

# A Review of Low-Dose Ritonavir in Protease Inhibitor Combination Therapy

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**The pharmacokinetics of protease inhibitors center around the microsomal enzyme cytochrome P-450 3A4. As a potent inhibitor of this enzyme, ritonavir can increase the bioavailability and half-life of coadministered protease inhibitors. Evidence suggests that increased exposure to protease inhibitors is clinically relevant. Antiretroviral treatment with low-dose ritonavir–boosted lopinavir, indinavir, and saquinavir has durable virological activity and shows impressive immune reconstitution. Although tolerable in most cases, gastrointestinal side effects, hepatotoxicity, and blood lipid abnormalities remain relevant issues. Additional study will elucidate the advantages and disadvantages of twice-daily, low-dose ritonavir–boosted regimens and determine whether once-daily regimens based on this principle will have a lasting role in clinical practice.**

Adequate plasma protease inhibitor (PI) concentrations are required for effective anti-HIV activity [1]. Because of low and variable bioavailability and relatively short plasma elimination half-lives, the PIs have to be administered 2 or 3 times per day in high doses, which may hamper the patient's adherence to the regimen. Drug-drug interactions between PIs can enhance pharmacokinetics, allowing for reductions in both dose and dosing frequency. Two distinct strategies can be discerned: combination of 2 PIs at a therapeutic dose (e.g., indinavir at 400 mg b.i.d. plus ritonavir at 400 mg b.i.d.), or the combination of a PI with a low dose of ritonavir, which is a potent inhibitor of cytochrome P-450 3A4 metabolism. The first is regarded as 2-drug

treatment, because both PIs contribute to the net activity. The second results in single-PI treatment, because a low dose of ritonavir does not contribute to the antiviral activity itself (e.g., saquinavir at 1000 mg plus ritonavir at 100 mg b.i.d.). Because of the poor tolerability of ritonavir, even at reduced doses (e.g., 400 mg b.i.d.), the second strategy is increasingly favored. This review focuses on the clinical experience with combinations of PIs with low-dose ritonavir in once- and twice-daily dosing regimens. A search of the MEDLINE database with the terms "ritonavir," "low-dose boosting," "dual protease inhibitors," and "pharmacokinetics" was conducted. Furthermore, relevant abstracts of key HIV and AIDS conferences since 1997 were included.

Received 26 December 2002; accepted 14 February 2003; electronically published 5 June 2003.

Financial support: Canadian HIV Trials Network, Ontario HIV Treatment Network, Canadian Institutes of Health Research (C.L.C.); Canadian HIV Trials Network, Abbott, Agouron, Boehringer Ingelheim (R.P.G.v.H.); Career Scientist, Ontario HIV Treatment Network/Ontario Ministry of Health; Canadian Institutes of Health Research, Ontario Ministry of Health, Canadian HIV Trials Network (D.W.C.).

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**Clinical Infectious Diseases** 2003;36:1585–92

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1058-4838/2003/3612-0014\$15.00

## RATIONALE FOR ADMINISTRATION OF LOW-DOSE RITONAVIR

Soon after the introduction of the PIs, it was recognized that coadministration with ritonavir improved their pharmacokinetics [2]. Potent inhibition of intestinal and hepatic cytochrome P-450 3A4 by ritonavir results in improved bioavailability and a prolonged elimination half-life of most coadministered PIs [3, 4]. Exposure

to nelfinavir, however, is only moderately enhanced by ritonavir, because this PI is primarily metabolized by cytochrome P-450 2C19 [5]. Detailed reviews of the pharmacokinetic rationale for combination of PIs with ritonavir have been published [6–8].

The first combination of PIs used in clinical trials was saquinavir and ritonavir (400 mg each b.i.d.) [9]. This combination, with both PIs in a therapeutic dose, proved to be safe and effective over 5 years [10]. Gastrointestinal symptoms related to dosing with ritonavir at 400 mg twice per day are improved compared with those seen with ritonavir at 600 mg twice per day, but they remain a concern. Because ritonavir-associated toxicity is related to ritonavir exposure, lower doses of ritonavir may further improve the tolerability [11]. Doses of 100 mg sufficiently enhance the pharmacokinetics of coadministered PIs to allow for twice- or once-daily dosing, which may improve patients' adherence [12–14]. Simultaneous ingestion of ritonavir and the boosted PI is required to realize the beneficial interaction, as illustrated by a study in which subjects received saquinavir 4 h before ritonavir [15]. The area under the concentration-time curve (AUC) of saquinavir was 37% of the AUC observed after simultaneous ingestion of these PIs.

