Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials

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Summary

Background To reduce lipid abnormalities and other side-effects associated with antiretroviral regimens containing lopinavir-ritonavir, patients might want to switch one or more components of their regimen. We compared substitution of raltegravir for lopinavir-ritonavir with continuation of lopinavir-ritonavir in HIV-infected patients with stable viral suppression on lopinavir-ritonavir-based combination therapy.

Methods The SWITCHMRK 1 and 2 studies were multicentre, double-blind, double-dummy, phase 3, randomised controlled trials. HIV-infected patients aged 18 years or older were eligible if they had documented viral RNA (vRNA) concentration below the limit of assay quantification for at least 3 months while on a lopinavir-ritonavir-based regimen. 707 eligible patients were randomly allocated by interactive voice response system in a 1:1 ratio to switch from lopinavir-ritonavir to raltegravir (400 mg twice daily; n=353) or to remain on lopinavir-ritonavir (two 200 mg/50 mg tablets twice daily; n=354), while continuing background therapy consisting of at least two nucleoside or nucleotide reverse transcriptase inhibitors. Primary endpoints were the mean percentage change in serum lipid concentrations from baseline to week 12; the proportion of patients with vRNA concentration less than 50 copies per mL at week 24 (with all treated patients who did not complete the study counted as failures) with a prespecified non-inferiority margin of –12% for each study; and the frequency of adverse events up to 24 weeks. Analyses were done according to protocol. These trials are registered with ClinicalTrials.gov, numbers NCT00443703 and NCT00443729.

Findings 702 patients received at least one dose of study drug and were included in the efficacy and safety analyses for the combined trials (raltegravir, n=350; lopinavir-ritonavir, n=352). Percentage changes in lipid concentrations from baseline to week 12 were significantly greater (p<0·0001) in the raltegravir group than in the lopinavir-ritonavir group in each study, yielding combined results for total cholesterol –12·6% *vs* 1·0%, non-HDL cholesterol –15·0% *vs* 2·6%, and triglycerides –42·2% *vs* 6·2%. At week 24, 293 (84·4%, 95% CI 80·2–88·1) of 347 patients in the raltegravir group had vRNA concentration less than 50 copies per mL compared with 319 (90·6%, 87·1–93·5) of 352 patients in the lopinavir-ritonavir group (treatment difference –6·2%, –11·2 to –1·3). Clinical and laboratory adverse events occurred at similar frequencies in the treatment groups. There were no serious drug-related adverse events or deaths. The only drug-related clinical adverse event of moderate to severe intensity reported in 1% or more of either treatment group was diarrhoea, which occurred in ten patients in the lopinavir-ritonavir group (3%) and no patients in the raltegravir group. The studies were terminated at week 24 because of lower than expected virological efficacy in the raltegravir group compared with the lopinavir-ritonavir group.

Interpretation Although switching to raltegravir was associated with greater reductions in serum lipid concentrations than was continuation of lopinavir-ritonavir, efficacy results did not establish non-inferiority of raltegravir to lopinavir-ritonavir.

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Introduction

Combination antiretroviral regimens have improved clinical outcomes in patients with HIV infection, saving millions of years of productive life.[1–3] The choice of regimen for the treatment of HIV-1 infection is based on relative efficacy and tolerability in comparative trials, the patient's underlying comorbidities, potential drug interactions, history of adverse drug effects, and concern over long-term complications.[4,5] Regimens containing lopinavir-ritonavir provide effective antiretroviral therapy, but can lead to lipid abnormalities and other side-effects that are disproportionately (although not exclusively) associated with the protease-inhibitor class of drugs.[6–13] Raltegravir is an HIV-1 integrase strand transfer inhibitor that offers another therapeutic option in addition to the older classes of antiretroviral agents.[14]

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Combination therapy with raltegravir has been generally well tolerated and efficacious in both treatment-naive and treatment-experienced patients.[15–20] In these studies, raltegravir-based regimens did not have major effects on serum lipid concentrations.

To enhance convenience or diminish side-effects, patients on effective combination antiretroviral therapy might want to switch one or more components of their treatment regimen. The SWITCHMRK trials were two phase 3 studies designed to investigate the potential of substituting raltegravir for lopinavir-ritonavir to improve the adverse event profile of lopinavir-ritonavir-based combination regimens in stable HIV-infected patients who had achieved viral suppression. We assessed the relative effects of a switch from lopinavir-ritonavir to raltegravir versus continuation of lopinavir-ritonavir on serum lipid concentrations, viral suppression, and adverse events.

Methods

Study design

The SWITCHMRK 1 and 2 studies (MK-0518 protocols 032 and 033, respectively) were identically designed, double-blind, randomised, active-controlled clinical trials. Patients were enrolled from 81 centres in five continents between June 11, 2007, and May 15, 2008. The protocols were approved by the institutional review boards or ethics review committees at each study site. All participants provided written informed consent.

Patients with HIV infection who were aged 18 years or older were eligible for the studies if they had documented plasma viral RNA (vRNA) concentration lower than 50 copies per mL by PCR or lower than 75 copies per mL by branched DNA assay for at least 3 months while on a lopinavir-ritonavir-based regimen. The current regimen had to include at least two nucleoside or nucleotide reverse transcriptase inhibitors and no other protease inhibitors. The lopinavir-ritonavir-based regimen at study entry was not required to be the patient's first-ever antiretroviral therapy. Patients who had virological failure on previous regimens but then achieved viral suppression on a lopinavir-ritonavir-based regimen for at least 3 months were eligible. Exclusion criteria were pregnancy, breastfeeding, treatment with lipid-lowering agents during the preceding 12 weeks, or a history of diabetes mellitus, coronary artery disease, acute or decompensated chronic hepatitis, renal insufficiency requiring dialysis, or any medical disorder likely to interfere with the execution or interpretation of the study. Patients with stable chronic hepatitis were eligible if their serum aminotransferase concentrations were less than or equal to five times the upper limit of the normal range.

Randomisation and masking

Once patients had satisfied all eligibility requirements and were stratified by duration of lopinavir-ritonavir use before study entry (≤1 year *vs* >1 year), study site personnel accessed a central interactive voice response system (IVRS) and allocated patients according to a computer-generated randomised allocation schedule in a 1:1 ratio to receive raltegravir or lopinavir-ritonavir, each in combination with the other antiretroviral agents in their baseline regimen. Drugs were packaged, assigned unique kit numbers, and aligned with a treatment group in the IVRS database. The IVRS selected a kit number associated with the patient's treatment assignment from the inventory at the study site. Treatment allocation was concealed from investigators, study site personnel, patients, monitors, and central laboratory personnel by use of blinded access codes. Masking was maintained through use of placebo tablets with identical appearance. In a double-dummy design, participants received a 400 mg tablet of raltegravir (Isentress; Merck, Whitehouse Station, NJ, USA) or identical placebo and two lopinavir-ritonavir 200 mg/50 mg tablets (Kaletra; Abbott, Chicago, IL, USA) or identical placebos twice daily approximately 12 h apart without regard to food intake. Other antiretroviral drugs were continued without change unless modifications were needed because of toxic effects.

Procedures

vRNA concentrations were measured at a central laboratory by the Ultrasensitive Amplicor HIV-1 Monitor assay version 1.5 (Roche Diagnostics; Branchburg, NJ, USA) with a low quantification limit of 50 vRNA copies per mL. Confirmed virological failure was operationally defined as a vRNA concentration 50 copies per mL or more on two consecutive measurements at least 1 week apart. Raltegravir resistance was investigated by integrase genotyping of virus from patients who had virological failure with vRNA concentration more than 400 copies per mL.[19] Other resistance testing was done on volumes of the samples from the same timepoint by the PhenoSense GT assay (Monogram Biosciences; San Francisco, CA, USA).

