Articles

Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease

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Summary

Background Ritonavir is a potent, orally bioavailable inhibitor of HIV-1 protease. We undertook an international, multicentre, randomised, double-blind, placebo-controlled trial of ritonavir in patients with HIV-1 infection and CD4-lymphocyte counts of 100 cells/μL or less, who had previously been treated with antiretroviral drugs.

Methods 1090 patients were randomly assigned twice-daily liquid oral ritonavir 600 mg (n=543) or placebo (n=547) while continuing treatment with up to two licensed nucleoside agents. The primary study outcome was any first new, or specified recurrent, AIDS-defining event or death. Open-label ritonavir was provided after 16 weeks in the study to any patient who had an AIDS-defining event.

Findings The baseline median CD4-lymphocyte count was 18 (IQR 10–43)/μL in the ritonavir group and 22 (10–47) /μL in the placebo group. Study medication was discontinued in 114 (21·1%) ritonavir-group patients and 45 (8·3%) placebo-group patients mainly because of initial adverse symptoms. Outcomes of AIDS-defining illness or death occurred in 119 (21·9%) ritonavir-group patients and 205 (37·5%) placebo-group patients (hazard ratio 0·53 [95% CI 0·42–0·66]; log-rank p<0·0001) during median follow-up of 28·9 weeks, with loss to follow-up of 15 (1·4%) patients. Ritonavir was then offered to all patients; at median follow-up of 51 weeks, 87 (16%) ritonavir-group patients had died of any cause versus 126 (23%) placebo-group patients (hazard ratio 0·69 [95% CI 0·52–0·91], log-rank p=0·0072).

Interpretation Although earlier intervention with combination therapy may provide much more effective treatment, ritonavir in patients with advanced disease and extensive previous antiretroviral use is safe and effective, lowers the risk of AIDS complications, and prolongs survival.

Lancet 1998; **351:** 543–49
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Introduction

Zidovudine was the first antiretroviral treatment shown to lower the rate of AIDS-related death significantly in a placebo-controlled trial of patients with advanced HIV-1 disease.[1] Subsequent placebo-controlled clinical trials have shown its clinical effectiveness in the prevention of minor opportunistic infections in patients with moderate immunodeficiency[2] and in those with primary HIV-1 infection.[3] Compared with zidovudine monotherapy, other nucleoside analogues (alone or in combination with zidovudine) have delayed the onset of HIV-1 disease progression or death in patients with moderate immunodeficiency in relatively long clinical trials, particularly as initial therapy.[4–7]

Ritonavir (Norvir, Abbott Laboratories, IL, USA) is a specific and potent inhibitor of HIV-1 aspartyl protease. The drug has high oral bioavailability and a long plasma half-life, which allows twice-daily dosing.[8] Compared with nucleoside analogues, ritonavir has a more potent and sustained effect on plasma viraemia, cellular HIV-1-infection loads, and lymphocyte immunophenotype subsets.[9–12] In clinical trials on HIV-1, some surrogate-marker responses predict clinical efficacy.[13,14] However, their usefulness in assessment of protease-inhibitor therapy is not clear. Therefore, this study was designed as a simple large-scale clinical trial to investigate rapidly, in a specific subpopulation of patients with HIV-1 disease (CD4-lymphocyte counts $\leq$100/μL [$0{\cdot}1\times10^9$/L]), the safety and clinical efficacy of ritonavir. These results might be generalisable to a larger population.

Methods

The primary objective of this randomised, double-blind, placebo-controlled, multicentre trial was to test the effectiveness of ritonavir oral solution (600 mg twice daily) in reducing the rate of death or any new, or specified recurrent, AIDS-defining illness in a population of HIV-1-infected adults with CD4-lymphocyte counts of 100/μL or less, while permitting concurrent use of licensed anti-HIV-1 therapy. Secondary objectives were to assess the effect of ritonavir on counts of CD4 and CD8 lymphocytes and plasma concentrations of HIV-1 RNA (Roche Amplicor; lower limit of detection 200 copies/mL). Plasma viraemia response was

studied in a subset of patients—the first 159 randomised patients with baseline plasma HIV-1 RNA concentrations higher than 15 000 copies/mL (antiviral activity subset). The study protocol was approved by the appropriate regulatory agencies and institutional review boards of the participating centres.

Patients

Participants provided written informed consent before they underwent any screening procedures. Eligible participants were at least 12 years old, had a confirmed serum antibody test for HIV-1, a CD4-lymphocyte count of 100/μL or less, and had received at least 9 months of therapy with at least one approved nucleoside (zidovudine, zalcitabine, didanosine, or stavudine). In addition, participants had at least 6 weeks of stable therapy up to baseline with a Karnofsky score of more than 70. Exclusion criteria included previous enrolment in this study or another study of an HIV-1 protease inhibitor, acute illness, predefined haematological or biochemical abnormality, current treatment with more than two nucleoside reverse-transcriptase inhibitors, experimental or illicit recreational drug use, treatment with specific contraindicated drugs, pregnancy, and breastfeeding.