It is important to consider the potential for numerous clinically relevant drug-drug interactions during treatment with low-dose ritonavir-containing regimens [16–18]. The inhibition of cytochrome P-450 3A4 by ritonavir partly offsets the enzyme-inducing effects of efavirenz and nevirapine, which may otherwise advise against combination of PIs and non-nucleoside reverse-transcriptase inhibitors. However, 100 mg of ritonavir given twice per day may not fully block enzyme induction. Addition of efavirenz or nevirapine to indinavir and ritonavir given at 800 mg and 100 mg twice per day caused a 50% reduction in the concentration of indinavir [19, 20]. Concentrations of lopinavir are significantly reduced when lopinavir and ritonavir at 400 mg and 100 mg, respectively, are combined with treatment with efavirenz or nevirapine [21]. Dosage adjustment of lopinavir and ritonavir to 533 mg and 133 mg, respectively, twice per day (4 capsules b.i.d.), and other ritonavir-boosted PIs are recommended when efavirenz or nevirapine is coadministered [21].

## TWICE-DAILY REGIMENS

**Clinical experience.** The theoretical benefits of boosted-PI versus single-PI regimens are obvious (e.g., higher drug concentrations and, thus, better efficacy, lower doses, less frequent dosing with fewer food or drink restrictions [and, thus, better adherence], and reduced cost). However, these factors are rel-

evant only if low-dose ritonavir-boosted regimens are virologically active and well tolerated in clinical practice.

A randomized trial comparing indinavir at 800 mg 3 times per day ( $n = 54$ ) versus indinavir and ritonavir at 800 mg and 100 mg, respectively, twice per day ( $n = 50$ ) found no differences in virological or immunologic outcome after 112 weeks of treatment of PI-naïve patients [22]. In an intent-to-treat analysis, HIV RNA levels were suppressed to <50 copies/mL in 64% of subjects taking indinavir and ritonavir and in 59% of subjects receiving indinavir. Comparable results were found in another study of treatment with indinavir and ritonavir at 800 mg and 100 mg twice per day for 89 PI-naïve patients (59% achieved virus loads of <50 copies/mL at 48 weeks) [23]. A study of pretreated subjects receiving indinavir and ritonavir at 800 mg and 200 mg twice per day demonstrated HIV RNA suppression to <400 copies/mL in 17 (58.6%) of 29 subjects at 6 months and in 8 (57.1%) of 14 subjects at 9 months [24].

Saquinavir is primarily used in combination with ritonavir, because saquinavir hard gelatin capsules (HGCs) have a low and variable bioavailability, resulting in low plasma concentrations and subsequent evolution of viral resistance [25]. Despite the introduction of a soft gelatin capsule (SGC) with improved bioavailability, it remains advantageous to combine saquinavir with ritonavir to improve bioavailability, to reduce the dosing frequency, and to reduce total drug costs. A commonly used combination is saquinavir SGC plus ritonavir at 1000 mg and 100 mg, respectively, twice per day, which results in adequate plasma saquinavir concentrations [13]. When combined with ritonavir, the saquinavir HGC formulation resulted in higher plasma concentrations than did the SGC formulation. Furthermore, the saquinavir HGC regimen may be better tolerated [26].

Studies evaluated cohorts who changed their treatment from effective saquinavir plus ritonavir regimens (400 mg each b.i.d.) to low-dose ritonavir-boosted saquinavir treatment, demonstrating continued suppression of viral replication [27]. Results of the MaxCmin1 study suggest that HAART based on saquinavir plus ritonavir at 1000 mg and 100 mg twice per day achieves maximum virological control in 60% of subjects (intent-to-treat analysis). Of note, the study population ( $n = 306$ ) was heterogeneous, because 39% were PI naïve, 25% were receiving failing PI-based therapy, and 36% were receiving PI-based therapy and had HIV RNA loads of <400 copies/mL at baseline [28].

