Effectiveness of ritonavir-boosted protease inhibitor monotherapy in the clinical setting: same results as in clinical trials?
The PIMOCS Study Group

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Objectives: Ritonavir-boosted protease inhibitor monotherapy (PIMT) is a maintenance strategy that prevents nucleoside reverse transcriptase inhibitor toxicity and reduces costs. Some trials compare PIMT with combined antiretroviral therapy, but restricted selection criteria and low sample size hamper data extrapolation to routine practice. Here, we analyse the effectiveness and safety of PIMT in clinical practice.

Methods: This was a retrospective, observational, multicentre study. Adult HIV-1 patients receiving PIMT with darunavir or lopinavir were included. A Cox regression model identified independent predictors for virological failure (VF).

Results: A total of 664 patients (435 on darunavir/ritonavir and 229 on lopinavir/ritonavir) [74% male, median age of 54 years, one-third with previous protease inhibitor VF, CD4 nadir 189 cells/mm3 and 42% coinfected with hepatitis C virus (HCV)] were analysed. After a median follow-up of 16 months, 78% of patients (95% CI 74%–81%) remained free from therapeutic failure (TF) (change between ritonavir-boosted PIs not considered failure). At 12 months, by intention-to-treat analysis (change between ritonavir-boosted PIs equals failure), 83% of patients were free from TF (87% darunavir/ritonavir versus 77% lopinavir/ritonavir, P = 0.001). Regarding VF, 88% of patients maintained viral suppression at 12 months (93% darunavir/ritonavir versus 88% lopinavir/ritonavir, P = not significant). CD4 nadir <200 cells/mm³ [hazard ratio (HR) 1.58, 95% CI 1.01–2.49] and undetectable viral load prior to PIMT <24 months (HR 1.86, 95% CI 1.20–2.91) were independent predictors for VF. Prior protease inhibitor failure, HCV coinfection and the protease inhibitor/ritonavir used were not associated with PIMT outcome. A total of 158 patients stopped PIMT, 6% due to adverse events. Two patients developed encephalitis.

Conclusions: PIMT effectiveness was consistent with data from clinical trials. Viral suppression duration prior to PIMT and CD4 cell count nadir were independent predictors for PIMT outcome.

Keywords: HIV, monotherapy, protease inhibitors, darunavir, lopinavir

Introduction

With the widespread use of combined antiretroviral therapy (cART), HIV morbidity and mortality have significantly decreased in the last decade. However, adverse events associated with some antiretroviral drugs, such as mitochondrial toxicity with thymidine analogues1 or kidney and bone concerns with tenofovir,2,3 have limited their use. At the same time, newer drugs with higher potency and better tolerability have become available. This has entailed the investigation of new strategies in treating HIV infection.

One of these strategies is ritonavir-boosted protease inhibitor monotherapy (PIMT), supported by the high potency and genetic barrier of this family. In addition to preventing the toxicity
associated with the use of nucleoside reverse transcriptase inhibitors (NRTIs), PIMT simplifies some antiretroviral regimens, lowers costs and preserves newer drugs for future use.

PIMT has been tested in different settings. It has shown non-inferior efficacy as a switch strategy in some studies and is accepted as an alternative regimen in some HIV treatment guidelines, especially in patients showing NRTI-related toxicity, although only in patients without history of failure on prior protease inhibitor-based therapy, undetectable viral load for ≥6 months and excellent adherence. On the other hand, it has not shown sufficient efficacy in patients with detectable viral load (either in naïve patients or as salvage therapy) or as an induction–maintenance strategy.

Focusing on switch studies, there are data mainly with ritonavir-boosted darunavir, having shown their efficacy in this setting. There are also data with atazanavir, but the results do not recommend its use as PIMT. We have scarce data with other protease inhibitors that are seldom used nowadays. However, all PIMT studies have similar limitations: the number of included patients is relatively small and the results are not generalizable as they have different inclusion criteria.

