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Double-Boosted Protease Inhibitor Antiretroviral Regimens
What Role?

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Abstract

Despite the clinical benefit observed with early highly active antiretroviral therapy, its toxicity and inconvenience, and the strategy of sequentially adding newly available drugs to failing regimens meant that for many patients, it was difficult to build an effective regimen soon after starting therapy. In this setting, the idea of using double-boosted protease inhibitors (PIs) to build a potent regimen emerged. The rationale for the simultaneous use of two PIs is (i) to provide synergistic or additive activity against HIV; (ii) to achieve higher plasma concentrations of both PIs with only one booster; (iii) to increase the genetic barrier to resistance; and/or (iv) to avoid toxicity with nucleoside reverse transcriptase inhibitor-sparing regimens.

Double-boosted PI strategies are not recommended in treatment-naive patients because of their low success rate and the availability of more convenient and effective regimens.

There are no adequate trials in treatment-experienced patients to establish the clinical efficacy of double-boosted PI regimens; however, the published non-comparative studies suggest considerable efficacy with certain combinations (e.g. lopinavir/ritonavir plus atazanavir, lopinavir/ritonavir plus saquinavir and others) in patients in whom a conventional regimen with one boosted PI could have little chance of success.

New drugs of old and new classes that are better tolerated and have different resistance profiles have become available in recent years. These drugs have demonstrated their efficacy in randomized clinical trials, even in patients with extensive treatment experience and high drug resistance. Nowadays, in almost all patients, it is possible to elaborate a regimen with three active drugs, achieving success rates similar to those obtained in treatment-naive patients with recommended regimens. In this context, it is unthinkable that double-boosted PIs could play any role.

Double-boosted PIs may be an alternative for those patients with limited therapeutic options in resource-poor settings, where new expensive drugs are not currently available. The fixed combination of lopinavir/ritonavir tablets makes it easier to boost with another PI at the same time, without requiring ritonavir refrigeration, and this may be particularly useful in this setting.

Since the widespread use of highly active antiretroviral therapy (HAART) in 1996, AIDS-related morbidity and mortality has declined sharply. Despite this clinical benefit of HAART, toxicity and

inconvenience meant that treatment failed in about 40–50% of patients a year after starting therapy, and treatment success in subsequent regimens was even lower.[1,2] The then current practice of adding sequentially new drugs to failing regimens played an important part in producing this low success rate in treatment-experienced patients. Thus, in clinical practice, clinicians were faced with a significant number of patients who had experienced several treatment failures after several years of therapy, accumulating multiple resistance mutations to the three available antiretroviral classes. The efficacy of nucleoside reverse transcriptase inhibitors (NRTIs) was notably decreased as a result of thymidine analogues, M184V and other mutation selections. The virus became fully resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in many patients. Moreover, some protease inhibitor (PI) mutations were selected, mainly due to virological failure with non-boosted PIs. With the widespread use of subtherapeutic doses of ritonavir as a booster, higher concentrations of the PIs were achieved, resulting in increased efficacy and more convenient regimens.[3] However, in those patients with primary mutations to PIs, resistant to NNRTI and with low activity of NRTIs, success rates with rescue boosted PI regimens remained low. It was in this context that the possibility of using a double-boosted PI to build a potent regimen was developed, with ritonavir at low doses boosting the two PIs simultaneously.

Moreover, after several years of HAART use, clinicians achieved better knowledge of NRTI involvement in some long-term dose- and duration-dependent adverse events, mainly mitochondrial toxicity and lipoatrophy. These toxicities, or the fear of developing them, prompted investigation of NRTI-sparing strategies, one of which was the use of double-boosted PI regimens.

In this article, we focus on the rationale of double-boosted PI strategies and their potential role in the current management of HIV-infected patients.

1. Rationale for the Use of Double-Boosted Protease Inhibitor (PI) Regimens

The theoretical bases that sustain the combination of full doses of two PIs are as follows:

- synergistic or additive activity against HIV;
- high plasma concentrations of both PIs with only one booster;
- different resistance patterns to PIs and the existence of different viral subpopulations; and
- to avoid toxicity with NRTI-sparing regimens.