Lopinavir has a negligible bioavailability and a short half-life when used alone, but it achieves therapeutic concentrations when combined with ritonavir [29]. In addition to the benefits of twice-daily dosing and a reduced pill burden because of coformulation of lopinavir and ritonavir, lopinavir plus ritonavir has been proven to be safe and effective [30–34]. At 48 weeks, virus loads were <50 copies/mL for 79 of 100 naïve

subjects receiving lopinavir plus ritonavir, and the mean CD4 T lymphocyte count increased by 213 cells/ $\mu$ L [32]. Four-year data suggest that lopinavir plus ritonavir is potent and durable and has good immune reconstitutive properties for treatment-naïve patients [35]. Lopinavir-ritonavir-based HAART is also active as salvage therapy [36, 37]. When treated with a combination of lopinavir plus ritonavir, nevirapine, and 2 nucleoside reverse-transcriptase inhibitors, 49% of subjects ( $n = 70$ ) had virus loads of  $<50$  copies/mL at 144 weeks (intent-to-treat analysis) [37]. For both treatment-naïve and experienced subjects, these results are among the best reported for any antiretroviral combination. This success is likely due to the high lopinavir concentrations relative to the  $IC_{50}$ . The ratio of the minimal concentration and the  $IC_{50}$  is called the inhibitory quotient. Retrospective studies found relationships between the inhibitory quotient of PIs and the virological response to therapy [38], suggesting the clinical relevance of this parameter.

Therapy with amprenavir at 600 mg twice per day plus ritonavir at 100–200 mg twice per day has been evaluated [39–41], but long-term studies are required before ritonavir-boosted amprenavir regimens can be endorsed. A new PI, tipranavir, is currently in clinical development for use with low-dose ritonavir at a twice-daily dosage [42].

**Tolerance and metabolic complications.** Taste disturbances and gastrointestinal disturbances remain of concern with regimens containing 100 mg of ritonavir [43]. In a study of indinavir-ritonavir combinations, regimens with ritonavir doses of  $>100$  mg twice per day were stopped twice as often as regimens with lower doses, primarily because of gastrointestinal intolerance [44]. Such symptoms caused discontinuation of therapy for 15% of subjects who changed their treatment from indinavir at 800 mg three times per day to indinavir-ritonavir (liquid formulation) at 800 mg and 100 mg twice per day, compared with 4% of subjects who continued indinavir therapy [43]. In a group of treatment-naïve persons treated with lopinavir- and ritonavir-based HAART for 48 weeks, 7 (2%) of 326 discontinued therapy because of drug-related adverse events [31]. The most common side effects associated with lopinavir-ritonavir included diarrhea (16%), nausea (7%), and abdominal pain (4%). Over 48 weeks, 3 (4%) of 70 PI-experienced subjects discontinued therapy as a result of drug-related adverse events in a study of lopinavir-ritonavir, nevirapine, and 2 nucleoside reverse-transcriptase inhibitors [45]. Diarrhea was reported by 21% of subjects, and asthenia was reported by 6%. Results of the MaxCmin1 study, in which indinavir-based regimens were compared with saquinavir-based regimens (each boosted with ritonavir at 100 mg b.i.d.), did not show a difference in grade 3 or 4 gastrointestinal toxicity (12% vs. 11%) at 48 weeks [46].

Indinavir-associated nephrotoxicity has been related to high

plasma concentrations of indinavir, resulting in crystallization of indinavir in the loop of Henle [47, 48]. The reported incidence of nephrotoxicity varies because of differing case definitions and follow-up periods and ranges from 4% to 36% [23, 49, 50]. The incidence may be reduced in subjects treated with indinavir plus ritonavir at 400 mg each twice per day [51]. This has not been demonstrated with indinavir plus ritonavir at 800-mg and 100-mg and 800-mg and 200-mg dose combinations [43, 52–54], probably because of an increased indinavir AUC and  $C_{max}$  with these regimens, compared with indinavir alone. After 48 weeks of follow-up, 17% of subjects treated with indinavir at 800 mg 3 times per day ( $n = 54$ ) and 22% of those taking indinavir plus ritonavir at 800 mg and 100 mg twice per day ( $n = 50$ ) developed signs and/or symptoms of nephrolithiasis [55]. Small studies suggest that a lower indinavir dose (400 mg b.i.d.) may be used in combination with low-dose ritonavir (100–200 mg b.i.d.), which may reduce the incidence of nephrolithiasis [56].