Primary endpoints were the mean percentage change in lipid concentrations from baseline to week 12, the proportion of patients with vRNA concentration less than 50 copies per mL at week 24, and the frequency of adverse events up to 24 weeks.

Statistical analysis

Unless otherwise noted, all analyses were specified by protocol and done with SAS software version 9.1/8.2. All randomised patients treated with at least one dose of study drug were included in the efficacy and safety analyses. Analyses of changes in lipid concentrations from baseline to week 12, and efficacy and safety analyses at week 24 were prespecified per protocol for each individual study for hypothesis testing. Analyses of the combined studies were done to provide more precise estimates of treatment

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effects; no hypothesis testing was specified on the composite data set in the data analysis plan.

The percentage changes from baseline in fasting LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and total cholesterol at week 12 were analysed with ANCOVA models with terms for baseline lipid concentration, duration of lopinavir-ritonavir-based regimen (≤1 year *vs* >1 year), and treatment assignment. The percentage change from baseline in fasting triglycerides was analysed with a non-parametric ANCOVA model with terms for baseline concentration, duration of lopinavir-ritonavir-based regimen, and treatment assignment. With 170 patients in each treatment group, the individual studies had more than 99% power to detect a between-treatment difference of 11%, 53%, and 13% in the mean percentage change from baseline in total cholesterol, triglycerides, and non-HDL cholesterol, respectively, and 71% power to detect a 4% treatment difference in the mean percentage change from baseline in LDL cholesterol.

In each study, raltegravir would be judged non-inferior to lopinavir-ritonavir if the lower bound of the two-sided 95% CI for the proportion of patients with vRNA concentration less than 50 copies per mL at week 24 in the raltegravir group minus the response rate in the lopinavir-ritonavir group was higher than –12%. 95% CIs for the treatment difference were calculated by the method of Miettinen and Nurminen.[21] On the assumption of a true response rate of 87·5% at week 24 for both the raltegravir and lopinavir-ritonavir groups with 170 patients in each group, the individual studies would have 90% power to show non-inferiority.

To calculate virological response rates, the primary approach for handling missing data was to regard all treated patients who did not complete the study as failures. In this analysis, missing vRNA measurements were imputed as failures, irrespective of the reason for absence, unless the values immediately before and after the missing value were both less than 50 copies per mL, in which case the absent value was recorded as missing. Sensitivity analyses with an observed-failure approach to missing data were also specified, in which no imputation was made for missing values unless the data were missing as a result of discontinuation because of lack of efficacy or the last value at discontinuation was a failure. The time to confirmed virological failure was defined as the time from randomisation until the first of two consecutive vRNA concentrations of 50 copies per mL or more measured at least 1 week apart. Kaplan-Meier estimates of time to virological failure were calculated by treatment group. Changes from baseline in CD4-cell counts were summarised over the course of the study by use of the data-as-observed method with no imputation for missing values.

Subgroup efficacy analyses were prespecified for age, ethnic origin, sex, region, hepatitis B and C status, and duration of lopinavir-ritonavir use before study entry (≤1 year *vs* >1 year). After reviewing the results from the protocol-specified hypotheses, we undertook exploratory analyses based upon retrospective collection of supplementary data from the two studies to examine virological response rates in patients for whom the lopinavir-ritonavir-based regimen was their first versus later antiretroviral regimen and in patients with a history of virological failure on a previous antiretroviral regimen versus those without.

Adverse events occurring at any time during the study or within 14 days after discontinuation were included in the safety analysis. Investigators assessed whether each adverse event was related to any drug in the study regimen. Investigators graded clinical adverse events as mild, moderate, or severe. Severity of laboratory abnormalities was graded according to the 1992 Division of AIDS (DAIDS) toxicity guidelines for adults.[22] Adverse event terms were adopted from the Medical Dictionary for Regulatory Activities (MedDRA version 11.0).[23] Frequencies of adverse events were not adjusted for duration of follow-up. The proportions of patients with clinical and laboratory adverse events were compared between treatment groups for the following categories: (1) at least one adverse event; (2) drug-related adverse events; (3) serious adverse events; (4) serious drug-related adverse events; and (5) discontinuation of study treatment because of an adverse event. For adverse events occurring in 20% of patients, each study had 80% power to declare with 95% confidence that the true difference between treatment groups was 12% or lower. If a particular adverse event was not recorded in 170 patients, it could be concluded with 95% confidence that its true incidence was 2% or lower.

A scientific advisory committee periodically reviewed blinded safety and efficacy results from each study. After examining data from the planned efficacy analyses at week 24, a recommendation to stop the studies was made because of lower than expected efficacy in patients who switched to a raltegravir-based regimen compared with patients who remained on a lopinavir-ritonavir-based regimen. These trials are registered with ClinicalTrials.gov, numbers NCT00443703 and NCT00443729.

Role of the funding source

The study was designed, managed, and analysed by the sponsor in conjunction with external investigators. Employees of the sponsor were involved in the writing of the report. The report underwent formal review by the sponsor. Authors had access to all study data upon request. The sponsor committed to publishing these data at the inception of the trial. The authors made the final decisions about when and where to publish the data.

Results

Figure 1 shows the trial profiles for the SWITCHMRK 1 and 2 studies. 702 patients received at least one dose of study drug and were included in the efficacy and safety analyses (raltegravir, n=350; lopinavir-ritonavir, n=352),