1.1 Synergistic or Additive Activity Against HIV

In vitro data of various PI combinations that included lopinavir boosted with ritonavir showed a significant synergy with saquinavir at all concentrations tested, and additive activity with amprenavir, atazanavir, indinavir, nelfinavir and tipranavir, without cellular toxicity.[4] A different *in vitro* study combined atazanavir with the five PIs approved at that time. Atazanavir showed modest synergy with saquinavir, and overall additive response with amprenavir, nelfinavir, indinavir and ritonavir. No antiviral antagonistic effects or increased cytotoxicity resulted from any combination.[5] In another study, the *in vitro* synergism between lopinavir or atazanavir and saquinavir was demonstrated only in PI-resistant virus.[6]

1.2 High Plasma Levels of Both PIs with Only One Booster

The main metabolic pathway of PIs is via the cytochrome P450 (CYP) enzymes, especially the isoenzyme CYP3A4 in the liver and, to a lesser extent, in the intestinal wall and other tissues, and also efflux proteins such as P-glycoprotein (P-gp) and other transporter proteins such as multidrug resistance-associated proteins. Inhibition or induction of these systems results in increased or decreased plasma drug concentrations, respectively. Ritonavir is a potent CYP3A4 and P-gp inhibitor, and, even at low doses (e.g. 100 mg), increases exposure to other PIs. Atazanavir also has a clinically significant activity inhibiting both systems, but this is modest when compared with ritonavir. Pharmacokinetic interactions using double-boosted PIs are complex and are still not fully understood. Some PIs, apart from the inhibitory activity of ritonavir, also have a variable inducing or inhibitory effect on CYP3A4 or P-gp, the final result of the combination being unpredictable. Thus, some combinations,

such as lopinavir/ritonavir plus saquinavir[7-11] or atazanavir with ritonavir plus saquinavir,[12-14] have shown a favourable pharmacokinetic profile with high exposures of both PIs. In the five pharmacokinetic studies published with the lopinavir/ritonavir plus atazanavir combination,[15-19] conflicting results have been seen, ranging from non-significant decreases to increases of both PI concentrations. On the other hand, the coadministration of fosamprenavir with ritonavir plus saquinavir resulted in a slight decrease in saquinavir concentrations,[20] and some combinations, such as lopinavir/ritonavir plus amprenavir[21-23] or lopinavir/ritonavir plus fosamprenavir,[24-26] have shown decreases in one or both PI levels, entailing dose adjustments or contraindicating the combination.

Because of the complex interactions when using these non-conventional regimens, it would be advisable to perform therapeutic drug monitoring (TDM) of plasma PI concentrations. Although therapeutic levels of PIs have not been established for all drugs, most clinical guidelines[27-29] recommend TDM and give at least minimum target concentrations to avoid excessively high drug concentrations (that could increase toxicity) or low concentrations (with risk of virological failure and selection of resistance mutations). These plasma concentrations should be interpreted together with resistance testing and inhibitory quotients, to take into account the sensitivity of the virus.[30]

1.3 Different Resistance Patterns to PIs and Existence of Different Viral Subpopulations

Some mutations confer cross-resistance to all PIs, and others are specific for certain PIs. Thus, in treatment-experienced patients, the virus shows variable degrees of genotypic and phenotypic resistance to the different PIs.[31] If the virus resistance patterns for two drugs are overlapping but not identical, the antiviral activity of both drugs will be diminished; however, if we combine them, especially at high concentrations, we might increase the genetic barrier.[32] Therefore, it is preferable to combine two PIs with resistance patterns as different as possible in order to increase the resistance barrier and thus the rate of therapy success.

Although the global viral population may show resistance to multiple drugs, viral subpopulations might have different resistance profiles. When giving a double-boosted PI combination, some 'quasispecies' may remain sensitive to one PI and others to the second PI, diminishing the risk of failure.

Some PI combinations have non-compatible resistance mutations, such as the I50L mutation that confers resistance to atazanavir and the I50V mutation that confers resistance to amprenavir and lopinavir. A single virus cannot have both mutations, so it cannot be resistant to both drugs by using this pathway. Furthermore, the acquisition of the I50L mutation confers hypersensitivity to other PIs.[33]

1.4 Avoid Toxicity with NRTI-Sparing Regimens

As a result of the high and stigmatizing long-term toxicity of the first NRTIs, several NRTI-sparing regimens have been investigated. A double PI combination could be an option to build sufficiently potent NRTI-sparing therapies, especially in those patients who are not able to take NNRTIs because of intolerance or resistance. Despite the availability of new and better tolerated NRTIs, some patients cannot take them for several reasons and these NRTI-sparing strategies still remain useful.

