784 (556–1093)
Triglycerides (mg/dl) [median (IQR)]	168 (117–270)	174 (114–236)
Triglycerides >200 mg/dl [*n* (%)]	57 (41)	51 (38)
Total cholesterol (mg/dl) [median (IQR)]	198 (171–226)	198 (171–223)
Total cholesterol >240 mg/dl [*n* (%)]	21 (15)	20 (15)
LDL cholesterol (mg/dl) [median (IQR)]	121 (97–141)	122 (97–147)
LDL cholesterol >160 mg/dl [*n* (%)]	17 (12)	16 (12)
HDL cholesterol (mg/dl) [median (IQR)]	44 (35–54)	43 (37–51)
HDL cholesterol <40 mg/dl [*n* (%)]	53 (38)	44 (33)
Lipid-lowering therapy at entry [*n* (%)]	27 (19)	28 (21)

3TC, lamivudine; ABC, abacavir; ddI, didanosine; FTC, emtricitabine; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor (nevirapine or efavirenz); PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir; ZDV, zidovudine.
[a]Although one mutually exclusive risk for acquiring HIV-1 infection was ascribed to each patient by the physician in charge, it should be noted that we could not definitively rule out that more than one category was present in each individual patient.
[b]Antiretroviral therapy containing one or two nucleoside reverse transcriptase inhibitors exclusively.

(patient 1: L10V, L33F, I54V, V82A, M41L, D67N, K70R, L74V, M184V, G190A, T215F, K219Q; patient 2: I13V, M36I, I62V, L63T; patient 3: M41L, M184V, T215Y). In the raltegravir group ($n=1$), genotypic analysis showed mutations in the integrase genes that do not appear to decrease susceptibility to raltegravir (M154I, V201I) without mutations in the protease or nucleoside reverse transcriptase genes. Prior suboptimal therapy with one or two NRTIs exclusively was present in two (50%) and three (50%) patients developing virological failure in the raltegravir vs. boosted protease inhibitor group, respectively. Previous virological failure was present in one (25%) and three (50%) patients developing virological failure in the raltegravir vs. boosted protease inhibitor group, respectively. The median number of previous suboptimal (2 vs. 2, $P=0.7823$, by Mann–Whitney *U*-test) or total (5 vs. 5, $P=0.7567$, by Mann–Whitney U test) antiretroviral regimens, previous virological failures (1 vs. 2, $P=0.1766$, by Mann–Whitney *U*-test), and years of

Table 2. Efficacy analyses according to prior virological failure or suboptimal therapy and a sensitivity analysis including all randomized patients.

	Response				
	Raltegravir		PI/r		
Subpopulation	*n/N*	Percentage (95% CI)	*n/N*	Percentage (95% CI)	Difference in percentage response [% (95% CI)]
Free treatment failure	124/139	89.2 (83–93.4)	116/134	86.6 (79.8–91.3)	2.6 (−5.2 to 10.6)
Has the patient experienced prior virologic failure on any drug?					
Yes	50/55	90.9 (80.4–96.1)	40/48	83.3 (70.4–91.3)	7.6 (−5.6 to 21.5)
No	74/84	88.1 (79.5–93.4)	76/86	88.4 (79.9–93.6)	−0.28 (−10.4 to 9.7)
Has the patient experienced prior virologic failure or suboptimal therapy?					
Yes	70/79	88.6 (79.7–93.9)	54/65	83.1 (72.2–90.3)	5.5 (−5.9 to 17.6)
No	54/60	90 (79.9–95.3)	62/69	89.9 (80.5–95)	0.14 (−11.2 to 10.9)
Free virological failure	124/128	96.9 (92.2–98.8)	116/122	95.1 (89.7–97.7)	1.79 (−3.5 to 7.5)
Has the patient experienced prior virologic failure on any drug?					
Yes	54/55	98.2 (90.4–99.7)	45/48	93.8 (83.2–97.9)	4.43 (−4.4 to 15.1)
No	81/84	96.4 (90–98.8)	83/86	96.5 (90.2–98.8)	−0.08 (−6.9 to 6.6)
Has the patient experienced prior virologic failure or suboptimal therapy?					
Yes	70/72	97.2 (90.4–99.2)	54/58	93.1 (83.6–97.3)	4.1 (−3.9 to 13.9)
No	54/56	96.4 (87.9–99.9)	62/64	96.9 (89.3–99.1)	−0.45 (−9.3 to 7.6)
All randomized patients					
Treatment failure	127/142	89.4 (83.3–93.5)	122/140	87.1 (80.6–91.7)	2.3 (−5.4 to 10)
Virological failure	138/142	97.2 (93–98.9)	134/140	95.7 (91–98)	1.5 (−3.3 to 6.5)

CI, confidence interval; PI/r, ritonavir-boosted protease inhibitor.