The aims of this study are to describe the characteristics of patients receiving PIMT in the clinical setting, to analyse the effectiveness and tolerability of these regimens in patients who might differ from those included in clinical trials and to analyse if there are any parameters that can help to predict virological failure (VF) with PIMT in daily practice.

Methods

This was a retrospective, observational, multicentre study carried out in seven Spanish university hospitals.

Adult patients (≥18 years old) with HIV-1 infection, currently receiving or having received at any time PIMT with lopinavir/ritonavir or darunavir/ritonavir, were selected from each centre’s HIV-infected patients database and evaluated for study inclusion. Their clinical charts and electronic medical records were reviewed to obtain relevant data. The database was closed for analyses on 31 December 2012. Participation in clinical trials was not an exclusion criterion. Patients with detectable HIV viral load at PIMT initiation or with no available viral load measurements while on PIMT were excluded from the study analysis.

Demographic data (age, sex and race), HIV-related data (transmission risk factor, years of infection, previous antiretroviral regimens and reasons for discontinuation and prior resistance testing) and hepatitis C virus (HCV) coinfection status were recorded for each patient. All previous resistance tests were taken into account to determine the potential susceptibility to antiretrovirals. Drug resistance–associated mutations (RAMs) were considered as defined by the International AIDS Society—USA guidelines. Frequency of follow-up visits was decided by the physician in charge of the patient. Information regarding CD4, HIV RNA, adverse events or reasons for discontinuing PIMT was recorded. If PIMT was stopped, the results of resistance testing when performed, the subsequent prescribed therapy and the outcomes with the new treatment were analysed.

VF was defined as two consecutive viral loads >50 copies/mL or a single determination >50 copies/mL if the treatment was changed or the patient was lost to follow-up (defined as not attending appointments and not collecting the antiretroviral treatment at the hospital pharmacy). Therapeutic failure (TF) included VF, antiretroviral therapy change due to adverse events or any other reason, death or loss to follow-up.

The primary objective of the study was to analyse the effectiveness of PIMT in the clinical setting, defined as the percentage of patients with no TF during the study period.

Secondary objectives were to describe the characteristics of patients receiving PIMT outside clinical trials, analyse the effectiveness of PIMT regarding VF, describe the evolution of HIV-related laboratory parameters (CD4 cell counts and HIV RNA blips), describe the safety of and reasons for stopping PIMT, investigate predictors for VF with PIMT and describe the outcome in case of TF. We also wanted to compare treatment outcomes between darunavir/ritonavir and lopinavir/ritonavir, the two ritonavir-boosted PI combinations currently accepted as PIMT in some guidelines.

The study protocol was approved by the institutional review boards of the participating centres and written informed consent was obtained from all patients.

Statistical analyses

For quantitative variables, medians and IQRs were used as measures of central tendency and dispersion. Numbers of patients and percentages were given for qualitative variables.

The changes from baseline (period of time between starting and stopping PIMT for any reason or closing of the database, whichever occurred first) were compared using the paired Student’s t-test for quantitative variables. Comparisons between quantitative non-paired variables were performed with Student’s t-test and the χ² test was used for qualitative variables.

For the primary PIMT effectiveness endpoint, we performed a modified intention-to-treat analysis (mITT: stopping or changing PIMT due to any reason equals failure, except for changes from one PIMT to another PIMT, censoring data at treatment change). For other effectiveness endpoints, an ITT analysis was used (VF, stop or change for any reason equals failure).

An on-treatment analysis of effectiveness (censoring any cause of TF apart from VF) was also performed.

Kaplan–Meier curves were used to estimate the time to TF and VF (censoring data at 24 months of follow-up as very few patients receiving darunavir/ritonavir were treated for longer than this timepoint). The log-rank test was used to compare ritonavir-boosted PIs.