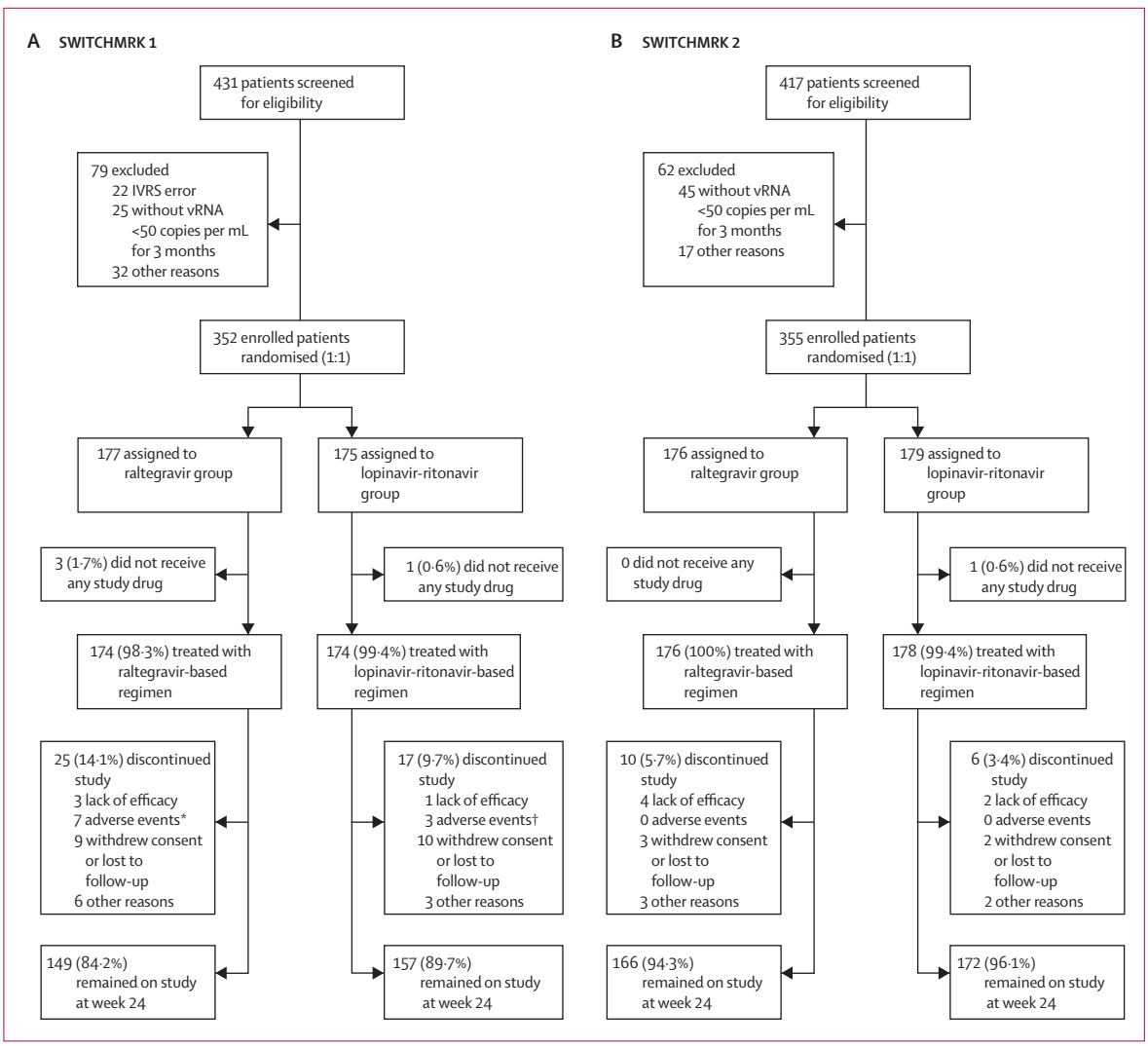

***Figure 1*: Trial profiles for the SWITCHMRK studies up to week 24**
Trial profiles for (A) SWITCHMRK 1 and (B) SWITCHMRK 2 up to the date when the last patient completed the visit at week 24. *One patient in the raltegravir group discontinued the study because of an adverse event based on the disposition record, but there was no associated adverse event recorded in the database. †One additional patient in the lopinavir-ritonavir group discontinued due to an adverse event after the last patient completed the week-24 visit. IVRS=interactive voice response system. vRNA=viral RNA.

of whom 249 (35%) were non-white and 152 (22%) were women. Table 1 shows baseline characteristics of patients. In the combined analysis of the two studies, patients in both treatment groups had received a median of five antiretroviral agents (IQR 4–7) before study entry over a median duration of 3·4 years (2·0–7·3) in the raltegravir group and 4·1 years (2·1–7·4) in the lopinavir-ritonavir group. 112 (32%) patients in the raltegravir group and 123 (35%) patients in the lopinavir-ritonavir group had virological failure on a previous antiretroviral regimen. 38 (5%) patients (raltegravir, n=17; lopinavir-ritonavir, n=21) had vRNA concentration 50 copies per mL or more at baseline (median 100·5 copies per mL [IQR 66·0–193·0]) despite screening for concentrations less than 50 copies per mL before randomisation. 35 (10%) patients assigned to raltegravir and 23 (7%) assigned to lopinavir-ritonavir discontinued the study (figure 1). The median time in the study ranged from 37 weeks to 41 weeks across treatment groups.

In both studies at week 12, raltegravir regimens were associated with significantly greater percentage reductions in baseline fasting total cholesterol, non-HDL cholesterol, and triglycerides than were lopinavir-ritonavir regimens ($p<0·0001$ for each pairwise comparison; figure 2). In the combined analysis, the changes in lipid concentrations for the raltegravir group compared with the lopinavir-ritonavir group were –12·6% versus 1·0% for total cholesterol, –15·0% versus 2·6% for non-HDL cholesterol, and –42·2% versus 6·2% for triglycerides. Changes in LDL cholesterol (1·1% *vs* 1·2%) and HDL

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	SWITCHMRK 1		SWITCHMRK 2		Combined SWITCHMRK studies	
	Raltegravir group (n=174)	Lopinavir-ritonavir group (n=174)	Raltegravir group (n=176)	Lopinavir-ritonavir group (n=178)	Raltegravir group (n=350)	Lopinavir-ritonavir group (n=352)
Sex (female)	28 (16%)	45 (26%)	39 (22%)	40 (22%)	67 (19%)	85 (24%)
Ethnic origin (non-white)	28 (16%)	33 (19%)	91 (52%)	97 (54%)	119 (34%)	130 (37%)
Region						
Africa	0	0	26 (15%)	20 (11%)	26 (7%)	20 (6%)
Asia*	0	0	23 (13%)	22 (12%)	23 (7%)	22 (6%)
Australia/Europe†	117 (67%)	121 (70%)	20 (11%)	20 (11%)	137 (39%)	141 (40%)
Latin America‡	0	0	75 (43%)	83 (47%)	75 (21%)	83 (24%)
USA/Canada	57 (33%)	53 (30%)	32 (18%)	33 (19%)	89 (25%)	86 (24%)
Age (years), mean (SD); median (IQR)	44·4 (8·9); 44 (39–49)	43·6 (9·1); 43 (38–50)	42·0 (9·4); 42 (35–47)	41·9 (9·0); 40 (35–48)	43·2 (9·2); 43 (37–48)	42·8 (9·1); 42 (36–49)
CD4-cell count (cells per µL)	436 (310–638)	479 (335–664)	436 (286–628)	426 (306–621)	436 (298–637)	454 (315–642)
Suppressed viraemia§	164 (94%)	161 (93%)	169 (96%)	170 (96%)	333 (95%)	331 (94%)
Duration of lopinavir-ritonavir therapy >1 year	145 (83%)	143 (82%)	145 (82%)	145 (81%)	290 (83%)	288 (82%)
Antiretroviral therapy before study entry						
Duration (years)	3·3 (1·8–7·6)	3·6 (1·9–6·9)	3·7 (2·4–7·0)	4·6 (2·7–7·7)	3·4(2·0–7·3)	4·1 (2·1–7·4)
Number of drugs	5·0 (4–7)	5·0 (4–7)	5·5 (4–8)	6·0 (4–7)	5·0 (4–7)	5·0 (4–7)
Lopinavir-ritonavir as first regimen¶						
Yes	73 (42%)	75 (43%)	57 (32%)	55 (31%)	130 (37%)	130 (37%)
No	101 (58%)	99 (57%)	119 (68%)	123 (69%)	220 (63%)	222 (63%)
History of previous virological failure¶‖						
Yes	48 (28%)	58 (33%)	64 (36%)	65 (37%)	112 (32%)	123 (35%)
No	122 (70%)	113 (65%)	108 (61%)	108 (61%)	230 (66%)	221 (63%)
Unknown	4 (2%)	3 (2%)	4 (2%)	5 (3%)	8 (2%)	8 (2%)
Fasting lipid concentrations (mmol/L)						
Total cholesterol	5·58 (1·25)	5·28 (1·35)	5·56 (1·81)	5·46 (1·20)	5·57 (1·56)	5·37 (1·28)
Non-HDL cholesterol	4·29 (1·26)	4·06 (1·37)	4·36 (1·86)	4·23 (1·18)	4·32 (1·60)	4·15 (1·28)
LDL cholesterol	2·99 (1·04)	2·71 (0·93)	2·68 (1·06)	2·70 (0·79)	2·83 (1·06)	2·71 (0·86)
HDL cholesterol	1·26 (0·42)	1·22 (0·36)	1·20 (0·33)	1·24 (0·33)	1·23 (0·38)	1·23 (0·35)
Triglycerides, median (robust SD)	2·14 (1·51)	1·83 (1·27)	2·31 (1·77)	2·46 (1·77)	2·26 (1·62)	2·05 (1·53)