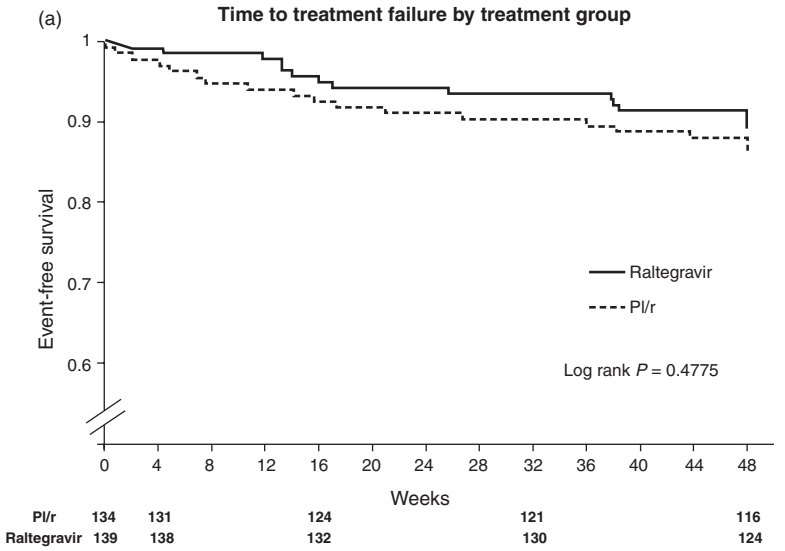
prior antiretroviral therapy (12 vs. 10, $P = 0.2643$, by Mann–Whitney *U*-test) was not significantly different between patients developing virological failure and those who did not, respectively.

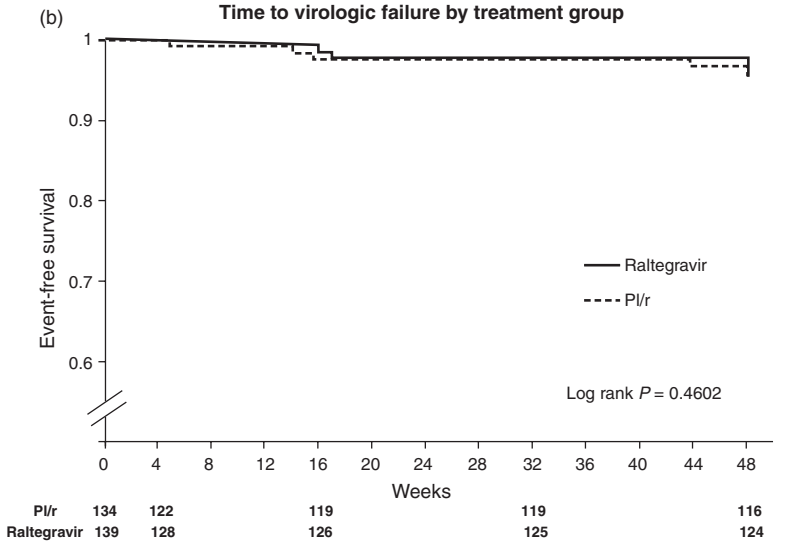
There were no significant differences between the treatment groups in CD4 cell count change from baseline to 48 weeks [median (interquartile range) 46 (−41 to 142) cells/μl in the raltegravir group vs. 44 (−28 to 161) cells/μl in the boosted protease inhibitor group ($P = 0.3275$, by Mann–Whitney *U*-test)]. However, CD8 cell count change remained stable in the raltegravir group [median (interquartile range) −1 (−203 to 175) cells/μl], whereas it increased in the boosted protease inhibitor group [median (interquartile range) 54 (−74 to 215) cells/μl] ($P = 0.0331$, by Mann–Whitney *U*-test). During the study, one patient assigned to raltegravir progressed to AIDS (progressive multifocal leukoencephalopathy, 1 month after self-decision to discontinue antiretroviral therapy), whereas no patient assigned to boosted protease inhibitor did so. No patient died during the study.