Cox proportional hazards regression was used to identify predictive factors for VF. Variables associated with VF in univariate analysis (P<0.2) and clinically relevant variables were considered for inclusion in the multivariate models.

All statistical tests were two-tailed and were performed at a level of statistical significance of 0.05. SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Initially, 725 patients who started PIMT between January 2004 and July 2012 were evaluated. Of them, 664 patients fulfilled the inclusion criteria and were analysed (Figure 1). The baseline characteristics and prior antiretroviral treatments of the patients included in the analysis are shown in Table 1. The median (IQR) CD4 nadir was 189 (76–297) cells/mm³ and 199 (30%) and 110 (17%) patients had CD4 nadir <100 and <50 cells/mm³, respectively. The median time with undetectable viral load prior to PIMT initiation was 49 (24–83) months and the percentage of patients with <6, <12 and <24 months of undetectable viral load was 7%, 14% and 26%, respectively. Most patients (90%) had been previously exposed to a protease inhibitor and one-third of them had experienced VF on a protease inhibitor-containing regimen. The protease inhibitors on which patients had previously failed included both old non-ritonavir-boosted protease inhibitors (indinavir and nelfinavir) and newer ritonavir-boosted protease
Inhibitors (atazanavir, fosamprenavir, lopinavir and saquinavir) in the same proportion (17% in each category).

**Effectiveness**

Patients were followed for a median of 16 (11–24) months on PIMT. Patients receiving lopinavir/ritonavir had a significantly longer follow-up compared with those receiving darunavir/ritonavir [21 (10–40) versus 15 (11–20) months, \( P < 0.001 \)].

Overall, by mITT analysis, 78% of patients (516/664, 95% CI 74%–81%) remained free from TF at the end of follow-up. By ITT analysis, cumulative survival at 12 months was 83.1% (453/545, 95% CI 78%–86%), 87.2% (293/336, 95% CI 83%–91%) for lopinavir/ritonavir and 76.6% (160/209, 95% CI 70%–82%) for darunavir/ritonavir (\( P = 0.001 \)).

Regarding VF (on-treatment analysis), overall, 88% (581/664, 95% CI 85%–90%) of patients were virologically suppressed at the end of follow-up. In 14 patients (out of 83 with VF), PIMT was changed with only one detectable viral load. The probability of being free from VF after 12 months was 91.1% (453/497, 95% CI 88%–93%); 92.7% (293/336, 95% CI 89%–95%) for darunavir/ritonavir and 88.4% (160/181, 95% CI 83%–93%) for lopinavir/ritonavir (\( P = 0.139 \) between ritonavir-boosted PIs).

At the end of follow-up, 24 (15%) patients did not have a viral load between 50 and 200 copies/mL, 31% (n = 26) between 200 and 500 copies/mL and 39% (n = 32) >500 copies/mL.

At month 24 of follow-up, time to TF was significantly shorter with lopinavir/ritonavir, but no differences were seen between the ritonavir-boosted PI combinations with regard to time to TF (Figure 2).

There was a significant gain in CD4 cell counts with both ritonavir-boosted PI combinations compared with baseline levels: 20 (−80 to +118) \( P = 0.048 \) and 33 (−66 to −159) \( P = 0.001 \) cells/mm\(^3\) with darunavir/ritonavir and lopinavir/ritonavir, respectively, without significant differences between the drugs (\( P = 0.074 \)).

One hundred and fifty-one (23%) patients presented viral blips during follow-up. When adjusting for time of treatment, we observed 1.7 blips per 100 patients/month with darunavir/ritonavir and 1.9 blips per 100 patients/month with lopinavir/ritonavir (\( P = 0.074 \)).