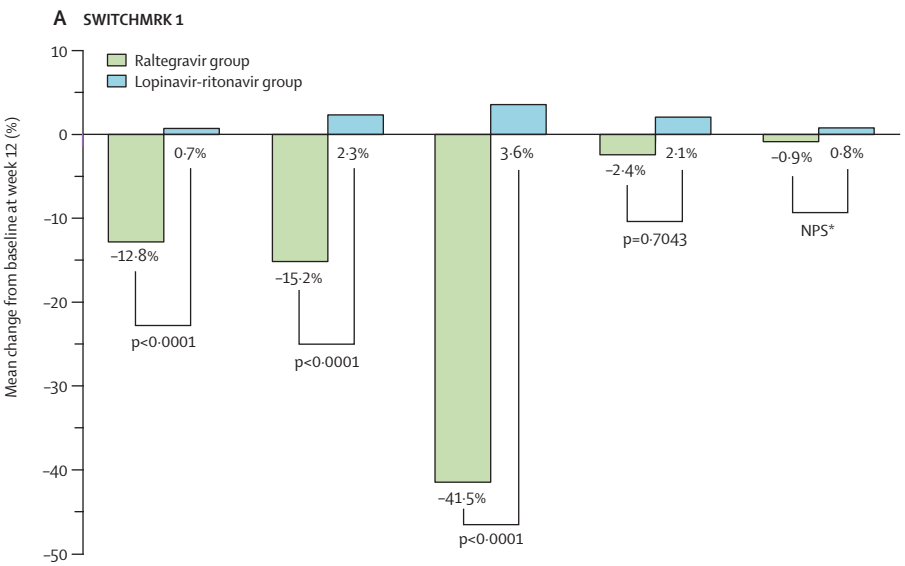
Data are n (%), median (IQR), or mean (SD), unless otherwise indicated. *Study sites in Asia were located exclusively in southeast Asia. †SWITCHMRK 2 had no sites in Europe. ‡Study sites in Latin America included sites in Central or South America. §Screening viral RNA concentrations had to be less than the limit of assay quantification for at least 3 months on a lopinavir-ritonavir-based regimen; baseline viral RNA concentrations were measured on the day of randomisation. ¶These data were obtained retrospectively after the protocol-specified analyses were reviewed. ‖Investigator-reported history of virological failure before entry.

Table 1: **Selected baseline characteristics by treatment group**

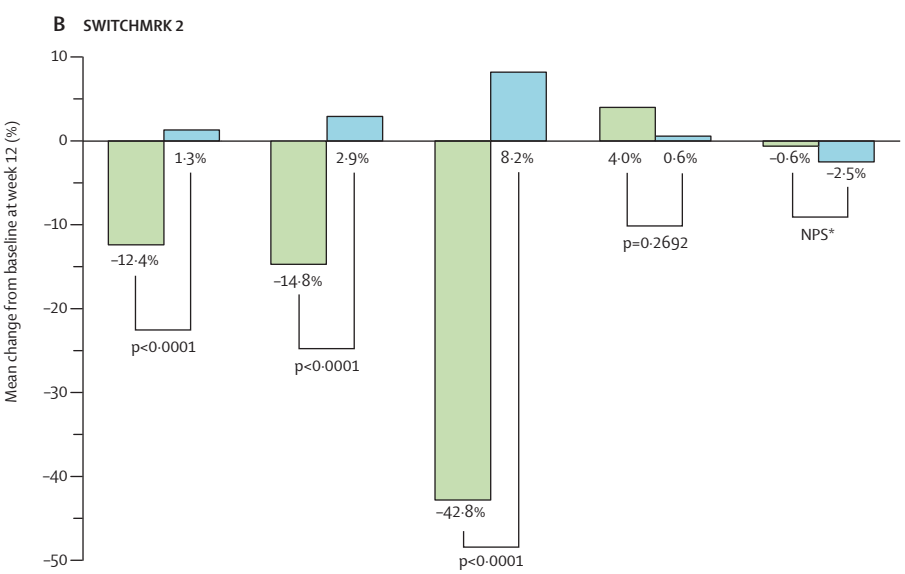
cholesterol (–0·7% *vs* –1·0%) were similar in the raltegravir and lopinavir-ritonavir groups.

In an analysis that judged all treated patients who did not complete the study as failures, viral suppression to less than 50 vRNA copies per mL at week 24 was achieved by 139 (80·8%) patients in the raltegravir group compared with 152 (87·4%) in the lopinavir-ritonavir group in SWITCHMRK 1, and by 154 (88·0%) patients in the raltegravir group compared with 167 (93·8%) in the lopinavir-ritonavir group in SWITCHMRK 2 (figure 3). The treatment differences were –6·6% (95% CI –14·4 to 1·2) for SWITCHMRK 1 and –5·8% (–12·2 to 0·2) for SWITCHMRK 2 (table 2). In the combined analysis, viral suppression to less than 50 copies per mL was achieved by 293 (84·4%) patients in the raltegravir group compared with 319 (90·6%) patients in the lopinavir-ritonavir group at week 24, (difference –6·2%, –11·2 to –1·3). Similar results were obtained in sensitivity analyses with an observed-failure approach to missing data (data not shown).

The analysis of time to confirmed virological failure included all available data up to the date when the last patient completed the visit at week 24. Time to confirmed virological failure was similar for the raltegravir and lopinavir-ritonavir groups in SWITCHMRK 1 (log-rank test, p=0·5023), whereas it was shorter for patients in the raltegravir group than for those in the lopinavir-ritonavir group in SWITCHMRK 2 (log-rank test, p=0·0136; figure 3). Of 38 patients with baseline vRNA concentration more than 50 copies per mL, seven (41%) of 17 in the raltegravir group and ten (48%) of 21 in the lopinavir-ritonavir group had a vRNA concentration



Mean concentration (SD) at baseline (mmol/L)	Total cholesterol	Non-HDL cholesterol	Triglycerides†	LDL cholesterol	HDL cholesterol
Raltegravir group	5·6 (1·3)	4·3 (1·3)	2·1 (1·5)	3·0 (1·0)	1·3 (0·4)
Lopinavir-ritonavir group	5·3 (1·4)	4·1 (1·4)	1·8 (1·3)	2·7 (0·9)	1·2 (0·4)
Mean concentration (SD) at week 12 (mmol/L)					
Raltegravir group	4·8 (1·0)	3·6 (1·0)	1·3 (0·8)	2·8 (0·9)	1·2 (0·4)
Lopinavir-ritonavir group	5·3 (1·4)	4·1 (1·4)	1·9 (1·6)	2·7 (0·9)	1·2 (0·3)



Mean concentration (SD) at baseline (mmol/L)	Total cholesterol	Non-HDL cholesterol	Triglycerides†	LDL cholesterol	HDL cholesterol
Raltegravir group	5·6 (1·8)	4·3 (1·9)	2·4 (1·8)	2·7 (1·1)	1·2 (0·3)
Lopinavir-ritonavir group	5·5 (1·1)	4·2 (1·1)	2·5 (1·8)	2·7 (0·8)	1·2 (0·3)
Mean concentration (SD) at week 12 (mmol/L)					
Raltegravir group	4·7 (1·3)	3·6 (1·3)	1·4 (0·8)	2·7 (1·1)	1·2 (0·3)
Lopinavir-ritonavir group	5·5 (1·2)	4·3 (1·2)	2·7 (2·1)	2·7 (0·8)	1·2 (0·3)

***Figure 2*: Changes in fasting lipid concentrations from baseline to week 12 in (A) SWITCHMRK 1 and (B) SWITCHMRK 2 studies**

The percentage change from baseline to week 12 in fasting total cholesterol, non-HDL cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. Mean changes are presented apart from triglyceride concentration where the median change is shown. In a post-hoc calculation, the mean percentage changes from baseline in the total cholesterol:HDL-cholesterol ratio were –9·2% in the raltegravir group and 3·4% in the lopinavir-ritonavir group in SWITCHMRK 1 and –9·2% in the raltegravir group and 6·3% in the lopinavir-ritonavir group in SWITCHMRK 2. The mean lipid concentrations (SD) at baseline and week 12 are given for each treatment group below the figures. *NPS=not prespecified for statistical testing. †Median change shown for concentration of triglycerides.

