

# Broadening the Perspective when Assessing Evidence on Boosted Protease Inhibitor-Based Regimens for Initial Antiretroviral Therapy

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## ABSTRACT

Several national and international guidelines recommend the use of antiretroviral therapy containing a protease inhibitor (PI) with ritonavir (RTV) boosting for human immunodeficiency virus (HIV)-infected treatment-naïve patients. RTV-boosted PIs such as lopinavir (LPV/r), atazanavir (ATV + RTV), darunavir (DRV + RTV), fosamprenavir (FPV + RTV), and saquinavir (SQV + RTV) are usually recommended in regimens for initial therapy. The guideline recommendations are generally based on the clinical efficacy of the regimens. A broadened perspective of assessing the evidence related to selection of a

PI for optimal first-line therapy might consider additional factors for evaluation, such as effectiveness in actual clinical practice and cost-effectiveness of individual drugs in formulating recommendations. Among the guideline-recommended PIs, LPV/r is one of the earliest PIs approved, has been a well-recognized boosted PI for treatment-naïve patients in all guidelines, and demonstrates the most evidence on long-term clinical and economic effectiveness. Studies have shown its efficacy in various controlled and real-world settings in different populations, the relationship of adherence to virologic efficacy, and the implications of resistance when used in sequence with other PI regimens. In the absence of published evidence for other guideline-recommended PIs that will greatly facilitate a fully transparent, comparative effectiveness evaluation, the cumulative evidence from this broader perspective indicates all PIs should not be viewed as equally safe and effective across all patients for initial therapy, nor should any single PI within the class be considered preferred for all treatment-naïve patients.

**Keywords:** AIDS; antiretroviral therapy; guidelines; HIV; lopinavir; protease inhibitor; sequencing

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## INTRODUCTION

Antiretroviral (ARV) therapy directed against human immunodeficiency virus (HIV) increases survival and improves quality of life for patients living with HIV/acquired immunodeficiency syndrome (AIDS).<sup>1-3</sup> The first ARV was approved by the United States Food and Drug Administration (FDA) in 1987, with more than 20 drugs now approved for the treatment of HIV worldwide. ARVs are grouped into six classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 antagonists, and integrase inhibitors.<sup>4</sup>

Several national and international guidelines have been published which interpret the scientific evidence supporting medical decisions relating to ARV therapy. The guidelines in the developed world usually recommend the use of two NRTIs in combination with either an NNRTI or a PI with ritonavir (RTV) boosting for initial therapy in ARV-naïve patients.<sup>4-7</sup> The Department of Health and Human Services (DHHS) guidelines have recently been revised to also recommend the use of an integrase inhibitor for initial therapy.<sup>4</sup> Most guidelines recommend efavirenz (EFV) as the only preferred NNRTI whereas a range of PIs have been recommended by the guidelines for initial therapy.<sup>4,6,7</sup> This makes the choice of PI for initial therapy far more strategic and various aspects associated with the therapeutic management need to be considered while choosing the right PI. The recommendations made by the guidelines are most often based on clinical efficacy of the drugs; however along with clinical efficacy, the preference for a PI by the physician and the patient can be highly influenced by other aspects, mainly by the effectiveness of the selected drug and its economic value.<sup>8</sup>

## SUMMARY OF GUIDELINE RECOMMENDATIONS ON PROTEASE INHIBITORS

We consider five guideline-recommended PIs: RTV-boosted atazanavir (ATV + RTV), RTV-boosted darunavir (DRV + RTV), RTV-boosted fosamprenavir (FPV + RTV), LPV coformulated with RTV (LPV/r), and RTV-boosted saquinavir (SQV + RTV). Since its approval in 2000, LPV/r has been a well-recognized boosted PI for treatment-naïve patients in all guidelines and the only preferred PI during July 2003 to May 2006.<sup>9</sup> Based on well-controlled noninferiority trials in comparison to LPV/r, CASTLE,<sup>10</sup> KLEAN,<sup>11</sup> ARTEMIS<sup>12</sup> and GEMINI<sup>13</sup> the guidelines have also recommended ATV + RTV, FPV + RTV, DRV + RTV, and SQV + RTV respectively, in the PI-containing regimens for initial therapy in ARV-naïve patients.