With the NRTI-sparing double-boosted PI regimens, NRTI toxicity is avoided, but often at the expense of an increased pill burden and a higher rate of adverse events than with single-boosted PI regimens, mainly gastrointestinal disturbances and metabolic alterations.

The consequences of using only PIs for viral eradication in some reservoirs, such as the CNS, where drug penetration is not the same as in plasma, remain to be determined. In a study with lopinavir/ritonavir monotherapy, failure to eradicate the virus from the CNS was seen.[34]

2. Efficacy of Double-Boosted PI Regimens in Clinical Trials

Three randomized pilot studies evaluating the efficacy of different NRTI-sparing double-boosted PI regimens in treatment-naive patients have been presented or published. The first study analysed Thai patients receiving the following doses of lopinavir/ritonavir plus saquinavir twice daily: (i) 400/100/1000 mg (n = 11); (ii) 400/100/600 mg (n = 9);

(iii) 266/66/1000 mg (n = 10); or (iv) 266/66/600 mg (n = 13). After 24 weeks, 39%, 63%, 55% and 69% of patients, respectively, had an HIV viral load <50 copies/mL.[35] Recently, preliminary results from the other two studies have been presented. The French National Agency for AIDS Research 2IP ANRS 127 study[36] compared fosamprenavir plus atazanavir with ritonavir (700 mg twice daily/300 mg once daily/100 mg twice daily [n = 30]) with saquinavir plus atazanavir with ritonavir (1500/300/100 mg once daily [n = 31]). The primary endpoint was virological success at week 16; if not reached, treatment was changed. Efficacy was low in both the fosamprenavir and saquinavir groups: only 40% and 41.9% of patients, respectively, achieved the endpoint. The LORAN trial[37] compared lopinavir/ritonavir plus atazanavir with zidovudine/lamivudine plus lopinavir/ritonavir. After 24 weeks, the NRTI-sparing arm had significantly lower efficacy (HIV RNA <50 copies/mL 49% vs 75%, respectively) and recruitment was stopped. Thus, because of the low success rate and the availability of more convenient and effective regimens, double-boosted PI strategies are not recommended in treatment-naive patients.

There are no published randomized studies in treatment-experienced patients comparing a double-boosted PI based regimen with a single-boosted PI conventional regimen, and it is unlikely that there will be any in the future. Because only appropriate comparative clinical trials can determine the utility of a therapeutic strategy, we will therefore not be in a position to know with certainty if two boosted PIs are better than one in these patients.

In a recent, retrospective, cohort study in treatment-experienced patients comparing single-boosted PI (n = 805) with double-boosted PI (n = 183) regimens, Petersen et al.[38] found no differences in virological outcome between the groups. However, the groups were not comparable because the patients included in the double-boosted PI group had more extensive treatment history, more resistance mutations and lower nadir CD4+ cell counts. Apart from the retrospective nature of the study, the authors only classified the treatment into single- or double-boosted PI regimens, and they did not analyse specific combinations of PIs or the dosages of each drug. We now have a better knowledge of the negative interactions between some PIs, making it necessary to increase doses or contraindicating the combination. Thus, it is difficult to draw too many conclusions from this study and we cannot state that there are no differences between regimens with one or two boosted PIs.

The majority of studies where the efficacy of double-boosted PI regimens is assessed were observational, non comparative and included a small number of patients with different levels of treatment experience, with or without NRTI backbones. Most of the studies were carried out with the old PI formulations (saquinavir hard or soft gel capsules, ten pills per day; lopinavir/ritonavir capsules, six pills per day; amprenavir capsules, ten pills per day; atazanavir 150 mg capsules, two pills per day). It is likely that treatment convenience has improved considerably with the new formulations (saquinavir 500 mg tablets, four pills per day; lopinavir/ritonavir tablets, four pills per day; fosamprenavir tablets, two pills per day; atazanavir 300 mg capsules, one pill per day), possibly increasing overall efficacy. Tables I and II summarize published studies including more than 15 treatment-experienced patients.[10,14,15,39-43] Although most of these studies were not designed to assess efficacy, they suggest a considerable efficacy with certain double-boosted PI combinations (e.g. lopinavir/ritonavir plus atazanavir or lopinavir/ritonavir plus saquinavir) in patients in whom a conventional regimen with one boosted PI would have little chance of success, either as a result of viral resistance or drug toxicity.

