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Ritonavir-Boosted Protease Inhibitor Monotherapy for the Treatment of HIV-1 Infection

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Abstract

Guidelines for the use of antiretrovirals for HIV-1 infection recommend combining at least three agents. Toxicities, cost, and the complexity of such regimens warrant the search for other options. Boosted protease inhibitor monotherapy is one of the appealing options being investigated. Herein we review uncontrolled and controlled clinical trials evaluating boosted protease inhibitor monotherapy in several clinical settings: maintenance therapy, induction-maintenance strategies, and first-line treatment. Boosted lopinavir monotherapy has been largely investigated in maintenance and induction-maintenance strategies, showing its ability to maintain viral suppression in the majority of participants. The major concern is the higher proportion of patients experiencing transient episodes of low-level viremia (HIV-RNA 50-500 copies/ml) when compared to classical triple regimens. No protease inhibitor-associated resistance mutation was detected in patients who failed on boosted lopinavir monotherapy. Three uncontrolled maintenance strategy studies with boosted atazanavir monotherapy showed conflicting results. Thus, the reassuring results obtained with lopinavir might not be extended to the whole protease inhibitor class, warranting further studies with new generation protease inhibitors such as darunavir. Finally, one controlled trial comparing first-line boosted lopinavir monotherapy to a standard triple combination showed that the latter outperformed the boosted protease inhibitor monotherapy in this clinical setting. In summary, a boosted protease inhibitor single-agent strategy can maintain continuous plasma HIV-RNA suppression in a large proportion of patients already suppressed on a standard triple combination. The more frequent occurrence of low-level viremia, however, does not allow the widespread use of such a strategy outside of clinical studies at this time. **(AIDS Rev. 2008;10:4-14)**

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Key words

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Introduction

Currently, gold-standard regimens for treatment of HIV-1 infection comprise three drugs, usually called highly active antiretroviral therapy (HAART), and include two nucleoside or nucleotide reverse transcriptase inhibitors (NRTI), together with either a protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor (NNRTI). While HAART has dramatically reduced AIDS-related morbidity and mortality[1], the absence of HIV eradication with those drugs requires their prolonged used for a lifetime, making long-term toxicity a critical issue in the management of HIV-infected patients. Mitochondrial toxicity and lipoatrophy are well-documented adverse effects of NRTI[2-6]. Facial lipoatrophy is the most common and distressing side effect for patients receiving anti-HIV therapy, and may lead to a reduction in patient adherence to therapy[7]. Studies evaluating structured treatment interruptions to limit exposure to anti-HIV drugs showed an increased risk in disease progression and mortality[8]. Thus, other strategies such as simplified maintenance therapy have to be evaluated.

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It has been shown that combining a PI to a backbone of two NRTI leads to a dramatically faster fat loss and increases the risk of lipodystrophy in comparison to what was seen with dual-NRTI therapy alone[5]. Conversely, antiretroviral therapy with PI alone appears rarely to cause lipodystrophy[9]. Moreover, discontinuation of the NRTI backbone may improve lipoatrophy[10], whereas PI withdrawal or substitution with a NNRTI has not proved helpful in correcting lipodystrophy[11-14]. Thus, one approach to improve lipoatrophy was to discontinue the NRTI backbone while maintaining a dual therapy with one ritonavir-boosted PI (PI/r) and one NNRTI in patients with full viral suppression on a classical triple combination with two NRTI and one PI/r[15]. However, many patients receiving a classical triple combination with a backbone of two NRTI and one PI/r cannot be switched to a NNRTI-based regimen for a variety of reasons (central nervous system side effects, risk of unplanned pregnancy, already resistant to NNRTI). Moreover, these regimens are not easy to manage because of potential deleterious drug-drug interactions. Interestingly, boosting second generation PI with ritonavir allowed revisiting the notion that using three drugs is a prerequisite for successful anti-HIV therapy. Indeed, ritonavir increases trough concentrations and half-lives of second generation PI, and these pharmacokinetic properties, along with the intrinsic antiviral potency of these second-generation PI, yield a high genetic barrier against viral resistance[16-18]. Thus, another approach to improve lipoatrophy was to discontinue the NRTI backbone while maintaining PI/r alone in patients with full viral suppression on a classical triple combination with two NRTI and one PI/r. Theoretically, the concept of boosted PI monotherapy is attractive as it would be expected to be less toxic, easier to use, and less costly than a triple combination. Here we review trials evaluating boosted PI monotherapy in several clinical settings: maintenance strategy, induction-maintenance strategy, and first-line treatment.