Endpoints

The primary outcome measure was the time to any new AIDS-defining illness or death not preceded by an AIDS-defining event. A new AIDS-defining event was any clinical illness specified by the US Centers for Disease Control and Prevention.[15] The recurrence of pneumocystosis, oesophageal candidosis, or chronic herpetic ulcer was also included as a primary outcome, but recurrence or progression of other events was not. A secondary primary outcome measure, analysed separately, was death from any cause. Each event reported as a disease outcome was assessed by two independent reviewers (DWC and SK) without knowledge of treatment allocation and according to predefined diagnostic criteria.[15] Source documentation to support a high degree of clinical confidence was required to confirm each event as a clinical endpoint.

Randomisation

Eligible patients were randomly assigned ritonavir (600 mg in a liquid oral solution twice daily) or a matching placebo (liquid oral solution twice daily) by means of a computer-generated schedule (prepared by Abbott Laboratories). The assignment of patients was done in blocks of four, stratified by geographical region (North America, Europe, and Australia). Allocation concealment was ensured by the use of an automated voice-response system.

Procedures

Patients who gave informed consent were screened by a complete medical history and a review of concurrent medications, a complete physical examination, electrocardiography, chest radiography, counts of CD4 and CD8 lymphocytes, and routine haematological and biochemical laboratory studies during a 28-day period before randomisation. Baseline counts of CD4 and CD8 lymphocytes and plasma concentrations of HIV-1 RNA were defined as the mean of two such measures obtained during the 10 days before randomisation. After randomisation, medical history, physical examination, laboratory testing for toxic effects and surrogate markers, and compliance checks (by measurement of residual amounts of study medication) were repeated weekly for the first month, every 2 weeks for the next 2 months, and monthly thereafter. The assessment was repeated on discontinuation of study medication. All haematological and biochemical tests were done in central laboratories.

Treatment and follow-up

There were three study periods of drug management with study medication and concurrent anti-HIV-1 treatment. During the first 16 weeks, patients received masked study medication and baseline concurrent anti-HIV-1 treatment that could not be changed under the protocol (unless it had to be stopped for intolerance). During the second period, from 16 weeks after randomisation until provision of open-label ritonavir to all patients after the primary study objective was met, patients who developed a confirmed AIDS-defining outcome during the first or the second period were given ritonavir openly. Patients who did not experience an AIDS-defining outcome during either period remained on masked study medication. In addition, during the second period physicians could alter the concurrent regimen of up to two licensed nucleosides including lamivudine, which became commercially available during the study. During the third period, after the primary objective was met, all patients were offered open-label ritonavir irrespective of disease status. Patients who stopped masked study medication continued scheduled visits throughout the trial.

	Ritonavir (n=543)	Placebo (n=547)
Demography		
M/F	499/44	500/47
Median (range) age in years	38 (19–70)	38 (15–72)
White/non-white	476/67	464/83
HIV-1 risk factor (number of patients)*		
Male homosexual or bisexual	444 (82%)	440 (80%)
Heterosexual, sex partner HIV-1-positive	81 (15%)	91 (17%)
Injection-drug user	25 (5%)	24 (4%)
Sex partner injection-drug user	18 (3%)	14 (3%)
Transfusion recipient	18 (3%)	19 (3%)
Haemophiliac	6 (1%)	6 (1%)
Other or unknown	44 (8%)	47 (9%)
Karnofsky performance score†	90 (80–90)	90 (80–90)
HIV-1 history		
Time since HIV-1 diagnosis (years)†	5·8 (3·4–8·5)	6·2 (3·3–8·5)
Duration of antiretroviral treatment (years)†	2·8 (1·6–4·6)	3·2 (1·7–4·7)
Duration of zidovudine treatment (years)†	2·1 (0·9–3·7)	2·2 (1·1–4·0)
Mean number of antiretroviral drugs used	2·6	2·5
CD4-lymphocyte count (number of patients)		
0–15 /μL	242 (46%)	218 (41%)
16–49 /μL	171 (32%)	188 (36%)
50–100 /μL	116 (22%)	120 (23%)
Missing‡	14	21
Lymphocyte count (per μL)†		
CD4	18 (10–43)	22 (10–47)
CD8	409 (245–625)	414 (244–680)
Plasma HIV-1 RNA load (log_{10} copies/mL)		
Antiviral activity subset§ n	80	79
Median (IQR)	5·4 (4·9–5·6)	5·2 (4·9–5·5)
All patients tested n	303	306
Median (IQR)	5·4 (5·0–5·7)	5·4 (4·9–5·6)
Baseline concurrent treatment taken by at least 15% of patients in either group		
Zidovudine	53%	52%
Stavudine	34%	31%
Zalcitabine	22%	20%
Didanosine	17%	22%
Trimethoprim	74%	74%
Sulphamethoxazole	73%	73%
Clarithromycin	36%	37%
Rifabutin	34%	32%
Pentamidine	16%	17%
Ciprofloxacin	15%	16%
Fluconazole	64%	68%
Acyclovir	58%	57%
Paracetamol	30%	31%
Ascorbic acid	13%	15%
Testosterone	18%	21%
Loperamide	25%	14%
Filgrastim	15%	17%

*Some patients had more than one risk factor.
†Median (IQR).
‡All had counts ⩽100/μL at screening.
§First 159 patients with HIV-1 RNA concentrations at baseline >15 000 copies/mL.