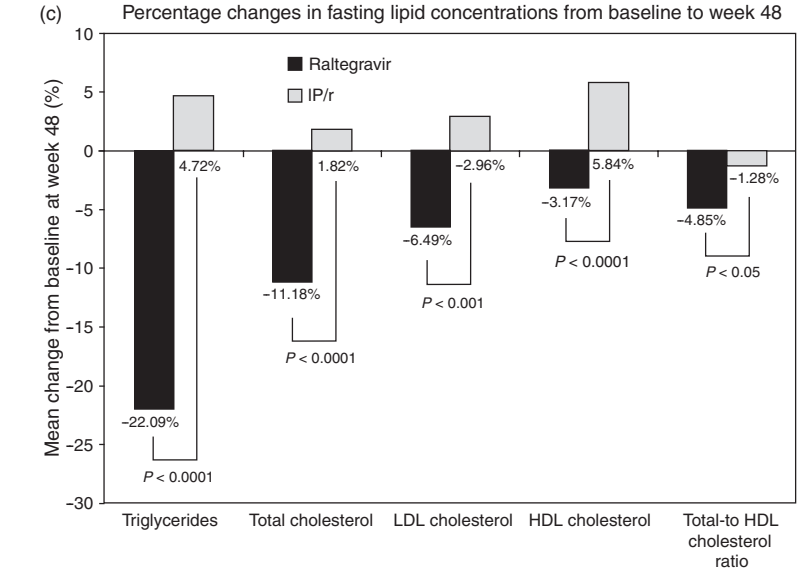
Lipid changes and overall tolerability

Mean changes from baseline to 48 weeks in fasting plasma lipid values (triglycerides, total, LDL and HDL cholesterols) and total-to-HDL cholesterol ratio were reductions in the raltegravir group compared with predominantly increases in the ritonavir-boosted protease inhibitor group (Fig. 2c). Individual lipids and total-to-HDL cholesterol ratio significantly decreased in the raltegravir group by week 4 and treatment differences persisted throughout follow-up ($P < 0.05$, by Mann–Whitney *U*-test). The proportion of patients with triglycerides higher than 200 mg/dl (14.6 vs. 28.9%, $P = 0.0068$, by Fisher's exact test) and total cholesterol higher than 240 mg/dl (3.7 vs. 17.2%, $P = 0.0004$, by Fisher's exact test) at 48 weeks were significantly lower in the raltegravir group than in ritonavir-boosted protease inhibitor group, whereas there were no significant differences in the proportion of LDL cholesterol higher than 160 mg/dl (2.9 vs. 7.8%, $P = 0.0997$, by Fisher's exact test) or HDL cholesterol less than 40 mg/dl (42.3 vs. 33.6%, $P = 0.1644$, by Fisher's exact test). At 48 weeks, 16 (12%) patients in the raltegravir group compared with

Fig. 2. Time to treatment and virological failure, and changes in fasting plasma lipids from baseline to week 48. (a) Time to treatment failure by treatment group. Treatment failure was defined as any of the following events: virological failure, discontinuation of study therapy, withdrawal of consent, lost to follow-up, progression to AIDS, or death. PI/ritonavir, ritonavir-boosted protease inhibitor. (b) Time to virological failure by treatment group. Virological failure was defined as the first of two consecutive measurements of plasma HIV-1 RNA equal to or above 50 copies/ml separated by at least 2 weeks. The numbers below the x-axis give the numbers of participants contributing to the analysis at each time point. PI/ritonavir, ritonavir-boosted protease inhibitor. (c) Changes in fasting lipid concentrations from baseline to week 48. The percentage change from baseline to week 48 in fasting triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein HDL cholesterol, and total-to-HDL cholesterol ratio. PI/ritonavir, ritonavir-boosted protease inhibitor.







32 (24%) patients in the ritonavir-boosted protease inhibitor group were using lipid-lowering therapy ($P=0.0104$, by Fisher's exact test). Although triglycerides and total cholesterol in patients switching from either atazanavir/ritonavir [mean (95% CI) 0.2 (−16.2 to 16.7) and −4.2 (−8.4 to 0.0)] or lopinavir/ritonavir [mean (95% CI) −35.9 (−51.3 to −20.6) and −14.4 (−18.3 to −10.4)] to raltegravir decreased at 48 weeks more than in patients maintaining either atazanavir/ritonavir [mean (95% CI) 7.1 (−11.3 to 25.5) and −1.1 (−5.9 to 3.6)] or lopinavir/ritonavir [mean (95% CI 7.8 (−7.6 to 23.2) and 2.8 (−1.2 to 6.8)], respectively, these differences were significant for lopinavir/ritonavir [difference between means (95% CI) −43.7 (−65.3 to −22.0) and −17.1 (−22.7 to −11.5)], but not for atazanavir/ritonavir [difference between means (95% CI) −6.9 (−31.6, 17.8) and −3.1 (−9.5, 3.3)].