3. The Current Role of Double-Boosted PI Regimens

In developed countries, there are currently more than 20 available antiretroviral drugs, within six classes with different mechanisms of action, which can be combined to design HAART regimens. These six classes include NRTIs, NNRTIs, PIs, fusion inhibitors, CCR5 antagonists and integrase inhibitors. The drugs of new antiretroviral families (e.g. raltegravir, maraviroc) have an excellent tolerability profile and completely different resistance patterns to each other. The new drugs of old classes (e.g. etravirine, tipranavir and darunavir) have resistance profiles that are very different from the old drugs of the same classes, which had important cross-resistance.

Table I. Summary of studies with double-boosted (DB) protease inhibitor (PI) regimens including lopinavir (LPV)/ritonavir (RTV) assessing efficacy in treatment-experienced patients (pts)[a]

Parameter	Hellinger et al.[10]	Ruiz et al.[39]	Staszewski et al.[40]	Chetchotisakd et al.[41]	Ribera et al.[15]	Gilliam et al.[42]
ART regimen						
PIs	LPV/RTV/SQV	LPV/RTV/SQV	LPV/RTV/SQV	LPV/RTV/SQV	LPV/RTV/ATV	LPV/RTV/ATV
Dosage (mg)	(400/100/1000 bid)	(400/100/1000 bid)	(400/100/1000 bid)	(400/100/1000 bid)	(400/100 bid/300 od)	(400/100 bid/300 od)
Accompanying drugs	No backbone	ABC/3TC/DDI	No backbone	No backbone	Backbone NRTI	Backbone NRTI
No. of pts	20	46	128	52	16	33
Follow-up (wk)	48	48	48	48	24	32 (12–76)
Baseline characteristics						
ART experience	PI naive (15% ARV naive)	Heavily pretreated	Heavily pretreated	Failure to NRTI + NNRTI	Heavily pretreated	Pretreated
Time receiving ART (y)	NR	5.7	6.3	2.6	NR	5
Previous ART	NR	NR	9	NRTI + NNRTI regimen	6	4
CD4+ (cells/μL)	274	339	172	95	299	173
VL (log)	4.1	4.3	5.1	4.44	3.5	4.8
Median PI mut.	0	5	2.5	NR	4	5
Median NRTI mut.	NR	6	NR	NR	7	4
Pharmacokinetics	LPV and SQV C_{trough} similar to SB PI historical controls	LPV and SQV AUC, C_{max} and C_{min} similar to SB PI controls[9]	No interactions among PIs; effective plasma concentrations of both LPV and SQV	NR	↑ in LPV AUC, C_{max}, C_{min} and in ATV C_{min}, regarding SB controls	NR
Efficacy and tolerability						
VL <50 copies/mL (% ITT)	65	46	NR	60	81	83
VL <400 copies/mL (% ITT)	70	NR	61	78	81	91
CD4+ change (cells/μL)	+194	+63 (no STI), −11 (STI)	+108	177	+118	+72
Total withdrawal (n/N)	4/20	NR	50/128	NR	1/16	1/33
Withdraw due to AE (n/N)	2/20	0/46	8/128	4/52	0/16	5/33