Table 1: **Baseline demographic and clinical characteristics**

Adverse events

Adverse events were defined as any change in a clinical sign or

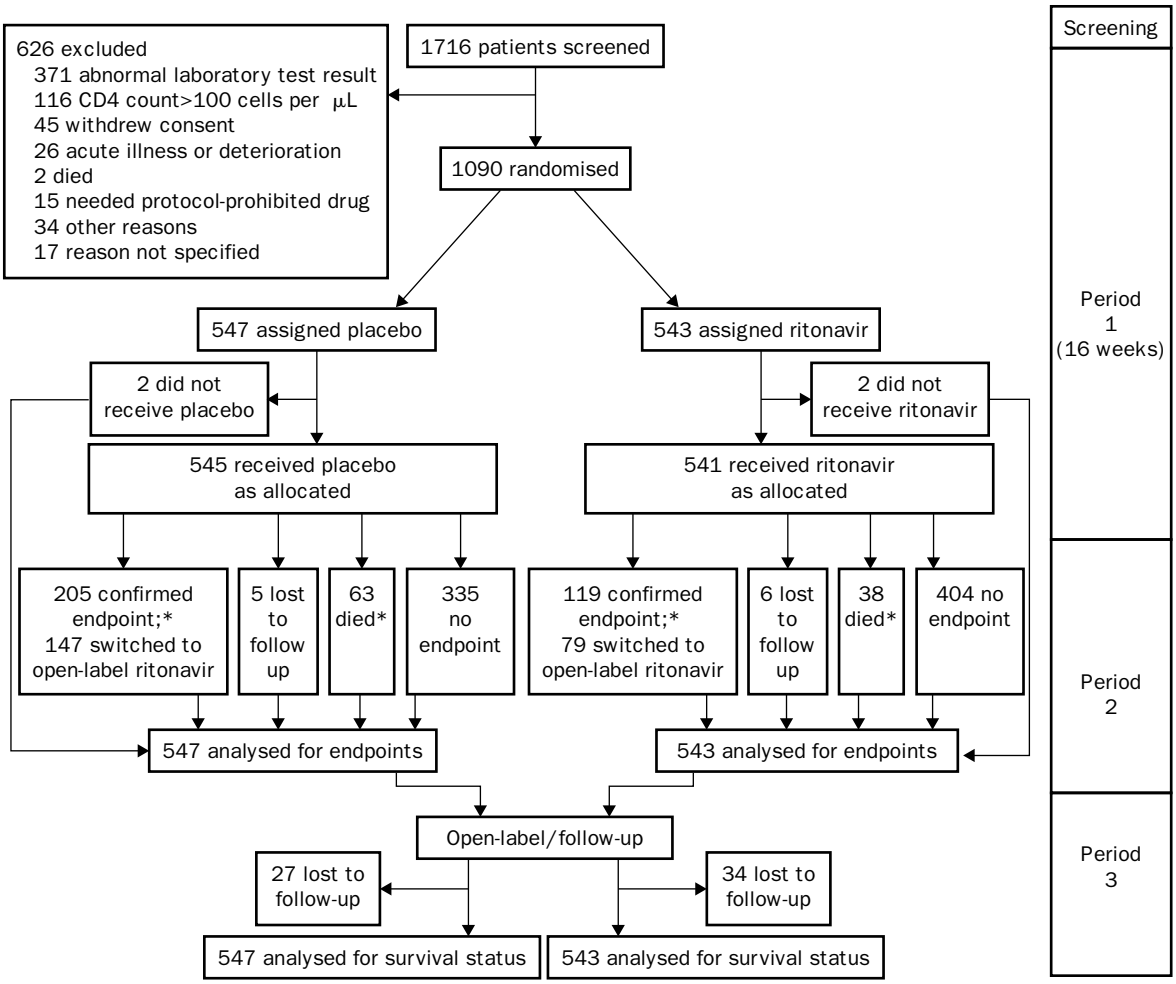


Figure 1: **Trial profile**
In period 2 there is some overlap between patients with confirmed endpoints (AIDS-defining illness or death) and numbers of deaths.

symptom, or meaningful laboratory-test abnormality, excluding disorders associated with HIV-1 infection. All adverse events were rated according to severity and relation to study drug.