Guideline recommendations change over time and agents may move from one category to another as guidelines are updated. For example, FPV + RTV twice daily and LPV/r, which were preferred PIs in the 2008 DHHS treatment guidelines, are now included in the “alternative” category in the 2009 version.<sup>4,14</sup> These recommendations are generally based on a number of factors.<sup>15</sup> In the most recent DHHS guideline update, the following criteria were used to distinguish between the preferred and alternative categories: (1) demonstrated superior or noninferior virologic efficacy when compared with at least one other PI-based regimen with at least 48-week published data; (2) RTV-boosted PI with no more than 100 mg of RTV per day; (3) once-daily dosing; (4) low pill count; and (5) good tolerability. FPV + RTV is now recommended as an alternative choice due to its requirement for twice-daily dosing whereas the RTV 200 mg/day content in LPV/r and the higher rate of gastrointestinal side effects and

hyperlipidemia when compared with boosted PIs using RTV 100 mg/day are cited as the reasons for LPV/r as an alternative regimen. The tolerability effects of RTV 100 versus 200 mg per day have not been rigorously studied in clinical trials.<sup>4</sup> The DHHS guidelines cite data associated with several ARV regimens from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) and the French observational cohorts that suggest a slightly increased risk of myocardial infarction for LPV/r.<sup>16,17</sup> It should be noted however, that similar comparative long-term data from observational cohort studies are as yet unavailable for other guideline-preferred PIs (ie, ATV + RTV and DRV + RTV). Additionally, a modeling study indicates that the effect of LPV/r on long-term risk of coronary heart disease may be minimal as compared with the increased risk of AIDS-related deaths associated with a less potent regimen of ATV + RTV, which has an improved lipid profile and is considered a preferred PI by the DHHS guidelines.<sup>18</sup> The current recommendations made in the DHHS guidelines rely on interpretations of clinical data that may benefit from additional considerations regarding the PIs for initial therapy based on the available evidence. A broadened perspective of assessing the evidence related to selection of a PI for optimal first-line therapy might consider additional factors for evaluation, such as effectiveness in actual clinical practice and cost-effectiveness of individual ARV drugs, in formulating recommendations. We consider three main aspects under a broadened perspective when assessing the preference for PI-based ARV regimens: (i) relationship of adherence to virologic efficacy, (ii) sequencing of ARV therapies, and (iii) economic value typically assessed by the cost-effectiveness of regimens. The specific aim of this paper is to review available evidence on the guideline-recommended PIs in comparison with LPV/r for initial therapy in ARV-naïve patients and highlight some important aspects of PIs

that will likely influence the selection of a PI for initial therapy.

## IMPORTANT ATTRIBUTES OF GUIDELINE-RECOMMENDED PROTEASE INHIBITORS

Table 1 compares and contrasts the guideline-recommended PIs in reference to LPV/r based on several characteristics that may be important when selecting an initial PI-based regimen from a broader assessment perspective.<sup>19–37</sup> Only LPV is coformulated with RTV, assuring RTV adherence in the real world necessary for PI potency.<sup>38</sup> Once-daily dosing is available for ATV + RTV and DRV + RTV.<sup>19,20</sup> LPV/r and FPV + RTV are available for both once-daily and twice-daily dosing<sup>21,22</sup> whereas SQV + RTV requires twice-daily administration.<sup>23</sup> Among the five PIs, LPV/r is the earliest approved PI and all other PIs have been compared through randomized noninferiority trials using LPV/r as the reference standard. DRV + RTV received approval by the FDA for use in treatment-naïve patients based on a randomized, noninferiority comparative trial with LPV/r.<sup>12,20</sup> All PIs were noninferior to LPV/r in terms of virologic response rates for the primary endpoint analysis and their immunologic efficacy was comparable with LPV/r.<sup>10–13</sup> In case of adverse side effects in the head-to-head trials, significantly higher elevations in certain lipid fractions (eg, triglycerides) have been observed in LPV/r when compared with ATV + RTV, DRV + RTV, and SQV + RTV.<sup>10,12,13</sup> Higher incidences of diarrhea have been observed with LPV/r when compared with DRV + RTV, FPV + RTV, and SQV + RTV,<sup>11–13</sup> whereas higher incidence of hyperbilirubinemia and jaundice has been observed in ATV + RTV when compared with LPV/r.<sup>10</sup>