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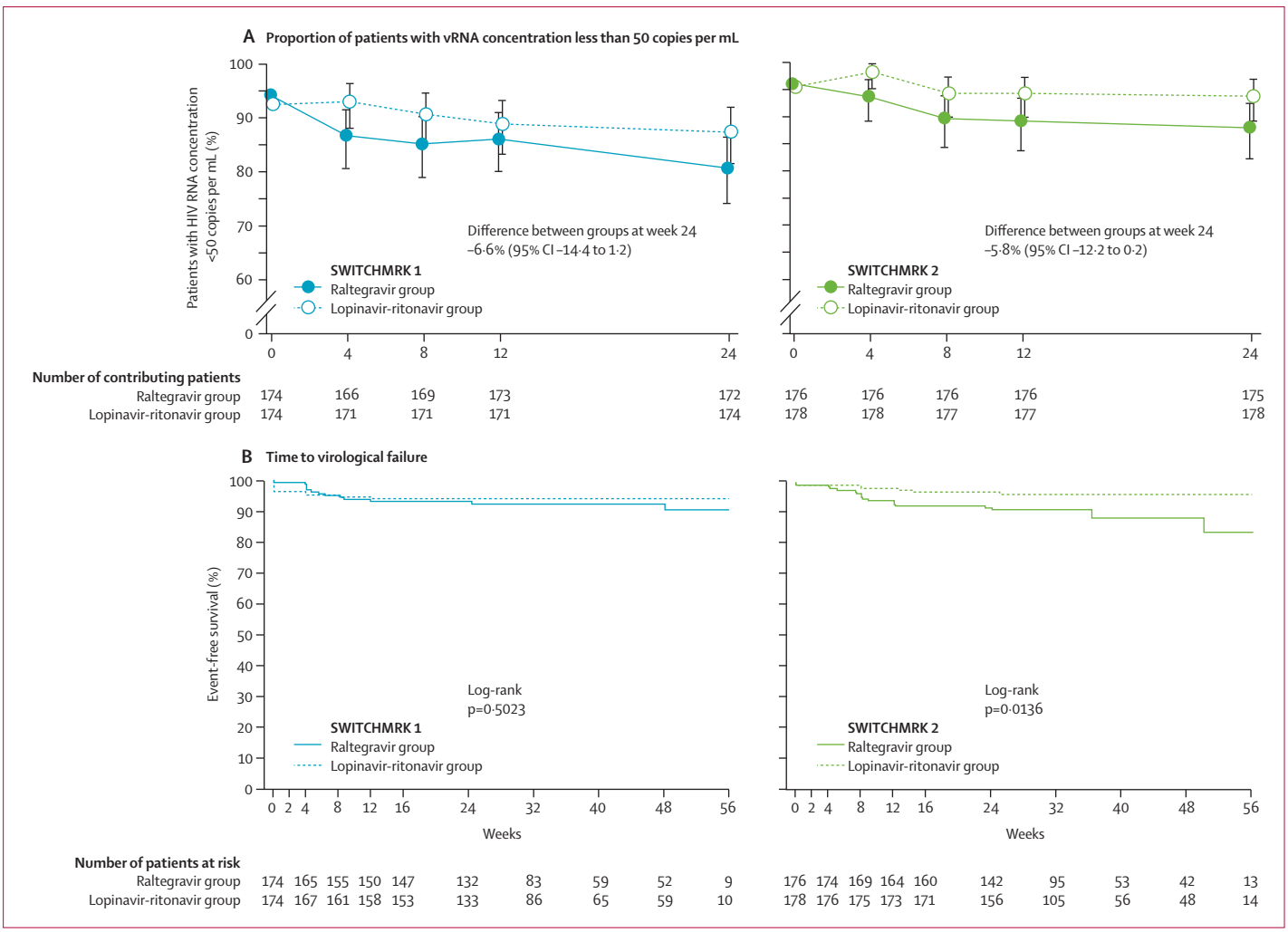

***Figure 3*: Virological results over time**

(A) Proportion of patients with HIV RNA concentration less than 50 copies per mL for SWITCHMRK 1 and SWITCHMRK 2. All patients who did not complete the study were regarded as failures. The numbers below the x axis give the numbers of participants with data at each timepoint. Error bars represent 95% CIs. (B) Time to confirmed virological failure by treatment group for SWITCHMRK 1 and SWITCHMRK 2. Time to virological failure was defined as the time on study until the first of two consecutive vRNA concentrations of 50 copies per mL or more measured at least 1 week apart. Kaplan-Meier estimates were computed for time to virological failure for each treatment group. All available samples obtained up to the date when the last patient completed the visit at week 24 were included in the analysis. The numbers below the x axis give the numbers of participants contributing to the analysis at each timepoint. vRNA=viral RNA.

more than 50 copies per mL at week 24. Mean changes in CD4-cell count from baseline to week 24 were small, ranging from 5 cells per µL to 17 cells per µL, and did not differ between treatment groups.

Table 2 compares virological results at week 24; results are shown in patients for whom the lopinavir-ritonavir-based regimen at study entry was their first antiretroviral regimen versus patients who had received previous antiretroviral treatment, and in patients with a history of virological failure on a previous antiretroviral regimen versus those without such a history. In the subgroup of patients from both studies for whom the lopinavir-ritonavir-based regimen at study entry was their first antiretroviral regimen, the between-treatment group difference was –2·5% (95% CI –10·6 to 5·4) at week 24 (regarding all patients who did not complete the study as failures); in the subgroup of patients without history of virological failure, the between-treatment group difference was –1·0% (–6·9 to 4·9) at week 24. Similar results were seen in the sensitivity analyses with an observed-failure approach to missing data (data not shown). The differences in response rates between treatment groups in the prespecified subgroup analyses by age, ethnic origin, sex, region, hepatitis B and C status, and duration of lopinavir-ritonavir use before study entry were generally similar to the overall results (data not shown).

