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
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).1-3 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.4

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.4-7 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.4 Most guidelines recommend efavirenz (EFV) as the only preferred NNRTI whereas a range of PIs have been recommended by the guidelines for initial therapy.4,6,7 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.8

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 2006.9 Based on well-controlled noninferiority trials in comparison to LPV/r, CASTLE,10 KLEAN,11 ARTEMIS12 and GEMINI13 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.4,14 These recommendations are generally based on a number of factors.15 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