Results of principal trials (Table 1)

Maintenance strategy: for HIV-1 infected patients with undetectable plasma HIV-RNA on a standard triple combination

Pilot studies

Kahlert study[19]

This pilot non-comparative study evaluated the potential of ritonavir-boosted indinavir monotherapy to maintain HIV-1 RNA suppression for 48 weeks duration.

Patients on indinavir/ritonavir-based triple therapy were eligible for enrolment if their HIV-RNA load was < 50 copies/ml for at least three months, with no previous treatment failure.

Twelve patients were recruited; the dose of indinavir was adapted to achieve trough concentrations ranging between 500-2000 ng/ml: 400 mg twice a day (n = 1), 600 mg twice a day (n = 4), 800 twice a day (n = 7).

At baseline, all NRTI were stopped and only indinavir/ritonavir monotherapy was maintained.

The primary endpoint was a treatment failure defined as one confirmed HIV-RNA level > 400 copies/ml or three consecutive values > 200 copies/ml. Eleven patients completed the 48-week study period, and no patient reached a predefined primary endpoint. After completion of the study at week 48, all 11 patients opted to remain on the study treatment and remained suppressed for a median of 78 weeks.

ATARITMO study[20]

This non-comparative, 24-week, pilot trial evaluated the possibility of a simplified maintenance strategy with ritonavir-boosted atazanavir to maintain viral suppression.

Patients on conventional HAART for at least six months (stable HAART during at least three months), or who previously participated in the indinavir/ritonavir monotherapy[19] study were eligible for this study.

The primary endpoint of this trial was defined as two consecutive HIV-RNA values > 400 copies/ml, or three consecutive HIV-RNA values > 200 copies/ml, or four consecutive HIV-RNA values > 100 copies/ml.

Thirty patients were included in the study (nine patients had previously been treated with indinavir/ritonavir monotherapy).

At baseline, all combination therapies or indinavir/ritonavir monotherapy were stopped and only ritonavir-boosted atazanavir was administered for up to 24 weeks.

According to endpoint criteria, three patients failed on atazanavir/ritonavir monotherapy; all other patients (n = 27) were virologically suppressed in plasma at week 24 (HIV-RNA load < 50 copies/ml).

ACTG 5201 study[21]

This was a single-group, open-label, multicenter, 24-week pilot study including 36 HIV-1-infected patients with sustained virologic suppression for at least 48 weeks, receiving their first PI-based regimen.

Table 1. Summary of results in protease inhibitor monotherapy studies

	Kahlert	ATARITMO	ACTG 5201	Karlström	Campo	Pierone	OK04		KALMO		Cameron (M03- 613)		IMANI2	MONARK	
Treatment group	experienced	experienced	experienced	experienced	experienced	experienced	experienced		experienced		naive		naive	naive	
Entry criteria	HIV-RNA < 50 c/ml	HIV-RNA < 50 c/ml	HIV-RNA < 50 c/ml	HIV-RNA < 20 c/ml	HIV-RNA < 50 c/ml	HIV-RNA < 75 c/ml	HIV-RNA < 50 c/ml		HIV-RNA < 80 c/ml $CD4^+$ > 100/ml		HIV-RNA > 1000 c/ml		No PI resistance mutation	HIV-RNA < 100,000 c/ml $CD4^+$ > 100/ml	
Results report to	48 weeks	24 weeks	24 weeks	72 weeks	24 weeks	48 weeks	96 weeks		96 weeks		96 weeks		48 weeks	96 weeks	
Treatment groups	IDV/r	ATV/r	ATV/r	ATV/r	LPV/r	LPV/r	LPV/r	LPV/r + 2 NRTI	LPV/r	Standard HAART	LPV/r	EFV + 2 NRTI	LPV/r	LPV/r	LPV/r + 2 NRTI
Baseline HIV-RNA (log_{10} c/ml), mean	< 50 c/ml	< 50 c/ml	< 50 c/ml	< 20 c/ml	< 50 c/ml	< 75 c/ml	< 50 c/ml		< 80 c/ml		5.0	4.8	4.48	4.39	4.34
Dosed all	12	30	36	30 (planned)	6	18	100	98	30	30	104	51	39	83	53
Discontinued (%)	8.3	7	5.5	Stopped at 15th participant	0	27.7	8	9	3.3	0	24	25	0	16	23
Sub-optimal response (%)	0	10	8.8	5/15 virologic failures = 33%	> 400 c/ml n = 2 (33%)	33	13	22	3.3	3.3	> 50 c/ml n = 25 (25%)	0	15	11	13
% VL < 50 c/ml (intent-to-treat)	NA	NA	NA	NA	NA	NA	77	78	86.7 VL < 80 c/ml	86.7 VL < 80 c/ml	48	61	NA	64	75

PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; EFV: efavirenz; VL: viral load; LPV: lopinavir; r: ritonavir; ATV: atazanavir; IDV: indinavir; copies: c.