**Tolerability and safety**

A total of 158 patients stopped PIMT, 17% (75/435) treated with darunavir/ritonavir and 36% (83/229) receiving lopinavir/ritonavir; the reasons were VF in 73 (11%) (10 other patients continued PIMT despite VF), loss to follow-up in 11 (2%), adverse events in 40 (6%) (including 20 patients changing between PIMT), patient’s decision in 8 (1%), death in 2 (0.3%) and other causes in 24 (4%) patients. The most frequently observed adverse events were gastrointestinal and metabolic side effects, with other toxicities occurring each in <1% of patients.

Interestingly, two patients presented CNS symptoms with lopinavir/ritonavir PIMT. One patient, with a nadir CD4 of 58 cells/mm\(^3\) and prior failure to nelfinavir, but without resistance testing, a baseline CD4 of 1100 cells/mm\(^3\) and 59 months of undetectable viral load prior to PIMT, had encephalitis with viral loads of 216 and 24 000 copies/mL in plasma and CSF, respectively. The other patient, with a nadir CD4 of 72 cells/mm\(^3\), without prior failure to protease inhibitors, a baseline CD4 of 483 cells/mm\(^3\) and 25 months of undetectable viral load prior to PIMT, had subacute cognitive impairment with undetectable viral load in plasma and low-level replication in CSF (435 copies/mL). Two other patients died, of unknown causes.

There were 20 patients who switched from one PIMT to another: 19 from lopinavir/ritonavir to darunavir/ritonavir due to gastrointestinal (n = 9) or lipid disturbances (n = 10) and one patient switched from darunavir/ritonavir to lopinavir/ritonavir due to a rash.

**Predictors of VF and outcome following TF**

By multivariate Cox regression analysis, CD4 nadir <200 cells/mm\(^3\) and time with undetectable viral load prior to PIMT <24 months were independently associated with VF (Table 2). No association was found between VF and other covariates included in the model (HCV coinfection, prior VF with protease inhibitors, baseline CD4 <350 cells/mm\(^3\) and ritonavir-boosted PI used).

Of the 158 patients who stopped PIMT, 24 (15%) did not have a subsequent antiretroviral therapy regimen (due to patient’s decision, loss to follow-up or death). Of the remaining patients, 48 (30%) reintroduced the previous NRTI backbone, 13 (8%) changed to two NRTIs + another ritonavir-boosted PI, 14 (9%) switched to two NRTIs + non-NRTI, 6 (4%) changed to two NRTIs + an integrase inhibitor, 20 (13%) switched to the other PIMT, 3 (2%) received three NRTIs, 8 (5%) received a regimen with three new drugs (ritonavir-boosted PI, etravirine, integrase inhibitor or maraviroc) and a non-negligible 22 (14%) received dual therapy with a ritonavir-boosted PI plus a non-NRTI, an integrase inhibitor or maraviroc. Of these 158 patients, 16 (10%) did not repress viral replication after PIMT change, 68 (43%) reached undetectable viral load with the new treatment and we do not have follow-up information for the other 74 (47%). Only 17 patients (out of 83 showing VF) had resistance testing performed after Vf. New resistance mutations in the protease were observed in three patients. In seven other patients, mutations were present in the protease (major RAM in one patient treated with...
lopinavir/ritonavir), but we cannot know if these were new mutations as these patients had previously failed on a protease inhibitor-containing regimen and prior resistance testing was not available.

**Discussion**

In this cohort, 78% of patients receiving PIMT in the clinical setting remained free from TF after a median follow-up of 16 months. The effectiveness of PIMT in our study is higher than that reported from a French cohort and consistent with efficacy data in randomized clinical trials. Small differences in the PIMT outcome between clinical trials and our cohort are probably driven by patients' characteristics. Indeed, the risk of VF in our study, 12% after 16 months of PIMT, was similar to that observed in randomized clinical trials.

When comparing the effectiveness of lopinavir/ritonavir versus darunavir/ritonavir, the TF rate was higher among patients receiving lopinavir/ritonavir. However, these differences must be taken cautiously as baseline characteristics were not comparable.
and no differences in terms of viral response were seen between both protease inhibitors. Similarly, differences between darunavir/ritonavir and lopinavir/ritonavir were not seen in the French cohort either, with both options being better than atazanavir/ritonavir.