The overall incidence of adverse events was similar in the raltegravir ($n=78$, 55%) and in the ritonavir-boosted protease inhibitor ($n=79$, 56%) group ($P=0.8116$, by Fisher's exact test) (Table 3). The incidences of any grade 3 or 4 adverse events ($n=16$, 11% vs. $n=18$, 13%, $P=0.7176$, by Fisher's exact test) was also similar in raltegravir and ritonavir-boosted protease inhibitor groups. The incidences of serious adverse events [$n=6$ (three drug-related), 4% vs. $n=5$ (one drug-related), 4%, $P=0.7687$, by Fisher's exact test] and adverse events leading to study drug discontinuation [$n=3$ (none drug-related), 2% vs. $n=3$ (one drug-related), 2%, $P=1$, by Fisher's exact test] were similarly low in raltegravir and ritonavir-boosted protease inhibitor groups.

Discussion

The final 48-week results of the SPIRAL study demonstrate that switching from the ritonavir-boosted protease inhibitor component to raltegravir in selected HIV-infected adults treated with combination therapy containing ritonavir-boosted protease inhibitor and showing sustained plasma HIV-1 RNA below 50 copies/ml may result in a better lipid profile and noninferior efficacy. For both treatment and virological failure, the lower limit of the 95% CI of the difference obtained was far from the required −12.5%. The SPIRAL efficacy results are in contrast with the efficacy results reported in the recently published SWITCHMRK 1 and 2 studies [20], although both studies demonstrated high levels of efficacy in both treatment groups. In a posthoc analysis of the combined SWITCHMRK studies, the

Table 3. Types and frequencies of clinical and laboratory adverse events during the SPIRAL study.

	Raltegravir ($N=142$)	PI/r ($N=140$)	P^a
Patients with at least one adverse event [*n* (%)]	78 (55)	79 (56)	0.8116
Patients with grade 3 or 4 side-effects			
Any [*n* (%)]	16 (11)	18 (13)	0.7176
Clinical [*n* (%)]	7 (5)	7 (5)	1.0000
Description of clinical grade 3 or 4 adverse effects			
Neuropsychiatric	3	2	
Respiratory	1	3	
Digestive	2	1	
Genitourinary	1	1	
Osteomuscular	0	1	
Cardiovascular	1	0	
Hepatic	0	1	
Laboratory [*n* (%)] 9 (6)		12 (9)	0.5048
Description of laboratory grade 3 or 4 adverse effects			
Triglycerides	3	4	
Total cholesterol	1	5	
Alanine and/or aspartate aminotransferases	5	3	
Patients with adverse events leading to study drug discontinuation [*n* (%)]	3 (2)	3 (2)	1.0000
Neuropsychiatric	2	1	
Hepatic	0	1	
Digestive	0	1	
Respiratory	1	0	
Patients with, and description of serious adverse events	6 (4)	5 (4)	0.7687
Neuropsychiatric	Psychotic break, multifocal leukoencephalopathy	Bacterial meningitis	
Digestive	Colon neoplasia, pancreatitis	Acute colitis	
Respiratory	Bacterial pneumonia	Lung neoplasia	
Genitourinary	–	Bacterial pyelonephritis	
Cardiovascular	Acute pulmonary oedema	–	
Hepatic	–	Increase in transaminases	

Among adverse events leading to study drug discontinuation and serious adverse events, those considered to be drug-related are specified in brackets. PI/r, ritonavir-boosted protease inhibitor.
[a]Fisher's exact test.

investigators assumed that the inability to show noninferiority of raltegravir to lopinavir–ritonavir was driven by patients who had prior virological failure, in accordance with other randomized clinical trials aiming to simplify protease inhibitor-containing regimens in which previous treatment was not restricted, such as NEFA study [21]. Nevertheless, at the time of NEFA study, prior virological failure was more common and probably more recent than in the SPIRAL and SWITCHMRK studies due to extensive suboptimal NRTI therapy.