Clinical and laboratory adverse events occurred at similar frequencies in both treatment groups (table 3). There were no serious drug-related adverse events or deaths. In the combined analysis, the only drug-related clinical adverse event of moderate to severe intensity

	Raltegravir group		Lopinavir-ritonavir group		Treatment difference
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI*)
Lopinavir-ritonavir-based therapy as the first regimen					
SWITCHMRK 1					
Overall	139/172	80·8% (74·1 to 86·4)	152/174	87·4% (81·5 to 91·9)	−6·6% (−14·4 to 1·2)
Yes	62/72	86·1% (75·9 to 93·1)	65/75	86·7% (76·8 to 93·4)	−0·6% (−12·2 to 10·9)
No	77/100	77·0% (67·5 to 84·8)	87/99	87·9% (79·8 to 93·6)	−10·9% (−21·6 to −0·3)
SWITCHMRK 2					
Overall	154/175	88·0% (82·2 to 92·4)	167/178	93·8% (89·2 to 96·9)	−5·8% (−12·2 to 0·2)
Yes	50/56	89·3% (78·1 to 96·0)	52/55	94·5% (84·9 to 98·9)	−5·3% (−16·9 to 5·7)
No	104/119	87·4% (80·1 to 92·8)	115/123	93·5% (87·6 to 97·2)	−6·1% (−14·1 to 1·4)
Combined studies					
Overall	293/347	84·4% (80·2 to 88·1)	319/352	90·6% (87·1 to 93·5)	−6·2% (−11·2 to −1·3)
Yes	112/128	87·5% (80·5 to 92·7)	117/130	90·0% (83·5 to 94·6)	−2·5% (−10·6 to 5·4)
No	181/219	82·6% (77·0 to 87·4)	202/222	91·0% (86·4 to 94·4)	−8·3% (−14·8 to −2·1)
Investigator report of a history of previous virological failure†					
SWITCHMRK 1					
Yes	34/47	72·3% (57·4 to 84·4)	52/58	89·7% (78·8 to 96·1)	−17·3% (−33·0 to −2·5)
No	103/121	85·1% (77·5 to 90·9)	97/113	85·8% (78·0 to 91·7)	−0·7% (−9·9 to 8·6)
SWITCHMRK 2					
Yes	51/64	79·7% (67·8 to 88·7)	61/65	93·8% (85·0 to 98·3)	−14·2% (−26·5 to −2·6)
No	99/107	92·5% (85·8 to 96·7)	101/108	93·5% (87·1 to 97·4)	−1·0% (−8·5 to 6·3)
Combined studies					
Yes	85/111	76·6% (67·6 to 84·1)	113/123	91·9% (85·6 to 96·0)	−15·3% (−24·9 to −6·2)
No	202/228	88·6% (83·7 to 92·4)	198/221	89·6% (84·8 to 93·3)	−1·0% (−6·9 to 4·9)

Patients who did not complete the trial were regarded as failures. Similar results were seen in the corresponding analyses that used an observed-failure approach to missing data. *95% CIs for the treatment difference calculated by the method of Miettinen and Nurminen.[21] †Patients with missing data for history of virological failure were excluded from this subanalysis.

Table 2: **Proportion of patients with viral RNA concentration less than 50 copies per mL at week 24 in the SWITCHMRK studies**

reported in 1% or more of either treatment group was diarrhoea, which occurred in ten patients in the lopinavir-ritonavir group (3%) and no patients in the raltegravir group. Six patients in the raltegravir group discontinued treatment early because of adverse events (hypersensitivity, n=1; diarrhoea, n=1; acute stress disorder, n=1; adverse drug reaction, n=1; raised serum concentration of alanine aminotransferase, n=2). In the lopinavir-ritonavir group, four patients discontinued treatment because of adverse events (vomiting, n=1; upper abdominal pain with diarrhoea, n=1; pulmonary tuberculosis, n=1; diarrhoea associated with an increased serum concentration of creatinine, n=1). Grade 3 or 4 laboratory abnormalities were infrequent and generally balanced between groups (table 4).

49 patients met the protocol definition of confirmed virological failure. Of 32 patients assigned to raltegravir with confirmed virological failure, 27 (84%) reported that their lopinavir-ritonavir regimen at study entry was not their first antiretroviral regimen. 18 (67%) of these patients had a history of virological failure on previous regimens. Of 17 patients assigned to lopinavir-ritonavir with confirmed virological failure, eight (47%) reported that their lopinavir-ritonavir regimen at study entry was not their first antiretroviral regimen and four (50%) of these patients reported a history of virological failure on previous regimens. Genotypic resistance testing was done on 14 of 16 patients with confirmed virological failure and vRNA concentration more than 400 copies per mL (table 5). Of the 11 assessable patients who rebounded on raltegravir-based therapy, virus with mutations known to confer raltegravir resistance was found in eight patients; in five of these eight patients,

	SWITCHMRK 1		SWITCHMRK 2		Combined SWITCHMRK studies	
	Raltegravir group (n=174)	Lopinavir-ritonavir group (n=174)	Raltegravir group (n=176)	Lopinavir-ritonavir group (n=178)	Raltegravir group (n=350)	Lopinavir-ritonavir group (n=352)
Clinical adverse events						
One or more adverse event	109 (62·6%)	106 (60·9%)	123 (69·9%)	112 (62·9%)	232 (66·3%)	218 (61·9%)
Drug-related adverse event*	24 (13·8%)	19 (10·9%)	23 (13·1%)	35 (19·7%)	47 (13·4%)	54 (15·3%)
Serious adverse event	15 (8·6%)	10 (5·7%)	4 (2·3%)	8 (4·5%)	19 (5·4%)	18 (5·1%)
Discontinuation due to adverse event†‡	4 (2·3%)	4 (2·3%)	0	0	4 (1·1%)	4 (1·1%)
Discontinuation due to drug-related adverse event*	2 (1·1%)	3 (1·7%)	0	0	2 (0·6%)	3 (0·9%)
Discontinuation due to serious adverse event	1 (0·6%)	1 (0·6%)	0	0	1 (0·3%)	1 (0·3%)
Laboratory adverse events						
One or more adverse event	11 (6·3%)	7 (4·0%)	8 (4·5%)	6 (3·4%)	19 (5·4%)	13 (3·7%)
Drug-related adverse event*	6 (3·4%)	2 (1·1%)	4 (2·3%)	1 (0·6%)	10 (2·9%)	3 (0·9%)
Serious adverse event	0	0	0	0	0	0
Discontinuation due to adverse event†	2 (1·1%)	1 (0·6%)	0	0	2 (0·6%)	1 (0·3%)
Discontinued due to drug-related adverse event*	2 (1·1%)	1 (0·6%)	0	0	2 (0·6%)	1 (0·3%)
Discontinuation due to serious adverse event	0	0	0	0	0	0

Data are n (%). For the individual studies, there were no significant differences at an α level of 0·05 between the raltegravir and lopinavir-ritonavir groups for any category of clinical adverse event listed in the table. *Deemed by the investigator to be drug-related. †One patient in the lopinavir-ritonavir group had both a clinical and laboratory-associated adverse event that together led to discontinuation. ‡One patient in the lopinavir-ritonavir group had a clinical adverse event leading to discontinuation that occurred after the last patient completed the week-24 visit. Consequently, this patient was not shown in figure 1 as a discontinuation.

Table 3: **Types and frequencies of clinical and laboratory adverse events during the SWITCHMRK studies**

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resistance mutations were also found in the reverse transcriptase gene. One additional patient had a mixture of viruses showing T97T/A, which might represent a polymorphism in the integrase gene; T97A confers a low-level decrease in susceptibility to raltegravir.

Discussion

In SWITCHMRK 1 and 2, HIV-infected patients with stable viral suppression on lopinavir-ritonavir-based combination therapy who switched to raltegravir had greater reductions in concentrations of triglycerides, total cholesterol, and non-HDL cholesterol from baseline to week 12 than did patients who continued on lopinavir-ritonavir. However, the efficacy results of the individual studies did not establish non-inferiority of raltegravir to lopinavir-ritonavir, measured by the proportion of patients with vRNA concentration less than 50 copies per mL at week 24. In the combined analysis of the two studies, switching to raltegravir was associated with a lower virological response rate at week 24 than was continuation of lopinavir-ritonavir, leading to early termination of the trials. Virus resistant to raltegravir was detected in most assessable patients who developed virological failure on raltegravir, and the mutational patterns were consistent with genotypes previously reported in treatment-experienced and treatment-naive patients who had treatment failure with this drug.[14,19,20,25] Both study drugs were generally well tolerated, and no deaths or serious drug-related adverse events occurred during the trials.