It is unclear whether the use of low-dose ritonavir-boosted regimens results in more-frequent or more-severe lipid abnormalities than does use of single PI-containing regimens. Cholesterol and triglyceride levels increased in 30 of 36 PI-experienced subjects after 32 weeks of indinavir-ritonavir-based therapy [57]. This increase was correlated with the dose of ritonavir (range, 100–400 mg), but not with the indinavir dose. In the MaxCmin1 study, the indinavir-ritonavir regimen produced greater lipid elevation than did the saquinavir-ritonavir regimen [58]. The frequency of cholesterol and triglyceride elevations associated with lopinavir-ritonavir regimens appears to be comparable to those associated with other PI-based regimens [31, 35, 37]. Although highly relevant to the selection of HAART, no information pertaining to lipodystrophy with low-dose ritonavir-boosted regimens is currently available.

Hepatotoxicity complicates PI-based therapy. In particular, ritonavir has been implicated as a more hepatotoxic PI by some investigators [59], but other work does not support this [60–63]. Acknowledging that the rate of transaminase increase and clinically relevant hepatotoxicity is somewhat contentious, low-dose ritonavir-related hepatotoxicity seems uncommon. In subjects with lopinavir-ritonavir treatment experience, the aspartate aminotransferase or alanine aminotransferase level increased to  $>5$  times the baseline value in 14 (4.3%) of 326 subjects during a 48-week period [31]. Viral hepatitis coinfection may be a risk factor for such observations [32]. Clinically relevant hepatotoxicity necessitating interruption or discontinuation of therapy was not reported in these studies [31, 32]. Transaminase elevations of  $>5$  times the upper limit of normal were reported in 2.2%–4.8% of subjects receiving indinavir plus ritonavir at 800 mg and 100 mg twice per day for 48 weeks [64, 65] and 112 weeks [54], respectively. These rates are similar

to those reported with other PI-based regimens and demonstrate the relative safety of low-dose ritonavir–boosted regimens in terms of hepatotoxicity [59, 60].

## ONCE-DAILY REGIMENS

**Rationale.** Although the advantages of once-daily versus twice-daily dosing with respect to patient adherence are in dispute, for certain patient populations (e.g., patients requiring direct observed therapy), a once-daily regimen may be the only realistic therapeutic option. Recent results suggest that saquinavir, indinavir, amprenavir, and lopinavir can be administered in a once-daily regimen when combined with low-dose ritonavir. Once-daily dosing of nelfinavir seems feasible on the basis of results of a pharmacokinetic study of healthy volunteers, but clinical data to support this dosing are lacking [66].

To maintain adequate plasma concentrations up to 24 h after dosing, relatively high maximum plasma concentrations of the boosted PIs need to be achieved. For indinavir and amprenavir, the  $C_{max}$  has been related to specific side effects (i.e., nephrotoxicity for indinavir and headache or oral numbness for amprenavir), which may make once-daily dosing of these PIs less attractive. However, no urolithiasis or hematuria has been observed in a cohort of 32 patients taking indinavir plus ritonavir at 1200 mg and 400 mg once per day for a median of 24 weeks, despite maximal indinavir concentrations well above 10  $\mu\text{g}/\text{mL}$  [66, 67]. These results may suggest that the time above a critical threshold concentration is related to the development of urolithiasis rather than the maximal indinavir concentration per se.

The ritonavir dose required in a once-daily dosing regimen differs between PIs. For saquinavir, a daily dose of ritonavir of 100 mg has been shown to produce adequate plasma saquinavir concentrations to allow for a once-daily regimen [14, 68]. For indinavir, however, several studies have suggested that 400 mg of ritonavir is required to maintain indinavir concentrations of  $>100$  ng/mL ( $IC_{50}$ ) throughout the 24-h dosing interval [69–71]. Differences in ritonavir dosage may be an important factor for the tolerance of once-daily regimens, given the relationships with gastrointestinal tolerance and changes in triglyceride and cholesterol levels [72, 73].