LPV/r continues to be designated as a preferred PI in certain specific patient populations in the DHHS guidelines. LPV/r is the only PI preferred

**Table 1.** Key attributes of guideline-recommended protease inhibitors (PIs) in comparison with LPV/r for treatment-naïve patients.

Attribute	ATV + RTV	DRV + RTV	FPV + RTV	LPV/r	SQV + RTV
Dosing	Once daily <sup>19</sup>	Once daily <sup>20</sup>	Once or twice daily <sup>21</sup>	Once or twice daily <sup>22</sup>	Twice daily <sup>23</sup>
Coformulation with RTV	No <sup>19</sup>	No <sup>20</sup>	No <sup>21</sup>	Yes <sup>22</sup>	No <sup>23</sup>
Virologic efficacy at primary endpoint analysis (proportion of patients with HIV RNA <50 copies/mL)	Noninferior to LPV/r <sup>10</sup>	Noninferior to LPV/r <sup>*12</sup>	Noninferior to LPV/r based on proportion of patients achieving HIV RNA <400 copies/mL <sup>11</sup>	–	Noninferior to LPV/r <sup>13</sup>
Immunologic efficacy (mean increase in baseline in CD4 cell counts)	No significant difference <sup>10</sup>	No significant difference <sup>12</sup>	Statistical significance not reported <sup>11</sup>	–	Statistical significance not reported <sup>13</sup>
Adverse events	Higher incidence of hyperbilirubinemia and jaundice in ATV + RTV whereas significantly higher change in total cholesterol, non-HDL cholesterol, and triglycerides in LPV/r <sup>10</sup>	Significantly higher incidence of diarrhea and increase in triglycerides and total cholesterol in LPV/r than in DRV + RTV <sup>12</sup>	Higher incidence of diarrhea and nausea in FPV + RTV whereas similar changes in lipid values <sup>11</sup>	–	Higher incidence of diarrhea and significantly higher elevation in triglycerides in LPV/r compared with SQV + RTV <sup>13</sup>
Recommendations in treatment-naïve adults	Preferred per DHHS, EACS. Alternative per BHIVA. Recommended by IAS USA	Preferred per DHHS, EACS. Recommended by IAS USA. Not yet recommended by BHIVA	Alternative per DHHS, EACS, BHIVA. Recommended by IAS USA	Preferred per EACS. Alternative per DHHS, BHIVA. Recommended by IAS USA	Preferred per EACS. Alternative per DHHS, BHIVA. Recommended by IAS USA
Recommendation in subpopulations:					
Pregnancy	Preferred per EACS. Alternative per DHHS	Not recommended by DHHS or EACS because of insufficient data	Not recommended by DHHS because of insufficient data	Preferred per DHHS, EACS	Preferred per EACS. Alternative per DHHS

*(continued on next page)*

**Table 1.** Key attributes of guideline-recommended protease inhibitors (PIs) in comparison with LPV/r for treatment-naïve patients. (Continued)