Statistical analysis

Sample-size calculations were based on an estimate that the annual rate of disease progression or death would be 40%. We assumed that up to 10% of the patients would be lost to follow-up before experiencing an AIDS-defining outcome event, and sought 80% power to detect a reduction of 33% in the hazard ratio. With rapid accrual of the estimated 350 patients per treatment group, the final analysis of disease progression or death was originally scheduled to occur after 191 patients experienced such an event. However, because accrual was more rapid than expected, the sample size was increased to about 500 patients per treatment group with the final analysis of disease progression or death occurring after the same threshold of events was achieved.

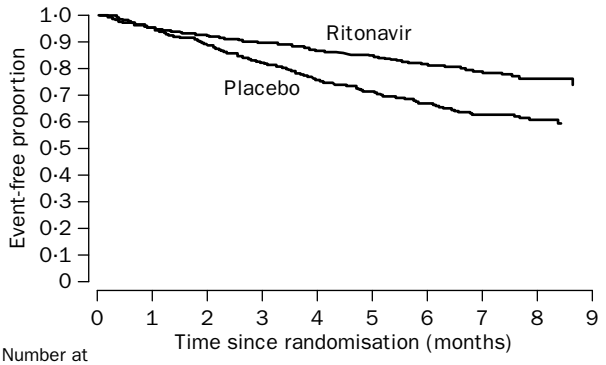
All analyses were by intention to treat, with two-sided hypothesis tests at the 0·05 level of significance. Calculations were done with SAS software (version 6, 4th edition). Time to disease progression or death, as well as the time to death from any cause, were analysed with a Cox proportional-hazards model stratified by geographical region. Comparisons between randomisation groups used the log-rank test. In addition, unstratified Kaplan-Meier curves were used to display these data. The assumption of a constant hazard ratio over time was tested by calculating the logarithm of the negative logarithm of the Kaplan-Meier estimates for intergroup parallelism within geographic region. Patients were further classified according to baseline demographic data (mean of all values for CD4-lymphocyte count obtained within 10 days before randomisation and number of nucleoside analogues taken at baseline). We then tested for interaction between randomisation group and baseline status by a likelihood ratio test comparing proportional-hazards models with and without the interaction term.

Reports of deaths were sent to an independent safety-monitoring board (RW, RP, DD). The protocol specified that the O'Brien-Fleming stopping rule[16] should be applied for the premature discontinuation of the study as a result of deaths. Two interim analyses were done before the end of the double-blind part of this study (based on results from the analysis of time to disease progression or death).

Results

Patients were recruited to the study between April, 1995, and July, 1995. 1716 patients were screened, and 626 were excluded (figure 1). Of the 1090 patients randomised (543 to ritonavir, 547 to placebo), two in each treatment group did not receive any trial medication. These patients were included in the primary, intention-to-treat analysis, but they were excluded from the analysis of adverse events attributable to study drugs.

Patients (table 1) were enrolled at 67 centres in Australia (42 patients), Europe (238 patients), and North America (810 patients). 97% of patients in the ritonavir group and 95% of those in the placebo group had had one or more HIV-1-associated disorders before



Number at risk

Ritonavir	543	499	466	434	92
Placebo	547	485	412	357	81

Figure 2: **Disease progression or death (to end of period 2)**

the study began. The most frequent HIV-1-related events reported before the study were oral candidosis (64%), herpes simplex (28%) or zoster (28%) infection, hairy leucoplakia (27%), peripheral neuropathy (26%), persistent generalised lymphadenopathy (25%), diarrhoea (20%), and *Pneumocystis carinii* pneumonia (25%). However, there was no apparent difference between the randomised groups in persistent HIV-1-related disorders present at entry to the study. Concurrent drug use in the ritonavir and placebo groups was similar before entry to the study, with a median number of 14 medications in each group (table 1). The most commonly used nucleoside analogues at the start of randomised treatment were zidovudine (45%), stavudine (26%), zalcitabine (19%), and didanosine (16%).

The median duration of masked study medication was 25·7 weeks in patients assigned ritonavir and 26·0 weeks in patients assigned placebo. 15 (1·4%) patients were lost to follow-up before period 3 (figure 1, including those who received no study medication), resulting in a median follow-up of 28·9 weeks (27·7–31·1) up to the end of period 2. During period 3, patients were offered open-label ritonavir and followed up for a median total of 51·3 weeks (39·4–56·3). 76 (7·0%) patients had been lost to follow-up by the end of period 3.

119 (21·9%) ritonavir-group patients and 205 (37·5%) placebo-group patients experienced an AIDS-defining event or death during periods 1 and 2 of this study. The hazard ratio was 0·53 (95% CI 0·42–0·66; log-rank p<0·0001; figure 2). The most common primary outcome event was death. The most common first disease event was new or recurrent oesophageal candidosis (table 2). The rates of first events were generally lower in the ritonavir group than in the placebo group. A secondary analysis of deaths during periods 1 and 2 gave an estimated hazard ratio of 0·60 (95% CI 0·40–0·89; log-rank p=0·0105).