The primary endpoint was to evaluate the risk of virologic failure, defined as two consecutive plasma HIV-1 RNA levels ≥ 200 copies/ml, through 24 weeks after simplification to atazanavir/ritonavir monotherapy.

A total of 36 participants were enrolled; 33 patients remained in the study through 24 weeks. Out of the 33 patients, 31 were in virologic success.

Karlström study[22]

This was a single-centre pilot trial investigating ritonavir-boosted atazanavir monotherapy in HIV-1-infected patients with stable antiretroviral therapy.

The patients were eligible if they had no prior history of PI therapy and if they had a sustained viral load < 20 copies/ml for a minimum of one year on conventional triple-antiretroviral therapy.

The study was intended to recruit 30 patients to be followed over 72 weeks. If five cases of virologic failures occurred during this period, the study was to be terminated.

The primary endpoint was the number of patients completing 72 weeks on monotherapy without experiencing virologic failure, defined by two consecutive plasma HIV-1 RNA load > 20 copies/ml.

The study was terminated according to protocol when 15 of the planned 30 patients had been recruited because five cases of virologic failure had already occurred.

The authors concluded that ritonavir-boosted atazanavir monotherapy might not be as potent as a conventional triple combination.

CAMPO study[23]

This small, 24-week, pilot, non-comparative study explored whether monotherapy with lopinavir/ritonavir maintains viral suppression after initial therapy with conventional HAART.

Six previously naive patients on therapy with lopinavir/ritonavir 400/100 mg, zidovudine 300 mg, and lamivudine 150 mg, given twice a day for at least 24 weeks, and with three determinations of HIV-RNA < 50 copies/ml, were included.

Treatment with zidovudine/lamivudine was discontinued and lopinavir/ritonavir was continued. At week 24, four out of six patients had HIV-RNA levels < 400 copies/ml. The two remaining patients had less consistent viral suppression, with HIV-RNA levels ≥ 1000 copies/ml at least once. No PI-associated resistance mutation was detected in these two patients.

Pierone study[24]

This was a 48-week prospective pilot study which evaluated the safety and efficacy of switching from NRTI plus NNRTI therapy to lopinavir/ritonavir monotherapy in HIV-infected patients with stable viral suppression < 75 copies/ml.

Patients were eligible for enrolment if they were over 18 years, naive to PI, and on a stable NNRTI-based antiretroviral regimen for more than six months, with two consecutive viral load determinations < 75 copies/ml. Patient not receiving their first HAART treatment regimen could be enrolled if the prior regimen had been interrupted for any reason other than viral failure. The primary endpoint was the proportion of participants with plasma HIV-RNA level < 75 copies/ml at week 48. Virologic failure was defined as HIV-RNA load > 400 copies/ml on two consecutive samples at least one week apart.

Eighteen patients discontinued NNRTI and started lopinavir/ritonavir during two weeks. Thereafter, NRTI were stopped and lopinavir/ritonavir monotherapy was continued. At week 48, 12 out of 18 (66%) participants met the primary endpoint. Thirteen (72%) participants completed the 48-week study on lopinavir/ritonavir monotherapy, and 12 out of 13 (92%) participants had HIV-RNA levels < 75 copies/ml at week 48 on study treatment.

Randomized studies

OK study[25]

This 48-week study evaluated maintenance with lopinavir/ritonavir monotherapy versus continuing lopinavir/ritonavir plus two NRTI in HIV-infected patients with sustained viral suppression for more than six months prior to enrolment. Patients were eligible if they had no history of virologic failure while receiving a PI.

The primary outcome measure for efficacy was the proportion of patients with HIV-RNA < 500 copies/ml at week 48. Virologic failure was defined as two consecutive HIV-RNA > 500 copies/ml two weeks apart.

Forty-two patients were randomized to continue or to stop the NRTI (21 per group).

Twenty patients in each group completed the study. After a 48-week follow-up, 81% of patients in the monotherapy group maintained an HIV-RNA < 50 copies/ml, versus 95% in the triple-therapy group ($p = 0.34$).