**Clinical experience.** A randomized trial comparing lopinavir plus ritonavir at 800 mg and 200 mg once per day versus 400 mg and 100 mg twice per day supports the safety and efficacy of once-daily dosing [74]. The  $C_{max}$  and  $AUC_{24h}$  of lopinavir were similar for both regimens, but once-daily dosing resulted in lower and more variable trough concentrations. Both regimens were equally well tolerated, with 3 of 38 patients discontinuing therapy because of adverse events, and the proportion of patients achieving maximal suppression of viral replication was comparable.

The combination of saquinavir plus ritonavir at 1600 mg and 100 mg has been identified as the preferred combination for once-daily dosing of saquinavir [14]. Reported median plasma saquinavir concentrations at 24 h after dosing in HIV-1–infected patients range from 120 to 350 ng/mL, with a marked interpatient variability [68, 75, 76]. These concentrations are considered to be close to, or less than, the proposed  $IC_{50}$  for saquinavir for wild-type HIV strains (100–200 ng/mL) [77]. However, a recent study showed that maximum virological suppression ( $<50$  copies/mL) was maintained for  $\geq 1$  year in 19 of 22 antiretroviral-naïve patients, despite there being saquinavir concentrations of  $<200$  ng/mL in 91% of the patients [78]. The satisfactory virological responses in this study, despite presumably low plasma saquinavir trough concentrations, may be explained by intracellular accumulation of saquinavir [79]. A median plasma saquinavir trough concentration of 191 ng/mL (range, 38–1966 ng/mL) was observed in HIV-1–infected patients treated with saquinavir SGC at 1600 mg plus ritonavir at 100 mg once per day, whereas the median intracellular concentration in peripheral blood mononuclear cells was 341 ng/mL (range, 115–884 ng/mL) [80]. It is currently unclear whether coadministration of low-dose ritonavir affects the intracellular accumulation of PIs [79, 81].

Once-daily administration of saquinavir plus ritonavir has been used successfully to simplify twice-daily saquinavir dosing for patients with undetectable plasma HIV RNA (63 of 69 patients maintained HIV RNA levels of  $<50$  copies/mL up to 48 weeks after changing their regimen) [82]. A pharmacokinetic study of saquinavir plus ritonavir at 1600 mg and 100 mg, respectively, once per day in treating HIV-1–infected patients undergoing stable methadone treatment suggest that this combination may be an attractive option for directly observed therapy programs, because dose adjustments for methadone were not required [75]. Results of the FOCUS study at 48 weeks provide reason to proceed cautiously; by intent-to-treat analysis, only 51% of treatment-naïve subjects randomized to receive saquinavir SGC at 1600 mg plus ritonavir at 100 mg per day plus 2 nucleoside reverse-transcriptase inhibitors achieved plasma HIV RNA levels of  $<50$  copies/mL, compared with 71% of those randomized to receive efavirenz-based therapy [83].

A dose-finding study of healthy volunteers concluded that indinavir at 1200 mg plus ritonavir at 400 mg was the best combination for once-daily administration, although it was noted that the pharmacokinetics of indinavir were not optimal [71]. The indinavir trough concentrations in this study were relatively low, with only one-half of the participants achieving the targeted trough concentration of 100 ng/mL (median, 90 ng/mL) [71]. However, later studies of HIV-1–infected patients undergoing treatment with indinavir at 1200 mg plus ritonavir at 400 mg once per day showed higher trough concentrations, which were  $<100$  ng/mL in only 1 of 32 patients [67, 71]. After 24 weeks of indinavir treatment at 1200 mg plus ritonavir at

400 mg once per day, 13 of 16 patients achieved plasma HIV RNA levels of <500 copies/mL [67].