	Number of patients	
	Ritonavir (n=543)	Placebo (n=547)
Deaths	26 (4·8%)	35 (6·4%)
AIDS-defining events*		
Total	93 (17·1%)	170 (31·1%)
Oesophageal candidosis	19 (3·5%)	40 (7·3%)
Kaposi's sarcoma	8 (1·5%)	19 (3·5%)
Cytomegalovirus retinitis	19 (3·5%)	18 (3·3%)
Pneumocystosis	12 (2·2%)	22 (4·0%)
Cytomegalovirus, non-retinal	5 (0·9%)	14 (2·6%)
Mycobacterium avium complex	9 (1·7%)	11 (2·0%)
Wasting syndrome	2 (0·4%)	9 (1·6%)
Lymphoma	4 (0·7%)	9 (1·6%)
Other	17 (3·1%)	30 (5·5%)
Total events*	119 (21·9%)	205 (37·5%)

*Two patients in each group had two simultaneous AIDS-defining events: 93 ritonavir-treated patients experienced a total of 95 AIDS-defining events, and 170 placebo-treated patients experienced a total of 172 AIDS-defining events.

Table 2: **Individual first outcome events at end of period 2**

	Number with primary outcome/total		Hazard ratio (95% CI)
	Ritonavir	Placebo	
Overall	119/543 (22%)	205/547 (37%)	0·53 (0·42–0·66)
Baseline antiretrovirals*			
None	29/100 (29%)	40/109 (37%)	0·75 (0·47–1·21)
One	58/287 (20%)	110/305 (36%)	0·51 (0·37–0·70)
More than one	32/156 (21%)	55/133 (41%)	0·44 (0·28–0·68)
Baseline CD4-lymphocyte count (/μL)†			
0–15	74/242 (31%)	97/218 (44%)	0·64 (0·47–0·87)
16–49	31/171 (18%)	72/188 (38%)	0·42 (0·28–0·64)
50–100	9/116 (8%)	21/120 (18%)	0·39 (0·18–0·85)

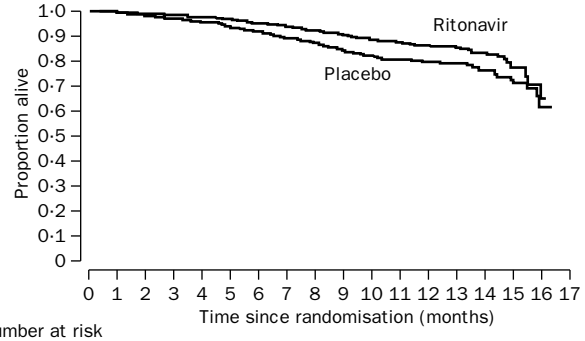
*p=0·31; test for randomisation group×baseline antiretroviral interaction.
†p=0·16; test for randomisation×baseline CD4 count interaction; baseline CD4 counts were missing for 14 ritonavir-group and 21 placebo-group patients.

Table 3: **Primary outcomes stratified by baseline characteristics**

Disease progression or death was also analysed with either baseline CD4-lymphocyte count or the number of baseline nucleoside analogues used as stratification factors (table 3). No significant interaction between randomisation group and baseline factor status was detected in either analysis. Ritonavir significantly reduced the risk of disease progression or death in all categories of baseline CD4-lymphocyte count used in this analysis. Furthermore, the results suggest that the risk of disease progression or death increased with decreasing baseline CD4-lymphocyte count. Ritonavir alone did not significantly reduce the risk of disease progression or death. However, a significant reduction in the risk of disease progression or death was found for ritonavir used in combination with at least one baseline nucleoside analogue.

After the clinical benefit of ritonavir had been demonstrated, events were no longer assessed by independent reviewers. Therefore, we could not include disease progression in an analysis to the end of period 3. However, analysis of the survival status of patients at the end of period 3 was possible. 87 (16%) patients assigned ritonavir and 126 (23%) patients assigned placebo died from any cause. The hazard ratio was 0·69 (95% CI 0·52–0·91; log-rank p=0·0072; figure 3).

In the ritonavir group (for patients who had data available for all time points), CD4-lymphocyte counts



Number at risk

Ritonavir	543	537	523	511	485	417	328	149	12
Placebo	547	538	518	498	464	398	324	149	17

Figure 3: **Overall survival (to end of period 3)**
Note time scale differs from figure 2.