Attribute	ATV + RTV	DRV + RTV	FPV + RTV	LPV/r	SQV + RTV
Recommendation in subpopulations: <i>continued</i>					
Pediatric <sup>25</sup>	Alternative for children age ≥6 years. Use in special circumstances unboosted for treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate RTV	Not recommended	Alternative for children age ≥6 years. Use in special circumstances unboosted for children ≥2 years and >39 kg who are unable to tolerate RTV	Preferred	Not recommended
Hepatitis B or C (HBV or HCV)	Short-term effectiveness and liver safety HBV and/or HCV coinfecting patients <sup>26</sup>	Well tolerated in treatment-experienced HBV or HCV coinfecting patients <sup>27</sup>	Low incidence of adverse hepatic events in patients coinfecting with hepatitis virus <sup>28</sup>	Effective and well tolerated in HIV patients coinfecting with HBV/HCV <sup>29</sup>	No data
Length of follow-up in prospective, protocol driven interventional studies	96 weeks <sup>30</sup>	96 weeks <sup>24</sup>	144 weeks <sup>31</sup>	7 years <sup>32</sup>	100 weeks <sup>33</sup>
Resistance data:	No data	No data	No data	Yes <sup>34</sup>	No data
Evidence on sustaining efficacy at suboptimal levels of adherence in nonclinical trial settings	No data	No data	No data	Yes <sup>34</sup>	No data
Cost-effectiveness and affordability relative to other "preferred PIs" in the US setting	No published data†	No published data#	No data	Cost-effective in comparison with ATV + RTV <sup>37</sup>	No data

\*Superiority has been established as a secondary outcome in the 96-week analysis.<sup>24</sup>

†Has been shown to be cost-effective in comparison with LPV/r in Scottish setting; however, the utility values used in the analysis were obtained from non-HIV populations.<sup>35</sup>

#Has been shown to be cost-effective in comparison with LPV/r in treatment-naïve patients.<sup>36</sup>

ATV + RTV =boosted atazanavir; BHIVA=British HIV Association; DHHS=Department of Health and Human Services; DRV + RTV =boosted darunavir; EACS=European AIDS Clinical Society; FPV + RTV =boosted fosamprenavir; HBV/HCV =hepatitis B/C virus; HDL=high-density lipoprotein; HIV =human immunodeficiency virus; IAS=International AIDS Society USA; LPV/r=boosted lopinavir; RNA=ribonucleic acid; RTV=ritonavir; SQV + RTV =boosted saquinavir.

for use in pregnant women as per the DHHS guidelines<sup>39</sup> whereas the European AIDS Clinical Society (EACS) guidelines list ATV + RTV and SQV + RTV in addition to LPV/r as preferred PI-based regimens for pregnant women.<sup>5</sup> ATV + RTV and SQV + RTV may be used as alternatives per the DHHS guidelines. LPV/r is the preferred regimen for pediatrics, with alternatives being ATV + RTV and FPV + RTV under special circumstances.<sup>25</sup> Except for SQV + RTV, all PI-based regimens have been found to be acceptable for use in patients coinfecting with hepatitis B or C.<sup>26-29</sup>

Published data from prospective protocol-driven studies on the durability and safety of all five PI-based regimens are available generally for up to 96 weeks. Data are published up to 144 weeks of follow-up for FPV + RTV. Notably, published data on the longest duration of follow-up for a PI, 7 years (360 weeks), are available for LPV/r.<sup>32</sup> The virologic efficacy of other PIs beyond 3 years has yet to be published, with uncertainties remaining about the level of adherence to these regimens, and the impact of varying levels of adherence on resistance and virologic efficacy.

### Relationship of Adherence to Virologic Efficacy

There is insufficient evidence available across all five PIs to compare their ability to sustain virologic efficacy in the setting of suboptimal adherence to the regimen. Shuter and colleagues reported findings from a prospective observational study of heavily pretreated patients on LPV/r-containing therapy.<sup>34</sup> High rates of virologic suppression were observed despite widely varying levels of adherence. Rode and colleagues studied the effects of once-daily versus twice-daily LPV/r on adherence and associated virologic efficacy.<sup>40</sup> Treatment compliance was assessed through the use of microelectromechanical systems (MEMS<sup>®</sup>) monitors (AARDEX Group, Sion, Switzerland),