OK04 study[26]

The eligibility criteria for this study were essentially the same as for the OK study.

A total of 198 patients were randomized to lopinavir/ritonavir monotherapy (n = 100) or lopinavir/ritonavir triple therapy (n = 98). The primary endpoint was the proportion of participants without therapeutic failure (defined as two consecutive HIV-RNA values > 500 copies/ml two weeks apart). Of note, patients in the monotherapy group who experienced viral rebound and were subsequently re-suppressed after intensification with two NRTI were not considered as therapeutic failures.

After 48 weeks, the proportion of patients without therapeutic failure was 94% in the monotherapy group and 89.9% in the triple-therapy group[26]. At week 96, the percentage of patients without virologic failure was 87% in the monotherapy group versus 78% in the triple-therapy group. The proportion of patients with HIV-RNA < 50 copies/ml was 77% in the monotherapy group versus 78% in the triple-therapy group[27].

KALMO study[28]

This was an open-label study in which 60 patients were randomized 1:1 to maintain their current regimen or to switch to lopinavir/ritonavir monotherapy.

Participants were eligible if their plasma HIV-RNA was < 80 copies/ml for at least six months on their current regimen, with no prior virologic failure, and with a CD4 cell count > 100 cells/mm^3. The primary endpoint was the proportion of patients with HIV-RNA < 80 copies/ml by week 96.

At week 48, by intent-to-treat analysis, 26 out of 30 (86.7%) patients in the monotherapy group, and 25 out of 30 (83.3%) patients in the control group had plasma viral loads < 80 copies/ml[29]. At week 96, 26 out of 30 (86.7%) subjects in both groups had viral loads < 80 copies/ml[28].

Induction-maintenance strategy

Cameron study M03-613[30]

This study was a randomized trial comparing the efficacy of lopinavir/ritonavir monotherapy following combination treatment with lopinavir/ritonavir plus lamivudine/zidovudine with a standard combination regimen (efavirenz plus lamivudine/zidovudine) in antiretroviral-naive subjects followed for 96 weeks.

Patients were eligible to participate in the study if they were naive for any antiretroviral treatment, with HIV-RNA ≥ 1000 copies/ml, and without resistance to any study drug on screening genotype.

A total of 155 patients were randomized to receive lamivudine/zidovudine twice daily with either lopinavir/ritonavir (n = 104) or efavirenz (n = 51). In the lopinavir/ritonavir group, subjects achieving three consecutive monthly HIV-RNA < 50 copies/ml between weeks 24-48 stopped zidovudine/lamivudine and continued with lopinavir/ritonavir monotherapy.

The primary endpoint was the proportion of subjects in the intent-to-treat exposed population with HIV-RNA < 50 copies/ml at week 96.

Viral rebound was defined as two consecutive plasma HIV-RNA > 50 copies/ml after achieving plasma HIV-RNA < 50 copies/ml.

In total, 112 (72%) subjects completed the study on their assigned regimen. In the intent-to-treat exposed population, 48% of the lopinavir/ritonavir group and 61% in the efavirenz group had HIV RNA < 50 copies/ml at week 96 (p = ns). Lopinavir/ritonavir monotherapy subjects had a significantly shorter time from simplification to confirmed virologic rebound > 50 copies/ml compared to similar efavirenz-treated subjects.

First-line strategy

Pilot studies

IMANI-2 study[31]

This pilot study evaluated the efficacy of a first-line lopinavir/ritonavir monotherapy regimen in 39 antiretroviral-naive HIV-1-infected patients without any PI resistance, followed during 48 weeks. The primary endpoint was the proportion of patients with HIV-RNA < 75 copies/ml at week 48.

All participants completed the study. There were six virologic failures of which five could be attributed to poor adherence to study treatment.

Randomized study

MONARK study[32]

MONARK was a prospective, pilot, open-label, randomized, 96-week trial comparing the safety and efficacy of lopinavir/ritonavir monotherapy to a standard triple therapy associating lopinavir/ritonavir with lamivudine/zidovudine, as an initial treatment

regimen in HIV-infected patients with HIV-RNA < 100,000 copies/ml.

Patients were eligible if they were 18 years or older, naive to antiretroviral therapy, had a CD4 cell > 100/mm^3, a plasma HIV-RNA < 100,000 copies/ml, and if they required initiation of anti-HIV therapy according to the IAS guidelines.

The primary endpoint was the proportion of patients with HIV-RNA < 400 copies/ml at week 24 and < 50 copies/ml at week 48. Patients were followed up to week 96.