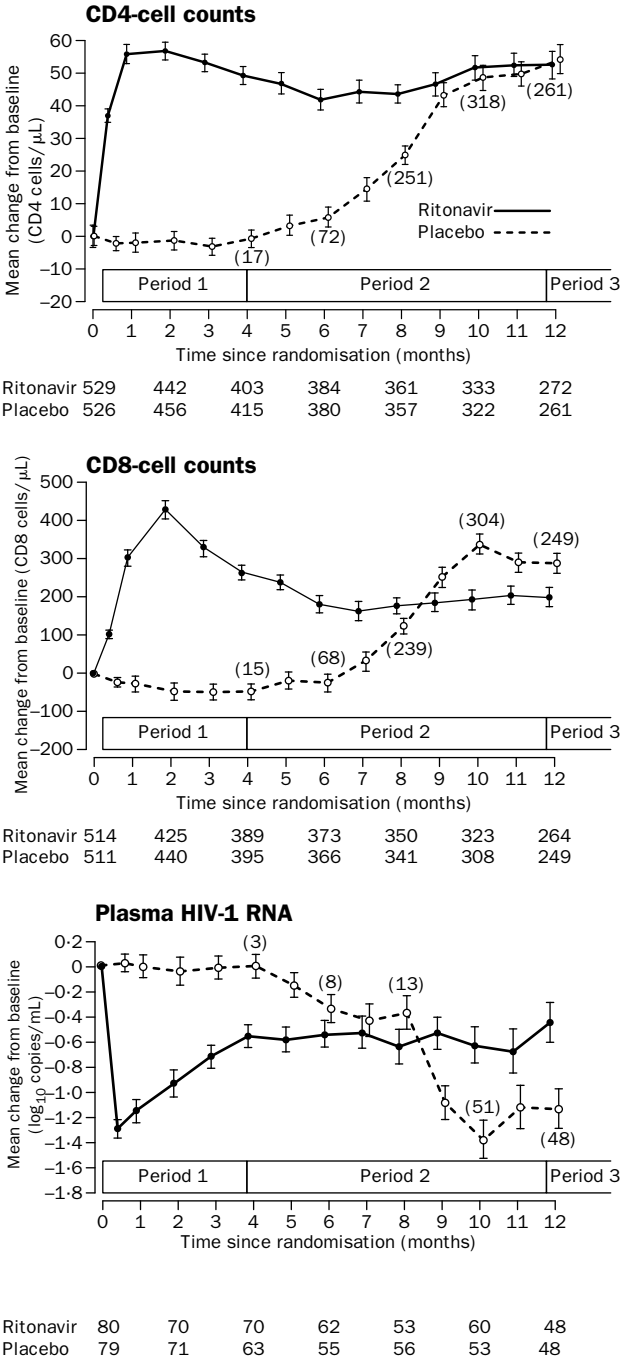


Figure 4: **Mean (with SE) changes in CD4-cell count, CD8-cell count, and plasma HIV-1 RNA concentration**
Number of placebo-group patients receiving open-label ritonavir after period 1 given in parentheses for visits every 2 months from month 4 onwards. Plasma HIV-1 RNA for antiviral activity subset only.

increased from a baseline mean of 31/μL (peak increase 57/μL), and CD8-lymphocyte counts increased from a baseline mean of 495/μL (peak increase 425/μL; figure 4). The higher CD4 counts were sustained for ritonavir-treated patients. The CD8 counts fell from the peak in period 1 but stabilised in periods 2 and 3, during which the mean effects for both CD4 and CD8 lymphocytes were matched in the placebo group.

In the antiviral activity subset, plasma viral load fell rapidly in patients assigned ritonavir, with a maximum mean reduction from baseline of 1·3 $\log_{10}$ copies/mL at 2 weeks, followed by a subsequent return toward

	Ritonavir (n=541)		Placebo (n=545)	
	Number with symptom	Number withdrawn*	Number with symptom	Number withdrawn*
Symptom				
Nausea	284 (52%)	56 (10·4%)	143 (26%)	6 (1·1%)
Vomiting	156 (29%)	26 (4·8%)	40 (7%)	5 (0·9%)
Diarrhoea	269 (50%)	23 (4·3%)	116 (21%)	5 (0·9%)
Weakness	134 (25%)	15 (2·8%)	72 (13%)	5 (0·9%)
Altered taste	66 (12%)	9 (1·7%)	22 (4%)	2 (0·4%)
Circumoral paraesthesia	151 (28%)	9 (1·7%)	23 (4%)	0 (0)
Total withdrawn	· ·	114 (21·1%)	· ·	45 (8·3%)

Events of possible, probable, or uncertain relation to study medication.
*Some patients had more than one reason for study discontinuation.

Table 4: **Treatment-related adverse events (in >1·5% of participants) and rates of withdrawal from study medication**

baseline (figure 4). HIV-1 RNA concentrations then stabilised during period two at a value of about 0·6 $\log_{10}$ copies/mL lower than baseline. During periods 2 and 3, when patients switched to open-label ritonavir, plasma viraemia in the remaining placebo-group patients fell to values below those observed in the remaining ritonavir-group patients.