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Table I. Contd

Parameter	Hellinger et al.[10]	Ruiz et al.[39]	Staszewski et al.[40]	Chetchotisakd et al.[41]	Ribera et al.[15]	Gilliam et al.[42]
Limitations and comments	Intensification with TDF at wk 12 in 2/20 pts (10%) due to no virological response; ↓ SQV dose to 600 mg bid in 6/20 pts (30%) due to GI AEs	STI random; prognostic factors at baseline: HIV RNA, no. of NRTI mut.	76/128 pts STI before ART (no differences in efficacy with non STI); prognostic factors at baseline: HIV RNA, CD4+ cell count, no. of ARV drugs, no. of PIs, PI mut.	Randomized to DB PI vs comparator arm of IDV/RTV + NRTI if active NRTIs	Many pts had received previous LPV/RTV with good tolerance; this may have influenced the good tolerability of the regimen	Retrospective chart review; all treatment failures were in pts who had >6 PI mut.
Author conclusions	Potent regimen, durable HIV control, improved CD4+ cell count; fat accumulation and poor lipid profile	Significant virological suppression without any benefit of performing STIs	Potential option as salvage therapy (RTI resistance or toxicity)	Poor tolerability and poor outcomes for 2nd-line regimen	Substantial antiviral efficacy with good tolerability in heavily pretreated pts	Combination safe, tolerable and efficacious in PI-resistant pts

a Only studies including more than 15 pts have been summarized. Those PI combinations with notable negative pharmacokinetic interactions have also been excluded.

3TC = lamivudine; **ABC** = abacavir; **AE** = adverse event; **ART** = antiretroviral treatment; **ARV** = antiretroviral; **ATV** = atazanavir; **AUC** = area under the concentration-time curve; **bid** = twice daily; C_{max} = maximum concentration; C_{min} = minimum concentration; C_{trough} = trough concentration; **DDI** = didanosine; **GI** = gastrointestinal; **IDV** = indinavir; **ITT** = intention-to-treat analysis; **mut.** = mutation; **NNRTI** = non-nucleoside reverse transcriptase inhibitors; **NR** = not reported; **NRTI** = nucleoside reverse transcriptase inhibitor; **od** = once daily; **RTI** = reverse transcriptase inhibitor; **SB** = single-boosted; **SQV** = saquinavir; **STI** = structured treatment interruptions; **TDF** = tenofovir disoproxil fumarate; **VL** = viral load (HIV RNA); ↑ indicates increase; ↓ indicates decrease.

Many randomized clinical trials in treatment-naive patients have standardized those drugs preferred as initial therapy, with different combinations of two NRTIs plus an NNRTI or a boosted PI classified as recommended or alternative regimens in guidelines.[27-29] We even find suggested regimens in the unlikely situation where neither NNRTIs nor PIs can be used (e.g. three or four NRTIs [zidovudine/lamivudine/abacavir or zidovudine/lamivudine/abacavir plus tenofovir disoproxil fumarate] or two NRTIs plus a new class drug such as maraviroc or raltegravir). Under no circumstances is the possibility of starting with a double-boosted PI regimen in treatment-naive patients considered.

In the salvage therapy setting, availability of new active drugs and treatment efficacy have increased significantly in recent years. The current general recommendation for antiretroviral therapy is the combination of three fully active drugs, with the target treatment goal to reach maximal virological suppression (HIV RNA <50 copies/mL), irrespective of drug history (e.g. treatment naive, first virological failure or deep salvage therapy).[27-29]

Currently, not many resistance mutations are present in those patients with just one or only a few treatment failures because we have learned to manage virological failure by seeking the reasons for such failure and quickly changing the treatment when necessary. Frequently, suboptimal adherence is the main cause of virological failure. Conditions that promote adherence should be maximized prior to a change in antiretroviral therapy, and convenience and tolerability of the new regimen are important factors that should be taken into consideration. With the currently available drugs, these premises can be achieved with high possibilities of success. In this setting, ritonavir boosted darunavir has shown higher efficacy than lopinavir/ritonavir, especially in those patients in whom the virus harbours any PI primary mutations, a fact never demonstrated or investigated with double-boosted PI regimens.[44]

The most challenging clinical scenario is that of patients with extensive prior treatment history and high drug resistance. Until recently, therapeutic options were few and it was in this setting that most of the previously mentioned double-boosted PI studies took place. In this context, the new drugs have

Table II. Summary of studies with double-boosted protease inhibitor (PI) regimens without lopinavir/ritonavir (RTV) assessing efficacy in treatment-experienced patients (pts)[a]