In large phase 3 studies of raltegravir in treatment-experienced[18] and treatment-naive patients,[20] raltegravir-based combination regimens rapidly suppressed HIV RNA concentrations below the limit of detection in most patients. In heavily pretreated patients infected with multiclass-resistant virus, virological response rates were better when raltegravir was combined with two or more other active agents; results were less robust but still substantial when raltegravir was combined with a single fully active drug or no active drugs.[19] In phase 2 and 3 clinical trials, modest changes in serum concentrations of cholesterol and triglycerides were seen up to at least 48 weeks of raltegravir treatment.[15–18,20] In view of the drug's antiretroviral efficacy in treatment-naive and treatment-experienced patients together with minor lipid effects and overall tolerability, a study of raltegravir as a substitute for a ritonavir-boosted protease inhibitor in a suppressive combination regimen was a logical step in the exploration of raltegravir use in patients with HIV infection.

Our finding that substitution of lopinavir-ritonavir for raltegravir did not achieve non-inferiority compared with continuation of lopinavir-ritonavir underscores the complex considerations involved in providing the best possible treatment regimens for individual patients. To understand the different virological response rates in the treatment groups of the SWITCHMRK trials, we undertook subgroup analyses. The prespecified set of subgroup analyses yielded virological results generally consistent with the overall results. However, when specific features of antiretroviral treatment history were examined from a retrospective collection of supplementary data, a plausible explanation for the virological results favouring lopinavir-ritonavir in the overall study population emerged. Participants whose lopinavir-ritonavir-based regimen at screening was their first regimen or patients without previous virological failure had similar virological response rates at week 24 in both treatment groups. Baseline resistance testing could not be done because patients needed to have

	Toxicity criteria*	SWITCHMRK 1		SWITCHMRK 2		Combined SWITCHMRK studies	
		Raltegravir group (n=174)	Lopinavir-ritonavir group (n=174)	Raltegravir group (n=176)	Lopinavir-ritonavir group (n=178)	Raltegravir group (n=350)	Lopinavir-ritonavir group (n=352)
Absolute neutrophil count	<0·75×10^9 per L	1/174 (0·6%)	0/174	1/176 (0·6%)	1/178 (0·6%)	2/350 (0·6%)	1/352 (0·3%)
Haemoglobin	<75 g/L	0/174	0/174	0/176	0/178	0/350	0/352
Platelet count	<50×10^9 per L	2/173 (1·2%)	0/173	0/176	0/178	2/349 (0·6%)	0/351
Fasting LDL cholesterol	≥4·92 mmol/L	2/153 (1·3%)	2/155 (1·3%)	2/170 (1·2%)	2/167 (1·2%)	4/323 (1·2%)	4/322 (1·2%)
Fasting total cholesterol	>7·77 mmol/L	0/158	3/160 (1·9%)	3/172 (1·7%)	7/170 (4·1%)	3/330 (0·9%)	10/330 (3·0%)
Fasting triglycerides	>8·48 mmol/L	0/158	3/160 (1·9%)	2/172 (1·2%)	8/170 (4·7%)	2/330 (0·6%)	11/330 (3·3%)
Fasting glucose	>13·88 mmol/L	0/158	0/160	0/172	0/170	0/330	0/330
Creatinine	>1·8×ULN	0/174	1/174 (0·6%)	0/176	0/178	0/350	1/352 (0·3%)
Total bilirubin	>2·5×ULN	0/174	0/174	1/176 (0·6%)	2/178 (1·1%)	1/350 (0·3%)	2/352 (0·6%)
Alkaline phosphatase	>5×ULN	0/174	0/174	0/176	0/178	0/350	0/352
Lipase	>3×ULN	0/174	1/174 (0·6%)	0/176	0/178	0/350	1/352 (0·3%)
Aspartate aminotransferase	>5×ULN	2/174 (1·1%)	2/174 (1·1%)	0/176	0/178	2/350 (0·6%)	2/352 (0·6%)
Alanine aminotransferase	>5×ULN	7/174 (4·0%)	1/174 (0·6%)	3/176 (1·7%)	2/178 (1·1%)	10/350 (2·9%)	3/352 (0·9%)

Data are number of patients with an abnormal result/number of patients with a baseline laboratory value for the specified test (%). ULN=upper limit of normal range. *Laboratory tests reported in this table were specified per protocol to be graded by DAIDS criteria.[22]

Table 4: **Patients with grade 3 or 4 abnormalities for prespecified laboratory tests during the SWITCHMRK studies**

	Study drug mutations (INSTI or PI)*	Reverse transcriptase inhibitor mutations
SWITCHMRK 1		
Raltegravir		
1	N155H	K103N
2	T97T/A	V118I, M184V
3	None	None
Lopinavir-ritonavir		
4	None	None
5	Not done	Not done
SWITCHMRK 2		
Raltegravir		
6	L74I, E138E/A, G140G/S, Q148Q/H/R, N155N/H	M184V, Y181C
7	N155H, V151V/I	M184M/V
8	L74I, Y143Y/C, Q148Q/R, N155N/H	D67D/N, K70K/R, M184V, K219Q
9	Q148H, G140S	M184V, K103N, P225H
10	G140G/S, Q148Q/H/R, N155N/H	None
11	N155H	None
12	L74I, Q148Q/R, Y143Y/S†	None
13	None	None
14	Not done	Not done
Lopinavir-ritonavir		
15	M46L, V82A, L90M	K65R, D67N, K219E, Y181C
16	None	None

Data were derived by population sequencing. The aminoacid changes listed were present in any of multiple independent polymerase chain reactions without regard to linkage. For raltegravir, the listed mutations potentially confer resistance to raltegravir. For lopinavir, the table only lists major PI resistance mutations from the Monogram report.[24] Nucleoside and non-nucleoside reverse transcriptase inhibitor mutations are similarly listed.[24] Genotyping was also done on virus from a convenience sample of nine additional patients with confirmed virological failure and vRNA concentration between 50 copies per mL and 400 copies per mL. Virus from four of the seven patients in the raltegravir group showed aminoacid changes in the integrase gene that confer decreased sensitivity to raltegravir, including two patients with virus having the N155H mutation only, one patient with virus having the Q148R mutation only, and one patient with virus having the L74I, E138E/A, G140G/S/R, Q148Q/H, and N155N/H mutations. Analysis of the protease region in virus from two patients in the lopinavir-ritonavir group showed that neither virus had any genotypic or phenotypic resistance to PIs. Known resistance mutations for raltegravir include L74M, E92Q, T97A, E138A, E138K, G140A, G140S, Y143C, Y143H, Y143R, Q148H, Q148R, Q148K, V151I, N155H, and S230R in the HIV-1 integrase gene. Known major resistance mutations for PIs include D30N, L33F, M46I/L, G48V, I50L/V, V82A/F/T/S/L, I84V, and L90M in the HIV-1 protease gene. vRNA=viral RNA. INSTI=integrase strand transfer inhibitor. PI=protease inhibitor. *Phenotypic analysis of the viruses with mutations showed decreased susceptibility to the study drug. †The importance of the Y143Y/S mutation is currently unknown.