## RESISTANCE

It has been proposed that, by achieving plasma PI levels that are many-fold greater than the HIV IC<sub>50</sub> with low-dose ritonavir–boosted regimens, virological suppression may be improved. The current literature is mixed on this issue. Phenotypic resistance profiles were predictive of virological response in subjects taking a combination of saquinavir and ritonavir at 1000 mg and 100 mg twice per day despite saquinavir trough levels that greatly exceeded those of saquinavir monotherapy [84]. In 20 treatment-experienced recipients of indinavir at 800 mg twice per day plus ritonavir at 100 or 200 mg twice per day, the L90M mutation was identified in nonresponders and partial responders but not in responders, despite more consistent trough levels, compared with standard indinavir dosing [85]. In contrast, Campo et al. [86] suggested that short-term virological suppression (HIV RNA level, <400 copies/mL) is possible for subjects with previous failure of PI-based treatment with phenotypic resistance to indinavir when treated with indinavir plus ritonavir at 800 mg and 200 mg twice per day. The absence of a correlation between baseline phenotypic susceptibility to lopinavir and virological response at 2, 24, and 48 weeks suggests that the high lopinavir plasma levels achieved while receiving lopinavir-ritonavir therapy may increase efficacy against resistant virus strains [45]. It is unclear whether genotypic mutations known to confer lopinavir resistance in vitro (I84V, M46I, L10F, T91S, V32I, and I47V) [87, 88] are predictive of therapeutic failure in vivo. An apparent additional advantage of lopinavir plus ritonavir is that the evolution of

lopinavir resistance in subjects not achieving maximum virus suppression may be prevented or at least delayed [83].

Because only subtherapeutic levels of ritonavir are achieved with use of low doses, it has been suggested that this may foster the development of viral resistance, although evidence to support this contention is lacking. It is reasonable to believe that, as long as plasma HIV RNA levels are maximally suppressed, the development of resistance to any of the antiretrovirals in the regimen is minimal. Table 1 summarizes key studies of low-dose ritonavir–boosted PI-based HAART.

## CONCLUSION

Coadministration of ritonavir results in improved pharmacokinetics of PIs. The current literature suggests that low-dose ritonavir–boosted regimens are potent and durable. The high rates of virological suppression achieved with lopinavir plus ritonavir suggest that achievement of a high inhibitory quotient is clinically relevant. This may be beneficial in the prevention of evolved mutational drug resistance while undergoing therapy and in overcoming preexisting resistance.

The PI-specific side effect profiles associated with low-dose ritonavir–boosted regimens remain of concern. Gastrointestinal and taste disturbances associated with these regimens are still significant and provide reason to challenge the suggestion that these side effects can be markedly reduced or abolished by reducing the ritonavir dose. Evidence suggests that nephrotoxicity occurs more frequently with low-dose ritonavir-indinavir regimens, but further dose reductions of indinavir may improve this adverse effect. Continued study is warranted to identify regimens that strike the right balance between antiviral activity and tolerance.

**Table 1. Summary of key studies of low-dose ritonavir–boosted protease inhibitor (PI)–based HAART.**

Reference	PIs (dosage, mg)	No. of subjects	Study duration, weeks	Mean baseline CD4 cell count, cells/ $\mu$ L	HIV RNA level, % of patients <sup>a</sup>		Comments
					<400 copies/mL	<50 copies/mL	
[37]	Lpv (400 b.i.d.) and Rtv (100 b.i.d.)	326	48	260	75	67	RCT; patients were PI naive
[74]	Lpv (400 b.i.d.) and Rtv (100 b.i.d.)	19	72	248	NR	58	RCT; patients were PI naive
[74]	Lpv (800 b.i.d.) and Rtv (200 q.d.)	19	72	235	NR	74	RCT; patients were PI naive
[35]	Lpv (400 b.i.d.) and Rtv (100 b.i.d.)	100	204	356	71	70	Patients were PI naive
[36]	Lpv (400 b.i.d.) and Rtv (100 b.i.d.)	57	72	126	67	61	Patients were PI experienced; salvage therapy with EFV used
[37]	Lpv (400 b.i.d.) and Rtv (100/200 b.i.d.)	70	144	211	55	49	Patients PI were experienced; salvage therapy with NVP used
[22]	Idv (800 b.i.d.) and Rtv (100 b.i.d.)	50	112	92	NR	64	Patients were PI naive
[28]	Idv (800 b.i.d.) and Rtv (100 b.i.d.)	158	48	280	NR	~48	RCT; patients were both PI naive and PI experienced
[28]	Sqv (1000 b.i.d.) and Rtv (100 b.i.d.)	148	48	272	NR	~58	RCT; patients were both PI naive and PI experienced

**NOTE.** Efv, efavirenz; Idv, indinavir; Lpv, lopinavir; NR, not reported; Nvp, nevirapine; RCT, randomized clinical trial; Rtv, ritonavir; Sqv, saquinavir.

<sup>a</sup> Analysis was intent-to-treat.

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