which electronically recorded and stored LPV/r bottle openings for patients in the study. The mean adherence rate (mean taking compliance defined as the ratio of number of openings to number of prescribed doses) declined from 93% to 97% with once-daily dosing to 80% to 92% with twice-daily dosing. Virologic efficacy, rates of resistance, and immunologic improvement were comparable over 96 weeks of treatment despite these differences in adherence. Experts have associated the relatively low rate of emergence of genotypic resistance to LPV/r with its enhanced forgiveness for nonadherence.<sup>41</sup> Evidence with other PIs from real-world clinical practice suggesting that the virologic efficacy can be maintained over varying levels of adherence has yet to be published.

Shuter and colleagues have reported results of an observational study to assess selective RTV nonadherence in HIV-infected patients receiving a regimen containing RTV-boosted ATV or FPV.<sup>42</sup> The authors reported that 8.3% of patients demonstrated selective RTV nonadherence over 24 weeks, although no significant impact of the selective nonadherent behavior was noted on virologic efficacy in this small study population. In an analysis recently published on two prospective observational cohort studies, maximal average percent adherence, rather than duration or frequency of treatment interruption, was shown to confer the highest probability of sustained viral suppression in HIV-infected patients treated with PI-based regimens mainly containing LPV/r (76%) and ATV + RTV (18%).<sup>43</sup> Coformulation with RTV as with LPV/r can be regarded as advantageous in reducing the impact of selective nonadherence to RTV.

### Sequencing of PI-Based Regimens

While comparing the guideline-recommended PIs, another important attribute to consider

from a broader assessment perspective is the optimal sequencing of PI-based regimens in the management of HIV. This attribute would ideally be addressed through a randomized controlled trial, where the sequencing of drugs was explicitly designed as part of the protocol. Until such a trial is undertaken, the next best available alternative is to examine evidence on resistance patterns after patients fail a regimen so as to optimize the sequencing of regimens and to ensure efficacy of subsequent regimens. Evidence reported by Kempf and colleagues and reported in the AIDS Clinical Trials Group (ACTG) Study A5142 highlight a high barrier of LPV/r to resistance, which is an important consideration in sequencing of regimens. Kempf and colleagues reported the incidence of resistance in a double-blind randomized study, comparing LPV/r plus stavudine and lamivudine versus nelfinavir (NFV) plus stavudine and lamivudine.<sup>44</sup> The study revealed significantly more primary protease mutations emerged on the NFV regimen than on LPV/r upon failure, and more resistance to the NRTI backbone associated with the NFV regimen than the LPV/r regimen. The ACTG Study A5142 team reported that virologic failure with EFV + 2 NRTI regimen was generally associated with resistance to the NNRTI (EFV) component of the regimen whereas virologic failure with LPV/r + 2 NRTI regimen was unlikely to be associated with resistance to the LPV/r component of the regimen; the pattern of NRTI resistance was similar in both groups.<sup>45</sup> Significantly, more patients in the EFV + 2 NRTI group than in LPV/r + 2 NRTI group developed mutations associated with resistance to two drug classes (26% vs. 1%,  $P < 0.001$ ). Hence, failure with EFV + 2 NRTIs renders it necessary in most cases to switch to a non-NNRTI-containing regimen, whereas failure with LPV/r + 2 NRTIs may often leave LPV/r, or at least another PI, as an option in the next regimen.<sup>45,46</sup>