Parameter	Manosuthi et al.[43]	Winston et al.[14]
ART regimen		
PIs	ATV/RTV/SQV	ATV//RTV/SQV
Dosage (mg)	(300/100/1600 od)	(300/100/1500 od)
Accompanying drugs	No backbone	No backbone
No. of pts	24	25
Follow-up (wk)	60	48
Baseline characteristics		
ART experience	Failure of NRTI + NNRTI	Pretreated (switch)
Time receiving ART (y)	0.6	8
Previous ART	NR	<4 (81% pts)
CD4+ (cells/μL)	179	511
VL (log)	4.6	Undetectable
Median PI mut.	NR	<2
Median NRTI mut.	NR	NR
Pharmacokinetics	95.8% of pts adequate ATV and SQV C_{min}	Favourable PK profile; similar SQV AUC with 200 or 500 mg; less interpatient variability with 500 mg
Efficacy and tolerability		
VL <50 copies/mL (% ITT)	58	87.5
VL <400 copies/mL (% ITT)	75	NR
CD4+ change (cells/μL)	210	+63
Total withdrawal (n/N)	NR	1/25 (HBsAg+)
Withdrawal due to AE (n/N)	0	0/25
Limitations and comments	Wide range of ATV and SQV C_{min}; low no. of pts; 100% NRTI mut. (92% TAM + M184V; 8% TAM + Q151M); 100% NNRTI mut.	Switch study in pts with undetectable VL
Author conclusions	Effective, safe and well tolerated od salvage regimen	Sustained virological efficacy with favourable lipid and tolerability profile; significant ↑ in CD4+ cell count

a Only studies including more than 15 pts have been summarized. Those PI combinations with notable negative pharmacokinetic interactions have also been excluded.

AE = adverse event; **ART** = antiretroviral treatment; **ATV** = atazanavir; **AUC** = area under the concentration-time curve; **C_{min}** = minimum concentration; **HBsAg+** = hepatitis B surface antigen positive; **ITT** = intention-to-treat analysis; **mut.** = mutation; **NNRTI** = non-nucleoside reverse transcriptase inhibitors; **NR** = not reported; **NRTI** = nucleoside reverse transcriptase inhibitor; **od** = once daily; **PK** = pharmacokinetics; **SQV** = saquinavir; **TAM** = thymidine-associated mutations; **VL** = viral load (HIV RNA); ↑ indicates increase.

shown an amazing clinical efficacy in large randomized studies.[45-51] When analysing subgroups of patients, the investigators saw that with each extra active drug available, the outcomes improved. In addition, when three entirely active drugs were combined (e.g. raltegravir, darunavir plus ritonavir and enfuvirtide,[51] or etravirine, darunavir plus ritonavir and another drug[48,49]), therapeutic efficacy was very high, similar to that obtained in treatment-naive patients with recommended regimens. Thus, physicians now find themselves in a state of euphoria thanks to the potency and efficacy of new drugs and it is difficult to conceive that any patient will need double-boosted PI regimens.

However, the new drugs also have drawbacks. Raltegravir has a low genetic barrier and shows cross-resistance with elvitegravir (an investigational integrase inhibitor). Maraviroc and vicriviroc (an investigational CCR5 antagonist), only work in patients infected with R5-tropic HIV-1 (which accounts for 50–80% of patients). Enfuvirtide has a low genetic barrier and requires subcutaneous administration that is associated with local reactions at the site of injection, which can limit its use in many

patients. Darunavir, tipranavir and etravirine activity can be diminished depending on previously existing mutations, and some adverse events can also limit their use. However, it is unlikely that in the near future we will have insufficient drugs to build an effective regimen in any patient. It is crucial that these new drugs are used properly, so that several active drugs are always given (three if possible), especially with those drugs with low genetic barrier, in order to avoid selecting resistance mutations that could invalidate these new drugs.