Adverse effects

Overall 114 (21·1%) of patients in the ritonavir group and 45 (8·3%) of patients in the placebo group withdrew from treatment with masked study medication ($p<0·0001$). However, many of those in the ritonavir group withdrew from treatment during the first 4 weeks of treatment; 9% of the ritonavir group and 1% of the placebo group withdrew from masked study medication during period 1. Table 4 lists the most frequently reported adverse events and reasons for withdrawal. These events were most commonly classified as gastrointestinal symptoms.

Abnormal results of biochemical laboratory tests were more common with ritonavir than with placebo: high concentrations of alanine aminotransferase (>215 IU/L) occurred in 9·0% versus 4·0%; γ-glutamyl transpeptidase above 300 IU/L in 21·1% versus 11·9%; creatine phosphokinase above 800 IU/L in 12·5% versus 8·2%; and fasting serum triglycerides above 16·9 mmol/L in 12·9% versus 0·4%. By contrast, haematological abnormalities were less frequent in the ritonavir group than in the placebo group: anaemia (packed-cell volume <30%) occurred in 20·3% versus 25·7%, and neutropenia ($<500\times10^9$/L) in 6·4% versus 10·2%.

Discussion

In this study ritonavir reduced the risk of AIDS complications and prolonged survival in patients with advanced HIV-1 disease. The participants in this large-scale clinical trial were representative of many patients with advanced HIV-1 disease. The effectiveness of ritonavir treatment against disease was conservatively estimated in terms of rigorously confirmed clinical outcomes. Common HIV-1-related disorders were consistently less common as first outcomes in the ritonavir group than in the placebo group.

Two main factors may have exerted potential bias on the overall outcome. First, significantly more patients in the ritonavir group than in the placebo group discontinued study medication early in the trial owing to drug-related adverse symptoms; this factor could have led to an underestimate of treatment efficacy by the

intention-to-treat analysis. Second, since CD4-lymphocyte responses were not concealed from investigators, the provision of open-label ritonavir treatment after period 1 for patients who had AIDS-defining events may have led to over-reporting of such events in the placebo group, resulting in a higher apparent disease rate in that group. However, the most frequent outcome event was death. Furthermore, the risk of developing an AIDS-defining illness was consistently reduced among expected disease outcomes. If such a reporting bias of primary disease endpoints had occurred, provision of ritonavir during period 2 for disease outcomes and during period 3 for all patients irrespective of disease status would have decreased the overall survival benefit observed for ritonavir in the analysis of all deaths from any cause. Our data may represent the effect of early versus deferred ritonavir treatment in this population of patients.

Despite the early intolerance shown by some patients for ritonavir liquid solution, severe adverse events were infrequent. Significant rises in serum concentrations of hepatocellular enzymes and triglycerides during ritonavir therapy were generally reversible and not associated with clinical symptoms. The benefit of ritonavir treatment, with a median of 14 concurrent medications on entry to the study, supports overall safety in this setting. Potentially serious drug interactions are suggested by expected or observed pharmacokinetic interaction of ritonavir on the metabolism of other drugs through the enteric and hepatic microsomal cytochrome P450 3A4 metabolic pathway. This trial excluded medications based on theoretical risks of potential drug interactions; however, rifabutin therapy was allowed. Rifabutin was the only agent associated with increased adverse events.[17]

The effectiveness of anti-HIV-1 therapy is reflected in treatment responses of CD4 lymphocytes and plasma viraemia; the previously reported responses to ritonavir treatment[9,10] were confirmed in this trial. The reported response of CD8 lymphocytes[14] was also confirmed. CD8 lymphocytes[18] and CD8-secreted factors[19] may be involved in the host reponse to HIV-1 infection. The changes in CD8 lymphocyte counts during ritonavir treatment may also represent either a direct effect or a therapeutic effect in which the initial rise and subsequent decline from peak response on potent therapy may reflect lower HIV-1 replication and subsequent decreased immune activation.[20]

Since initial reporting of this study's results and US licensing of ritonavir, controlled trials have been continued[22] or started[23] to confirm the clinical benefit of a protease inhibitor on health and life in HIV-1 disease and AIDS.

The need to prove successively the effectiveness of individual drugs of a class, as opposed to their comparative safety, activity, and efficacy, must be balanced against the rights of human trial volunteers. This ethical issue becomes increasingly important as guidelines on treatment standards become established.

Although ritonavir was the first protease inhibitor for which clinical benefit was demonstrated, understanding of the clinical correlation of changes in HIV-1 RNA concentrations and counts of CD4 and CD8 lymphocytes requires further analysis. A greater and more sustained suppression of HIV-1 RNA than seen in this study was reported in patients with less advanced HIV-1-related immunodeficency[9] and when zalcitabine and zidovudine were given together with ritonavir as initial therapy.[21] Preliminary results from continuing studies have shown suppression of HIV-1 RNA below standard quantification values with ritonavir plus saquinavir[24] or plus zidovudine and lamivudine[25,26] in the majority of patients.