Although similar evidence has yet to be published in treatment-naïve patients, it would be important to consider a finding from the TITAN trial that compared DRV + RTV with LPV/r when used in combination with an optimized background regimen of NRTIs ± 1 NNRTI in treatment-experienced patients.<sup>47</sup> Virologic response was significantly higher with DRV + RTV than LPV/r if there were two or more resistance-associated mutations (RAMs) at baseline, regardless of whether the mutations were from LPV/r or DRV + RTV. For example, if there were two DRV RAMs, the virologic response was 89% with the DRV + RTV regimen compared with 36% in the LPV/r regimen. By contrast, if there were  $\geq 6$  LPV RAMs, the virologic response rate was substantially higher with DRV + RTV than LPV/r.<sup>48</sup> The resistance data observed in TITAN nevertheless suggest that sequencing of regimens could matter; that is, treatment with DRV + RTV after LPV/r failure could confer a higher likelihood of long-term virologic suppression than treatment with LPV/r after DRV + RTV failure. A study by King and colleagues assessed changes in viral susceptibility to DRV and tipranavir (TPV) before and after LPV/r-based treatment in patients demonstrating evolution of LPV resistance.<sup>49</sup> In this study, it was suggested that treatment with TPV or DRV based on genotype and phenotype resistance testing may be useful for salvage therapy following evolution of resistance while on a LPV/r-based regimen, presenting additional evidence for potential value in determining a PI for initial therapy and sequencing of PIs thereafter.

### Pharmacoeconomic Evidence

Finally, we compare the guideline-recommended PIs with respect to yet another important attribute, pharmacoeconomics, while considering a broader assessment perspective.

Evidence on health economics and affordability of various regimens is critical in optimizing the management of HIV but is limited across the PI regimens within the US context. With the exception of LPV/r, such information for other PIs has yet to be published in peer-reviewed journals. LPV/r is reported to be cost-effective compared with ATV + RTV.<sup>37</sup> An important finding is that prevention of HIV progression drives cost-effectiveness, while cardiovascular considerations, a concern raised in the 2009 DHHS guidelines associated with LPV/r, have relatively less influence on the cost-effectiveness when LPV/r is compared with ATV + RTV. Some of the important considerations to be addressed in cost-effectiveness analyses of PI regimens are the extent to which the analysis incorporates factors that have been shown to have varying effects over time, including; decrease in the rate of regimen discontinuation over time,<sup>50</sup> effect of nonadherence to the regimen due to treatment fatigue,<sup>51</sup> worsening of cardiovascular risks as people age,<sup>52</sup> increased lipodystrophy with longer exposure to ARV,<sup>53</sup> and the economic effects of the development of viral resistance and lipodystrophy over time.<sup>54</sup> The brief model descriptions provided on economic poster presentations for PIs do not allow us to judge if the aforementioned factors have been included in the analyses. Thus, interpretation of the validity of economic evidence for most PIs must await publication of these studies. At this point, pharmacoeconomic evidence has only been published on LPV/r considering some, but not all, of the factors mentioned previously and similar evidence on other PIs will inform a broader assessment of PIs.

## CONCLUSION

For the treatment of HIV-infected patients with no prior treatment experience, several boosted

PIs have been recommended by the national and international guidelines. Although the guidelines are not consistent globally, they generally provide recommendations for five PI-based regimens. It is unclear if the recommendations consider any pharmacoeconomic evidence. Here, we have summarized published evidence that distinguishes these regimens, and have highlighted relevant areas of uncertainty that remain among them. Among the five guideline-recommended PIs, LPV/r is one of the earliest PIs approved, remains the only PI with RTV coformulation, and demonstrates the most evidence on long-term clinical effectiveness. Studies have shown its efficacy in various controlled and real-world settings in different populations, the relationship of adherence to virologic efficacy, and the implications of resistance when used in sequence with various PI regimens. Similar evidence will greatly facilitate a fully transparent, comparative effectiveness evaluation among the several guideline-recommended preferred PI-based regimens. The guidelines have proven highly relevant and useful towards improving the quality of HIV management. As evidence progresses, the guidelines need to reflect a broader perspective, incorporating considerations of effectiveness in the real world and cost-effectiveness along with the clinical efficacy of the recommended regimens. The cumulative evidence from this broader perspective indicates that all PIs should not be viewed as equally safe and effective across all patients being considered for initial therapy, nor should any single PI within the class be considered preferred for all treatment-naïve patients.

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