Even before the latest drugs (maraviroc, raltegravir and etravirine) were available, the use of double-boosted PI regimens was significantly reduced with the advent of the new the PIs tipranavir and darunavir. Usually, one of these new PIs, together with several well tolerated NRTIs with variable residual activity, with or without enfuvirtide, were given. These regimens were probably more effective than two previously existing boosted PIs combined, as seen in the POWER (Performance of TMC114/ritonavir When Evaluated in Treatment-Experienced Patients with PI Resistance) trials,[47] where as much as 23% of the comparator PIs were double-boosted and did not perform better than single-boosted PIs, far behind the darunavir plus ritonavir efficacy. Furthermore, it seems unlikely that these new PIs will be given together with older PIs in double-boosted regimens. The pharmacokinetic studies suggest that tipranavir and other PIs should not be combined as a result of marked decreases in plasma concentrations of the latter (amprenavir, lopinavir, saquinavir minimum concentrations [C_{min}] decreased 51%, 45% and 84%, respectively).[52] With darunavir, decreases in plasma concentrations (about 40%) were observed when given together with lopinavir/ritonavir[53] or saquinavir plus ritonavir,[54] and investigators advised not to combine them, while administration with atazanavir resulted in increases in atazanavir levels (C_{min} increased 52%), probably due to the ritonavir 200 mg dose.[55] All of these are pharmacokinetic studies, without data on clinical efficacy. On the other hand, given the potency, high genetic barrier (greater than other PIs) and resistance profile of darunavir that is widely different from other PIs, it is unlikely that adding a second PI will provide additional clinical benefit.

Double-boosted PIs might become a good option in resource-poor settings, where very expensive new drugs are not currently available and are unlikely to be available in the near future. In these settings, the fixed-dose combination of stavudine, lamivudine and nevirapine is widely used as initial therapy.[56] As viral load testing is not accessible in most developing countries, patients may stay on a failing regimen for months or years, and with, in most patients, the development of resistance to NNRTIs and selection of some resistance mutations to NRTIs.[57] Thus, after one or more treatment failures, it becomes very difficult to build an effective regimen, given that, unfortunately, the new therapeutic options are not available in these settings. Some PIs are obtained at a low price in many limited-resource countries. The fixed combination of lopinavir/ritonavir makes it easier to boost another PI at the same time, preferably atazanavir or saquinavir. The tablet formulation of lopinavir/ritonavir also has the advantage of not needing refrigeration, and this could be particularly useful in these settings, allowing relatively convenient rescue regimens to be designed. Many HIV-infected patients in these countries are children. Recently, the HIV Netherlands, Australia, Thailand research collaboration HIV-NAT 017 study team have published 48-week efficacy, safety, pharmacokinetic and resistance data with the lopinavir/ritonavir plus saquinavir combination in 50 Thai children whose NRTI/NNRTI regimen had previously failed. The study showed 64% efficacy (viral load <50 copies/mL), a rise in CD4+ cell counts, no major PI mutation selection in those patients whose treatment had failed, and high plasma PI concentrations, but also high hyperlipidaemia incidence.[58]

4. Summary and Conclusions

Double-boosted PI regimens play no role in treatment-naive patients. Three studies including a small number of patients showed low success rates (HIV RNA <50 copies/mL about 40–50% at 16 or 24 weeks), notoriously lower than those achieved with standard regimens.

There are no randomized studies assessing the clinical efficacy of double-boosted PI regimens in treatment-experienced patients. Several non-comparative studies suggest that the efficacy of some

double-boosted PI combinations with favourable pharmacokinetic profiles, such as lopinavir/ritonavir plus saquinavir, lopinavir/ritonavir plus atazanavir or atazanavir plus ritonavir with saquinavir, could be relatively high in patients where single-boosted PI based regimens would probably fail, although there is not enough evidence to support this perception.

Several novel agents have been approved in recent years for treatment-experienced patients, having demonstrated their clinical efficacy even against highly resistant virus. The new PIs, tipranavir and especially darunavir, probably provide a higher threshold to resistant virus than double-boosted standard PIs. Combining one of them with two other fully active drugs such as raltegravir, maraviroc, etravirine, enfuvirtide or others, allows us to build an effective regimen for almost all patients. Thus, in the developed world, double-boosted PI strategies are no longer an option. However, we must use these new drugs appropriately to avoid the selection of resistance, as we could find ourselves in a few years with patients who have no therapeutic alternatives, forcing clinicians to go back to using non-conventional strategies such as double-boosted PIs.

The main setting in which double-boosted PI regimens may have a role is in resource-poor countries, where new drugs may not be available. Although it would be desirable that all patients could have at their disposal all currently available drugs, the truth is that many patients will not have therapeutic options after several antiretroviral treatment failures. The combination of lopinavir/ritonavir tablets and another PI, such as atazanavir or saquinavir, may provide a potentially useful, relatively convenient and tolerable regimen that does not require refrigeration.

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