A total of 136 patients were randomized to the monotherapy (n = 83) or the triple-therapy (n = 53) groups. The on-treatment analysis indicated that 80% in the monotherapy group and 95% in the triple-therapy group reached the primary endpoint (p = 0.02). Less patients on lopinavir/ritonavir monotherapy had an HIV-RNA < 50 copies/ml at week 48 compared to those on lopinavir/ritonavir triple therapy (84 vs. 98%; p = 0.03). The authors concluded that lopinavir/ritonavir monotherapy demonstrated a lower rate of virologic suppression when compared to lopinavir/ritonavir triple therapy and therefore should not be considered as a preferred treatment option in antiretroviral-naive patients.

Development of resistance mutations at failure on boosted protease inhibitor monotherapy (Table 2)

Boosted PI combination therapy is associated with a high genetic barrier to development of resistance, as reflected by the very low rate of PI resistance observed over periods of up to seven years of treatment[33]. Indeed, combination therapy with lopinavir/ritonavir rarely selects for PI resistance in antiretroviral-naive patients[34,35].

In the context of antiretroviral monotherapy, it will be of major importance to study the risk of selection of drug-resistant viruses. In addition, the polymorphism of HIV-1 non-B protease could decrease the genetic barrier as some polymorphism mutations may impact PI susceptibility, thus increasing the risk of resistance development.

Single-drug maintenance therapy with atazanavir/ritonavir in pilot studies described rates of virologic failure varying from 7-36%[20-22]. In these three studies, resistance testing at failure did not identify PI resistance mutations, and no sample showed any primary resistance mutations, including I50L which is the mutation selected in the case of atazanavir virologic failure.

Maintenance strategy with lopinavir/ritonavir monotherapy showed that after full viral suppression obtained with HAART, efficacy of maintenance was demonstrated in comparison to triple therapy[27,30]. In the OK study, after 48 weeks of follow-up, 21 patients in each group were still in the study; 81% patients in the monotherapy group remained with an HIV-RNA < 50 copies/ml, versus 95% for the triple-therapy group (p = 0.34). No PI resistance was detected in patients with virologic failure and genotypic resistance test available (Table 2). In the Cameron study, 48% of the lopinavir/ritonavir group and 61% in the efavirenz group had an HIV-RNA < 50 copies/ml at week 96. In the lopinavir/ritonavir monotherapy group, three patients selected a resistant virus at week 40 (M46L, V82A), week 44 (L90M) and week 60 (M46I). In the lopinavir/ritonavir triple-therapy group, one patient selected a resistant virus at week 40 (I54V) (Table 2). The PI resistance patterns observed in patients included in the Cameron study were already described for lopinavir/ritonavir resistance in the context of triple therapy, with the emergence of major PI mutations such as M46I, I54V, V82A, and L90M[34,35]. The pattern of mutations including V32I, M46I, and I47A was not evidenced in these studies in contrast to the Friend report.

In the MONARK study, where lopinavir/ritonavir was used as monotherapy in naive patients, preliminary results until week 48 reported that resistance mutations were detected in the protease gene in three out of 83 patients (3.6%) in lopinavir/ritonavir monotherapy, and in the reverse transcriptase gene in one out of 53 on lopinavir/ritonavir triple therapy[32]. More recently, at the last HIV Drug Resistance Workshop, Delaugerre, et al. reported the rate and profile of resistant virus at week 96[36]. In the lopinavir/ritonavir monotherapy group, 32 subjects qualified for genotypic resistance testing, seven due to suboptimal response, five discontinued study treatment, and 20 requested because of the occurrence of low-level episodes of viremia of 50-500 copies/ml after an HIV-RNA < 50 copies/ml. Of these 32 subjects, five had a virus with major PI mutations: M46I, L63P at week 40; L76V at week 44; I13V, M46I, L76V at week 62; L10F, V82A at week 76; L76V at week 90 (Table 2). The five viruses with major PI mutations belonged to subtype B in two cases and to CRF02_AG subtype in three cases. Major PI mutations were detected between weeks 40 and 90. The selected PI-associated resistance mutations (M46I and V82A) have been previously described in patients failing on a triple combination containing lopinavir/ritonavir. Interestingly, three out of the five patients selected protease muta-