Table 5: **Resistance mutations in HIV from 16 patients with confirmed virological failure and vRNA concentration more than 400 copies per mL by week 24, by treatment group**

undetectable vRNA concentrations at screening; however, these subgroups of patients were likely to have been receiving at least two active reverse transcriptase inhibitors in their background therapy, providing adequate antiretroviral support for raltegravir. Our results are consistent with those of the STARTMRK trial,[20] in which treatment-naive patients received two active agents in addition to raltegravir, and the findings of the BENCHMRK trials,[18,19] in which treatment-experienced patients who received two or more active agents in combination with raltegravir had better virological responses than did those who received less active background regimens.

Major protease-inhibitor mutations are rarely selected by treatment failure when boosted protease-inhibitor regimens are used as first-line therapy.[6–10,26] Lopinavir-ritonavir monotherapy either as initial or as simplification therapy maintains viral suppression in around 60–85% of patients.[27–29] As with ritonavir-boosted protease inhibitors in general, lopinavir-ritonavir has a high genetic barrier to resistance. Long-term monotherapy with raltegravir has not been studied; however, in the BENCHMRK studies,[19] functional monotherapy sustained suppression in approximately 50% of patients. Since patients who had received previous antiretroviral therapy and patients with a history of virological failure were not excluded from the SWITCHMRK studies, this implied difference in efficacy between lopinavir-ritonavir and raltegravir when used as the only fully active agent could partly explain the 6% between-treatment difference in response rates at week 24 seen in our trials. However, resistance to reverse transcriptase inhibitors was documented at the time of virological failure in only five of eight assessable patients in the raltegravir group who were infected with raltegravir-resistant virus.

Efficacious antiretroviral regimens can be modified for a variety of reasons, such as better tolerability or lower toxicity of the new regimen, as well as convenience or simplification. The SWITCHMRK studies were double-blind trials in which treatment was switched, rather than simplified. The studies have similarities to and differences from earlier studies of switching versus continuation of stable therapy. All participants in the SWITCHMRK trials were changed to a more complicated regimen with an increased number of pills, possibly reducing adherence and affecting responses in both treatment groups. The double-dummy design helped to limit bias and prevent the differential dropout across treatment groups that was seen in the SLOAT trial.[30] The SWAN[31] and ATAZIP[32] studies were randomised, open-label trials in which treatment was switched (within the same drug class) to simpler regimens but eligibility was restricted on the basis of previous virological failure or resistance, possibly accounting for the higher suppression rates in these studies than those seen in the SWITCHMRK study populations. In the NEFA study,[33] in which previous treatment was not restricted and all patients were switched to a new drug class, most patients with virological failure had received suboptimum regimens in the past, resembling the SWITCHMRK findings. More recently, highly treatment-experienced patients suppressed on combination regimens containing twice-daily injections of enfuvirtide were randomly assigned to remain on enfuvirtide or to switch to raltegravir while continuing their background regimen.[34–35] In an open-label study, raltegravir was non-inferior to enfuvirtide as measured by the cumulative proportion of patients with confirmed vRNA concentration 400 copies per mL or more at 24 weeks.[36]

Limitations of our studies include the non-uniformity of the nucleoside and nucleotide drug regimens and the

failure to account upfront for past virological failures. Although our exploratory analyses provide a plausible explanation for the SWITCHMRK findings, these inferences will need to be confirmed in prospective studies.

The SWITCHMRK studies showed that switching from lopinavir-ritonavir to raltegravir was associated with greater reductions in serum lipid concentrations than was continuation of lopinavir-ritonavir in HIV-infected patients with stable viral suppression on lopinavir-ritonavir-based combination therapy. In the heterogeneous population enrolled in the studies, a higher rate of HIV suppression was achieved in patients who continued lopinavir-ritonavir than in patients who switched to raltegravir, especially in patients who had virological failure before entry. Virological rebound in patients assigned to raltegravir was usually associated with the development of mutations associated with raltegravir resistance. By contrast, patients without previous virological failure had similar viral suppression rates in both treatment groups. Because participants were not stratified before randomisation by the subcategories used in the post-hoc analyses, imbalances in potentially important covariates might confound interpretation of these data. In practice, clinicians need to gather all available background information, including past resistance tests and treatment outcomes, when contemplating the potential risks and benefits of modifying a suppressive antiretroviral regimen. Efficacy, tolerability, and safety data from rigorous clinical trials that can be applied contextually to individual patients will help to inform these difficult decisions.

Contributors

RL and B-YN designed the studies in collaboration with academic and other Merck scientists. XX and AJR undertook the statistical analyses. JJE, BY, ED, AJR, MJD, B-YN, RL, XX, and PS were involved in the initial interpretations of the data. All authors contributed to refining and expanding the understanding of the results. This report was principally drafted by JJE, MJD, XX, and PS, and was critically reviewed and subsequently approved by each co-author in its essentially final form.

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Conflicts of interest

JJE has been an investigator for Merck, Panacos, GlaxoSmithKline, and Abbott on research grants to the University of North Carolina (Chapel Hill, NC, USA), and has served as a paid consultant or speaker for Merck, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Tibotec, Roche, and Pfizer. BY has been an investigator for Bristol-Myers Squibb, Cerner, Gilead Sciences, GlaxoSmithKline, Roche, and Merck, and has served as a paid consultant for Bristol-Myers Squibb, Cerner, Gilead Sciences, GlaxoSmithKline, Roche, Merck, Monogram Bioscience, Pfizer, and Tibotec. DAC has been an investigator, speaker, and adviser for Merck. MY has been an investigator for Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Science, GlaxoSmithKline, Medivir, Merck, Roche, Pfizer, and Tibotec, and has served as a paid consultant for Abbott, Bristol-Myers Squibb, Gilead Science, GlaxoSmithKline, Merck, and Tibotec. ED has been an investigator for Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Science, GlaxoSmithKline, Merck, Roche, Pfizer, Schering Plough, Tibotec, Achillion, Avexa, Taimed, Tobira, and Vertex, and has served as a paid consultant or speaker for Bristol-Myers Squibb, Gilead Science, GlaxoSmithKline, Merck, Vertex, Virco, and Tibotec. JA-V has been an investigator for Merck. CW has been an investigator for Merck, Abbott, Bristol-Myers Squibb, Roche, Tibotec, GlaxoSmithKline, Pfizer, Jansen-Cilag, Johnson & Johnson, Boehringer Ingelheim, Panacos, Myriad, NeurogesX, Danone, Sanofi, Gilead, Novartis, and Virax, a paid consultant for Merck, Abbott, Bristol-Myers Squibb, Roche, Tibotec, GlaxoSmithKline, Boehringer Ingelheim, Panacos, and Gilead, and a speaker for Merck, Abbott, Bristol-Myers Squibb, Roche, Tibotec, GlaxoSmithKline, and Boehringer Ingelheim. RZ has been an investigator for Merck, Bristol-Myers Squibb, Gilead Sciences, Roche, Abbott, Boehringer Ingelheim, Pfizer, and Tibotec. GF has been an investigator for Merck, and has received honoraria from Merck, Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Roche, Schering Plough, Pfizer, and Tibotec. DSB has been an investigator for Merck, Gilead, Bristol-Myers Squibb, Tibotec, GlaxoSmithKline, Pfizer, Progenics, and Theratechnologies, has served as a paid consultant and speaker for Merck, Gilead, Tibotec, GlaxoSmithKline, and Theratechnologies, and owns stock in Gilead Sciences. PNK has been an investigator for Merck and GlaxoSmithKline, and has received consulting fees or lecture honoraria from Merck, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Abbott, Pfizer, and Tibotec. Authors who are employees of Merck Research Laboratories may own stock or stock options in the company. All other authors declare that they have no conflicts of interest.

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