Despite design similarities between the SPIRAL and SWITCHMRK studies, some factors may account for differences in efficacy. The double-blind, double-dummy design undoubtedly represents scientific excellence, but it made therapies more complex, possibly reducing adherence and compromising efficacy preferentially in the raltegravir group due to its lower genetic barrier to resistance [22]. In fact, the efficacy rates in the protease inhibitor groups in the SPIRAL and SWITCHMRK studies were remarkably similar, whereas that in the raltegravir group of SWITCHMRK studies was lower than that observed in the SPIRAL study. It also seems that the virological suppression prior to study entry was stronger in SPIRAL study than in the SWITCHMRK study. SWITCHMRK patients required less time with HIV-1 RNA below detection at entry compared with SPIRAL patients. Of interest, 5% of patients in both treatment groups in the SWITCHMRK studies met criteria for virological failure at baseline. Although a substantial proportion of patients in SPIRAL study had experienced prior virological failure, median time with virological suppression before entry was longer than 6 years. We do not know exactly for how long patients in the SWITCHMRK studies had been virologically suppressed, but this factor might also be important in explaining the differences between the SPIRAL and SWITCHMRK studies. A longer duration of viral suppression has been associated with a lower risk of virological failure [23]. In a recent analysis from the EuroSIDA study [24], patients making a change to their antiretroviral regimen while maintaining a suppressed viral load showed a lower risk of virological failure if they had spent a longer time on antiretroviral therapy with suppressed viral load or had not experienced a viral rebound close to the time of treatment switch.

Compared with patients continuing boosted protease inhibitor-containing therapy, patients switching from boosted protease inhibitor to raltegravir in the SPIRAL study had sustained decreases not only in their plasma lipids but also in their total-to-HDL cholesterol ratio, therefore indicating a better lipid profile. In SWITCHMRK studies, there were also significant differences between groups in changes in triglycerides and total cholesterol at 12 weeks, but changes in LDL or HDL cholesterols at 12 weeks were not significant and total-to-HDL cholesterol ratio data were not reported [20]. As reported with other drugs replacing protease inhibitor [25], lipid changes in patients switching to raltegravir within the SPIRAL study occurred early and the magnitude of the initial decrease remained relatively stable throughout the study. The magnitude of triglycerides (but not cholesterol) reduction in SPIRAL patients switching to raltegravir was lower than that observed in the SWITCHMRK 1 and 2 studies probably reflecting the heterogeneity in the ritonavir-boosting dose and the type of protease inhibitor used in the SPIRAL study. In an exploratory subanalysis restricted to the most common protease inhibitor used in the SPIRAL study, differences in triglycerides and total cholesterol changes in patients assigned to raltegravir were significant when switching from lopinavir–ritonavir but not from atazanavir–ritonavir, although these results should be taken with caution due to lack of power. Apart from a reduction in plasma lipids and total-to-HDL cholesterol ratio, there was a significantly lower use of lipid-lowering agents at 48 weeks in patients switching to raltegravir compared with patients maintaining ritonavir-boosted protease inhibitor.

In the SPIRAL study, we did not collect some data directly involved in the estimation of cardiovascular risk with Framingham score [26], such as smoking or blood pressure. If we assume that smoking is quite prevalent and hypertension not so much in HIV-infected adults cared for in Spain [27], a fictitious patient representative of the population included in the SPIRAL study (45-year, smoker, nonhypertensive man with total and HDL cholesterols 198 and 43 mg/dl, respectively, at baseline) would have an absolute risk for coronary heart disease of 10.2% in 10 years. In such a patient, changes in plasma total cholesterol (−22.09%) and HDL (−3.17%) cholesterol as those seen in the raltegravir group at 48 weeks would have resulted in a risk reduction of 1.2% points. In the same patient, changes in plasma total cholesterol (+1.82%) and HDL (+5.84%) cholesterol as those seen in the boosted protease inhibitor group at 48 weeks would have resulted in a risk reduction of only 0.4% points. Moreover, the reduction in triglycerides in the raltegravir group might be also associated with an additional, although modest, reduction in the risk of myocardial infarction that cannot be directly estimated from Framingham score, as recently reported in a substudy of the D:A:D study [28].

In summary, switching from ritonavir-boosted protease inhibitor to raltegravir in patients with sustained virological suppression on ritonavir-boosted protease inhibitor-based therapy in the SPIRAL study demonstrated noninferior efficacy and resulted in a better lipid profile at 48 weeks than continuing ritonavir-boosted protease inhibitor.

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