Table 2. Main characteristics of studies using protease inhibitor monotherapy

Article	Study	Previous treatment	Study treatment after switch	Patients (n)	Virologic success (%)	Virologic failure (%)	Genotypic resistance test
Boosted protease inhibitor maintenance study							
ACTG 5201 study Swindells S, et al. JAMA. 2006	Non-comparative 24 week pilot study	First PI-based regimen with VL < 50 c/ml for at least 48 w	ATV/r (300/100 mg qd)	34	31/34 (91%) at week 24	3/34 (9%) wk 12: 4730 c/ml w k 14: 1285 c/ml wk 20: 28 397 c/ml	Absence of PI resistance
Karlström O, et al. J. AIDS.	Non-comparative pilot study	PI naive ART therapy with VL < 20 c for at least 48 w	ATV/r (300/100 mg qd)	15	9/14 (64%) median time of 36 weeks (16-48)	5/14 (36%) wk 12: 3400, 100 c/ml wk 12: 100, 400 c/ml wk 16: 100, 200 c/ml wk 12: 50, 200 c/ml wk 16: 50, 300 c/ml	Absence of PI resistance (n = 3) 2 patients not tested
ATARITMO study Vernazza P, et al. AIDS. 2007	Non-comparative 24-week pilot study	HAART treatment with VL < 50 c/ml for at least 12 w	ATV/r (300/100 mg qd)	30	27/30 (90%) at week 24 (VL < 50 c/ml)	*2/30 (7%) wk 8: > 400, > 400 c/ml wk 20: > 400, > 400 c/ml	Not tested
OK study Arribas J R, et al. J. AIDS. 2005	Randomized controlled, pilot study (1:1)	No history of virologic failure with HAART containing PI	LPV/r (400/100 mg bid) monotherapy	21	17/21 (81%) at week 48	4/21 (19%) (wks 14, 16, 25, 29)	Absence of PI resistance (n = 3) 1 patient lost of follow-up
		2 NRTI + LPV/r > 1 month and VL < 50 c/ml for at least 24 w	2 NRTI + LPV/r	21	20/21 (95%) at week 48	1/21 (5%)	Absence of PI resistance (n = 1)
Cameron D W, et al.	Randomized controlled, study (2:1)	ARV naive patients ZDV/3TC/LPV/r (bid) with 3 consecutive VL < 50 c/ml between w 24 and w 48	LPV/r (400/100 mg bid)	71	48% VL < 50 c/ml at week 96		LPV/r monotherapy (n = 14) 3 PI resistance w 40: M46L, V82A w 44: L90M w 60: M46I LPV/r tritherapy (n = 1) w 40: I54V ZDV/3TC/EFV (n = 5) 1/5 NNRTI resistance K103N
		EFV (600 mg qd)/ZDV/3TC	EFV (600 mg qd)/ZDV/3TC	51	61% VL < 50 c/ml at week 96		

(Continue).

Table 2. Main characteristics of studies using protease inhibitor monotherapy *(Continued)*

Article	Study	Previous treatment	Study treatment after switch	Patients (n)	Virologic success (%)	Virologic failure (%)	Genotypic resistance test
Boosted protease inhibitor monotherapy in naive patients							
MONARK study Delfraissy JF, et al. AIDS [in press]. Delaugerre C, et al. Antivir. Ther. 2007	Randomized controlled study (2:1)	Naive patients VL < 100 000 c/ml CD4 cell count > 100/mm^3	LPV/r (400/100 mg bid)	83	53/83 (64%) VL < 400 c/ml at w 24 and < 50 c at w 48		Absence of PI resistance (n = 27) 5 PI resistance w 40: M46I, L63P w 44: L76V w 62: I13V, M46I, L76V w 76: L10F,V82A/V w 90: L76V
			ZDV/3TC/LPV/r (bid)	53	40/53 (75%)		Absence of resistance (n = 1) 3TC resistance w 24: M184V

* ATARITMO study: Two patients failed the ATV/r monotherapy (2 consecutive HIV-RNA > 400 copies/ml). One patient was identified as a protocol violator having previously failed indinavir-based HAART, one patient decided to stop treatment after week 20, one patient had persistent low-level replication > 50 copies/ml but never reached the failure criteria.
PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; VL: viral load; ART: antiretroviral therapy; ATV: atazanavir; LPV; lopinavir; EFV: efavirenz; ZDV zidovudine; 3TC: lamivudine; c: copies.

tion L76V and all three were infected with HIV-1 CRF02_AG subtype. In the lopinavir/ritonavir triple-combination group, none had a virus with a major PI mutation.