This study used the design of adding ritonavir to at most two licensed nucleoside antiretroviral agents as tolerated by individual patients. This strategy was then consistent with common clinical practice. In patients with extensive previous therapy and advanced immunodeficiency, the approach of adding a single new agent simulates monotherapy with that agent. The pattern of incomplete and transient suppression of HIV-1 RNA observed in this study is similar to that in other studies of ritonavir monotherapy, in which stepwise HIV-1 drug resistance emerged.[9,10] The apparently greater efficacy of ritonavir in patients with higher baseline CD4-lymphocyte counts and in patients taking at least one other anti-HIV-1 medication at baseline may reflect the better general health or tolerance of ritonavir in these patients. However, it may also represent increased and more durable anti-HIV-1 activity or greater efficacy of ritonavir therapy in earlier combination as a result of decreased or delayed drug resistance afforded by combination therapy.

This trial showed the efficacy of ritonavir in treatment of heavily pretreated patients with advanced HIV-1 disease. The tactic of adding a single potent anti-HIV-1 drug to a stable or failing underlying treatment in a clinical trial may be improved upon in clinical practice. Further studies should assess whether initial combination treatment with ritonavir and other antiretroviral agents[21,25,26] or the simultaneous change of two or more anti-HIV-1 drugs[24] will confer greater and more durable clinical benefit than measured here, as promised by surrogate marker studies.

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T Kocian); Milton S Hershey Medical Center (E Eyster, J Zurlo); AIDS Healthcare Foundation (C Farthing, M Moran); Shared Medical Research Foundation (J Galpin, V Ramirez); University of Kentucky Medical Center (R Greenberg, R E Vanderpool); Tuttleman Center (D H Henry III, B Rensman); Duke University Medical Center (C B Hicks, B Glennon); Nalle Clinic (J G Jemsek, W Evans); Houston VA Medical Center (C Lahart, K Breaux); Therafirst Medical Center (A LaMarca); ViRx, Inc (W Lang, B Wagner); University Hospitals of Cleveland (M Lederman, M Chance); AIDS Research Alliance: Chicago St Joseph's Hospital (R Luskin-Hawk, L Cleary); Aaron Diamond AIDS Research Center for NYC (M Markowitz, A Hurley, R O'Donavon); Beth Israel Medical Center (L J Bessen, D Mildvan); Center for Clinical AIDS Research and Education (S A Miles, A Johiro, S Chafey); Private Clinic (K Murphy); Tulane University Medical Centre (D Mushatt, E Nelson, E Plain); Novum Inc Washington DC (M Mustafa); Phoenix Body Positive, Inc (R Myers, J Rayl); Dallas ID Associates (P Pate, D A Watson); Private Clinic (David Payne); Infectious Diseases Physicians, Inc (D Poretz, K Wood); Chicago Center for Clinical Research (J C Pottage, J Burdgick); Community Research Initiative of South Florida (K Raben, I Madera); Tower Infectious Diseases Medical Associates, Inc (P Ruane, J Ida); Research and Education Group, Portland (J H Sampson, T Guenzburger); Novum Inc Seattle (T J Smith); Community Research Initiative on AIDS New York (J Sonnabend); Albany Medical College (D S Stein, D L Mehlhaff, G L Drusano); AIDS Research Consortium of Atlanta (M Thompson, L Ray); AIDS Center/St Vincent's Hospital and Medical Center (R A Torres, K McIntyre); Emerald Hills Professional Park (N Zide).

Abbott Laboratories—J Valdes, R Mills, D Jordan, R Rode, H Glassman, J Smith, J Beirise, D Moyse, A Hsu.

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William Cameron shared in design, development, endpoint review process, and analysis. Margo Heath-Chiozzi was responsible for development, coordination, conduct, and analysis. Sven Danner contributed to development, enrolled patients, and contributed to analysis. Calvin Cohen enrolled patients and contributed to analysis. Stephen Kravcik contributed to development and shared in endpoint review and analysis. Clement Mawrath, David Henry, and Richard Rode were responsible for data management and statistical analysis. Eugene Sun shared responsibility for coordination, conduct, and analysis. Amy Potthoff was responsible for the coordination and conduct. John Leonard was responsible for all aspects of this trial. All the investigators wrote the paper on behalf of the study group.

Acknowledgments

We thank P Morgan (*a priori* Editorial Service), and R Whitley, R Pollard, and D DeMets (Data and Safety Monitoring Board).

This study was supported by Abbott Laboratories, Abbott Park, IL, USA. DWC is supported by a career scientist award of the Ontario Ministry of Health. SK is supported by a clinical trials associateship award of the Canadian HIV Trials Network.

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