The strongest predictor of VF in our cohort was time on a suppressive viral regimen before PIMT switching. In agreement with previous studies, the risk of VF was almost 2-fold higher among patients with viral suppression <24 months previous to change.20,22 Prolonged viral suppression might be a surrogate marker of lower viral reservoir size, which has been associated with lower risk of VF with PIMT,22 although it could also be a marker for better adherence to antiretroviral therapy. In addition, the risk of VF was 1.6-fold higher in patients with a CD4 nadir count <200 cells/mm³. Consistent with these data, a trial evaluating PIMT with lopinavir/ritonavir was prematurely stopped because of a high rate of VF and the only predictor of failure was a low nadir CD4 cell count (<200 cells/mm³).23 Also, a nadir CD4 count <100 cells/mm³ was a predictor of VF in another study with lopinavir/ritonavir.24 Taken together, these data support guideline recommendations to avoid PIMT in patients with a low CD4 nadir.9 In contrast with data from the MONET study,10 in our cohort including 40% of patients infected with chronic hepatitis C, HCV coinfection was not associated with treatment outcome.

Remarkably, one-third of patients in our study had previously failed on a protease inhibitor-containing regimen, but the risk of VF was not increased in these patients, which highlights the high genetic barrier of both lopinavir/ritonavir and darunavir/ritonavir. Indeed, very few patients had new mutations in the protease after failing PIMT, confirming the difficulty of selecting mutations after failing on a ritonavir-boosted PI, as observed in clinical trials.25,26 Conversely, in the French cohort, a trend for a higher probability of VF and TF was seen among the 9% of patients who had previously failed with protease inhibitors.20 Notwithstanding this, our data do not support the use of PIMT in patients who have previously failed with protease inhibitors, even if no protease inhibitor-associated RAMs are present.

Regarding safety, adverse events leading to PIMT discontinuation were relatively rare. The most common side effects were

### Table 2. Predictors of VF

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analysis[^a] [HR (95% CI)]</th>
<th>Multivariate analysis[^a] [HR (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at PIMT initiation, y</td>
<td>1.03 (0.65–1.64), P=0.903</td>
<td>—</td>
</tr>
<tr>
<td>Time viral load &lt;50 copies/mL prior to PIMT</td>
<td>1.26 (0.73–2.17), P=0.414</td>
<td>—</td>
</tr>
<tr>
<td>CD4 nadir &lt;200 cells/mm³</td>
<td>1.80 (1.14–2.75), P=0.011</td>
<td>1.86 (1.20–2.91), P=0.006</td>
</tr>
<tr>
<td>CD4 at PIMT initiation &lt;350 cells/mm³</td>
<td>1.48 (0.95–2.32), P=0.085</td>
<td>1.58 (1.01–2.49), P=0.048</td>
</tr>
<tr>
<td>HCV coinfection</td>
<td>1.02 (0.66–1.57), P=0.944</td>
<td>—</td>
</tr>
<tr>
<td>Prior VF with protease inhibitor/ritonavir</td>
<td>1.32 (0.77–2.26), P=0.309</td>
<td>—</td>
</tr>
<tr>
<td>CD4 nadir &lt;100 cells/mm³</td>
<td>0.94 (0.60–1.46), P=0.768</td>
<td>—</td>
</tr>
</tbody>
</table>

[^a]: Cox proportional hazards regression model; HR, hazard ratio.

![Figure 2](image-url). Outcomes of PIMT according to the ritonavir-boosted protease inhibitor used. Darunavir (DRV) is shown in black and lopinavir (LPV) in grey. (a) TF. (b) VF.
Protease inhibitor monotherapy in the clinical setting

gastrointestinal and lipid disturbances, mainly with lopinavir/ritonavir. In 19 patients, PIMT was changed from lopinavir/ritonavir to darunavir/ritonavir for these reasons.