In summary, no PI-resistant virus was identified in pilot studies using atazanavir/ritonavir as single-drug maintenance therapy. In studies using lopinavir/ritonavir as single-drug maintenance therapy or as monotherapy in naive patients, the barrier for selection of PI resistance mutations appears to be lower than with lopinavir/ritonavir-based three-drug regimens. In addition, mutation L76V in protease gene has not been yet described in patients failing on triple therapy, and was selected in three HIV-1 patients treated with first-line lopinavir/ritonavir monotherapy and infected with a CRF02_AG virus. A first explanation could be the reduced potency of antiretroviral regimens in naive patients due to the absence of NRTI. A second explanation could be the polymorphism of HIV-1 non-B protease gene that could decrease the genetic barrier, subsequently increasing the risk of resistance development.

Efficacy of boosted protease inhibitor monotherapy in anatomical sanctuaries

Triple combination with two NRTI and one PI has been shown to efficiently reduce HIV-1 shedding in semen of most patients[37]. However, little is known about the impact of PI monotherapy on HIV-1 shedding in semen. One concern about boosted PI monotherapy is its ability to control HIV-1 replication in sanctuary anatomical reservoirs such as the male genital tract. Indeed, drug disposition in semen is influenced by drug ionization, lipophilicity, molecular weight, the degree of protein binding, affinity for membrane transporters, and semen pH[38]. The biochemical characteristics of most PI suggest they may not penetrate the blood-testis barrier well, being more lipophilic and extensively bound to blood plasma proteins. We and others have previously shown that penetration of boosted amprenavir, saquinavir, lopinavir, and atazanavir in semen was poor[39,40], contrasting with that of indinavir which achieved therapeutic concentrations in semen[39]. This issue raises concerns about the local selection of drug resistance, with potential replenishment with resistant virus into circulation[41].

Two studies describing seminal plasma antiretroviral activity of boosted atazanavir when used as sole agent are available. These two studies involved patients who had an already suppressed HIV replication on a triple combination before switching to boosted atazanavir

monotherapy[20,21]. These two studies provided conflicting results, one showing no detection of HIV-RNA in seminal plasma of eight patients after 24 weeks on boosted atazanavir monotherapy[21], while in the other study, high levels of HIV-RNA were detected in seminal plasma of 2/15 patients tested at week 24, despite full viral suppression in blood[20]. No pharmacologic measurement was performed in these two studies.

The only study in the male genital tract with data on both viral quantification and pharmacologic measurements in semen was performed in antiretroviral-naive patients starting a first-line monotherapy with lopinavir/ritonavir, or a standard triple combination with zidovudine/lamivudine plus lopinavir/ritonavir in the MONARK trial[32]. In this study, semen HIV-RNA was undetectable in five out of five men on lopinavir/ritonavir monotherapy, despite undetectable semen lopinavir and ritonavir concentrations[42]. Semen HIV-RNA was also undetectable in five out of five men after 48 weeks on zidovudine/lamivudine plus lopinavir/ritonavir[42].

Only one study explored the impact of lopinavir/ritonavir monotherapy in the female genital tract, with available data on both viral quantification and pharmacologic measurement. In this study, HIV-RNA was undetectable in the cervicovaginal fluid of all seven women studied[43]. Lopinavir/ritonavir penetration into cervicovaginal fluid exceeded the reference population median IC_{50} (1.9 ng/ml) in all but one sample, despite significant dilution of lavage samples[43].

Finally, two studies addressed the issue of boosted PI monotherapy virologic impact in cerebrospinal fluid (CSF). The first study, IMANI-2, involved antiretroviral-naive patients who started a first-line lopinavir/ritonavir monotherapy, and who had achieved at least two plasma HIV-RNA measurements < 75 copies/ml after a minimum of 24 weeks on treatment[44]. The HIV-RNA in CSF was undetectable in 10 out of the 11 patients studied. The lopinavir CSF median concentration was 24.3 ng/ml. The median lopinavir IC_{50} ratio was 12.8 (range, 3.7-44.9). All individual-subject lopinavir concentrations exceeded the reference population median IC_{50} by at least threefold, and the mean CSF lopinavir concentration exceeded the reference population median IC_{50} by 16-fold. The authors concluded that lopinavir/ritonavir delivers adequate lopinavir concentrations that reliably exceed the reference population median IC_{50} for wild-type virus[44]. The second study involved already suppressed patients and switched for boosted atazanavir monotherapy[20]. At week 24, CSF was obtained from 20 patients with plasma HIV-RNA < 50 copies/ml. Three patients (15%) had elevated viral loads in CSF (2.8, 2.2, and 3.8 $\log_{10}$ cp/ml) despite viral suppression in plasma. Mean ratio of CSF/plasma drug concentration was 0.9% (± 0.8, range 0.1-2.7%). These levels were slightly above the EC_{50} (1 ng/ml) for wild-type virus.