Consistent with data obtained in randomized clinical trials, almost one-quarter of patients receiving PIMT in our study had transient viraemia, with no differences in the incidence risk between both ritonavir-boosted PI combinations.\textsuperscript{10,27,28} Low-level replication and transient elevations of viral load are frequently observed during PIMT, underscoring a lower antiviral potency of PIMT and less forgiveness for suboptimal adherence as compared with cART.\textsuperscript{10,11} In fact, the main concern with PIMT is in regard to its efficacy to suppress viral replication in reservoirs, mainly in the CNS. In our cohort, two patients had evidence of CNS replication. In both cases the CD4 nadir was <100 cells/mm\textsuperscript{3}.\textsuperscript{20} In the French cohort also, with a slightly smaller sample size, two patients had HIV-related encephalopathy.\textsuperscript{20} The MOST study with lopinavir/ritonavir PIMT was prematurely stopped due to an unexpected higher rate of VF both in blood and CSF, with CNS symptoms in four out of six patients failing therapy.\textsuperscript{23} Another study showed increased astrocyte inflammatory markers with lopinavir/ritonavir PIMT\textsuperscript{19} and there is a report of two cases of CSF breakthrough with darunavir/ritonavir PIMT,\textsuperscript{30} although this is not exclusive to PIMT and has also been seen with triple therapy.\textsuperscript{31} In another prospective trial, there was no greater cognitive decline or CSF viral escape in patients with PIMT compared with cART.\textsuperscript{32} Thus, the actual risk of CNS escape among patients on PIMT is far from clear, but the incidence seems to be low.

Some limitations of our study must be pointed out. Its retrospective nature does not allow controlling for factors such as adherence and prevents us having information about replication in anatomic reservoirs, or fat or bone changes. This design does not allow the drawing of conclusions on the two main potential advantages of PIMT: avoiding long-term side effects of other drugs and cost reduction, which has fuelled PIMT use in Spain in the last few years and makes this strategy very appealing in areas with economic restrictions. Clinical trials have data for up to 48 months with lopinavir/ritonavir,\textsuperscript{33} with an efficacy of 67% by ITT; with darunavir/ritonavir there are two trials, one with 24 month follow-up and an efficacy of 88%,\textsuperscript{28} and another with 36 month follow-up and an efficacy of 69%.\textsuperscript{34} However, differences in those trials when comparing monotherapy with standard triple therapy did not become larger. Further follow-up of our cohort will be necessary to confirm if our patients maintain effectiveness or similar decreases over time are seen. Finally, information from some patients after PIMT discontinuation is lacking, which can bias the results.

Despite these limitations, the results from our cohort, the largest reported to our knowledge, may be very useful as they describe the effectiveness of PIMT in routine practice, without the thorough control that takes place in trials, refine the risk of VF with PIMT and help clinicians to select the most suitable candidates. Although with a lower antiviral potency as compared with standard cART and concerns regarding ongoing viral replication in the CNS, PIMT might be an alternative strategy, mainly to avoid long-term toxicity and/or to save costs in the setting of economic restrictions.

In conclusion, almost 80% of patients receiving PIMT in our cohort remained free from TF after a median of 16 months of therapy and 88% remained free from VF. Sustained viral suppression >2 years prior to PIMT initiation and a nadir CD4 cell count >200 cells/mm\textsuperscript{3} were independently associated with a favourable PIMT outcome.

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Members of the PIMOCS Study Group

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Author contributions

A. C. and M. C. conceived the study, participated in its design and coordination, participated in data analysis and drafted the manuscript. P. M., P. D., J. V., A. I., E. M., I. F., H. K., D. P., J. A. I. and M. P. recruited patients, carried out the study protocol and supervised data integrity and analysis. All the authors contributed to the final version of the manuscript.

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