Clinical use of protease inhibitor monotherapy in clinical practice

The challenge currently facing HIV researchers and clinicians is to find a simple and potent treatment strategy that might not only avoid cumulative toxicities associated with long-term use of antiretrovirals, but also reduce the cost of a lifespan-planned antiretroviral therapy. Regarding these issues, boosted PI monotherapy seems an appealing approach. All boosted PI monotherapy studies reported herein showed that this strategy is effective in a surprisingly high proportion of patients. This clearly challenges the notion that a three-drug regimen is a definite prerequisite for successful antiretroviral therapy.

The major concern with such a strategy is the higher proportion of patients experiencing transient episodes of low-level viremia (50-500 copies/ml) when compared to classical triple regimens. Of note, the proportion of patients with low-level, transient viremia seems to depend on the clinical setting in which it is used, being lesser in studies of maintenance therapy than in first-line studies. In most cases, this low-level viremia did not favor the development of resistance mutations. A simulated model of treatment simplification with boosted PI monotherapy suggested that subjects who do not develop PI resistance at the time of virologic failure are projected to live longer than subjects receiving the standard-of-care regimen because they can receive an additional line of therapy without compromising future options[45]. In the very few cases where resistance mutations were selected on suboptimal boosted PI monotherapy[36], they did not affect phenotypic or genotypic viral susceptibility to the PI used and did not jeopardize future therapeutic options. Indeed, intensification with two NRTI yielded a plasma HIV-RNA < 50 copies/ml. All randomized studies showed a similar increase in CD4 cells in patients on triple combination or on boosted PI monotherapy, despite higher rates of low-level viremia in the latter group[30,32], suggesting that low-level viremia had minimal, if any, impact on restoration of immune function. The origin of this low-level viremia is at present unclear. Adherence may be a critical determinant[21]. In addition, a recently published mathematical model suggested that this low-level viremia

may also be facilitated by differential drug penetration in anatomic sanctuary sites[46]. The consequences of suboptimal drug penetration in the central nervous system or in the genital tract have major clinical and public health implications, especially in the setting of boosted PI monotherapy. Indeed, despite full viral suppression in blood plasma, some patients may develop HIV encephalopathy[47]. Given that, in the vast majority of cases, viral particles in anatomic reservoirs originate from passive diffusion from blood plasma[48], we would therefore, in keeping with Vernazza, et al.[20], caution against the wide use of PI-based monotherapies until complete suppression of viral load in the central nervous system is documented or at least probable after a sufficient induction period with a triple combination. Compartmentalization of HIV-1 in the genital tract is also a source of concern. It might not only increase the risk of development of local resistance, but also enhance the risk of HIV transmission of resistant strains from treated individuals[49]. The few existing data on the impact of boosted PI monotherapy on HIV-1 shedding in the male genital tract showed conflicting results[20,21,42], which suggest that the reassuring results obtained with lopinavir might not be extended to the whole PI class.

Another important issue is patient quality of life; this issue, however, has been poorly addressed in most randomized studies. Fat distribution has been studied by Cameron, et al., who showed that peripheral fat loss occurred significantly less frequently on lopinavir/ritonavir monotherapy compared to a triple regimen with efavirenz. Moreover, lipohypertrophy occurred with a similar frequency in both treatment groups[30].

Finally, a boosted PI monotherapy strategy offers an interesting cost saving compared with the standard-of-care triple combination[24,45].

In conclusion, a boosted PI monotherapy strategy can maintain continuous plasma HIV-RNA suppression in a large proportion of patients already suppressed on a standard triple combination. The more frequent occurrence of low-level viremia, however, does not allow the widespread use of such a strategy outside of clinical studies at this time. Moreover, we believe that the suboptimal efficacy of such a strategy in anatomical viral sanctuaries requires a sufficient induction period on standard triple combination, which makes first-line boosted PI monotherapy not suitable in antiretroviral-naive patients. Ongoing large randomized studies with new generation PI such as darunavir, with a high genetic barrier and low induction of resistance mutations in case of virologic failure[50], will help to better identify the most appropriate patient populations that might benefit most from a boosted PI single-agent strategy and to better understand the potential risks and benefits associated with this therapeutic strategy.

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