Human Immunodeficiency Virus 1 Protease Inhibitors in Clinical Practice

Predictors of Virological Outcome

Hernan Valdez, MD; Michael M. Lederman, MD; Ian Woolley, MD; Courtney J. Walker, BA; Lance T. Vernon, BA; Amy Hise, MD; Barbara M. Gripshover, MD

Objectives: To ascertain whether prolonged suppression of viral replication can be achieved in clinical practice and to identify factors associated with virological outcome.

Design: Retrospective observational study.

Setting: University-affiliated human immunodeficiency virus (HIV) clinic in Cleveland, Ohio.

Participants: Patients treated with regimens that included protease inhibitors between June 1995 and December 1997. We identified 366 patients; 310 had sufficient virological follow-up data to be included.

Main Outcome Measure: Virological success was defined as plasma HIV-RNA levels lower than 400 copies/mL at the last clinic visit. Virological failure was subdivided according to the maximum degree of suppression of viral replication achieved. Multivariate analysis was performed to identify baseline factors associated with virological outcome.

Results: Virological success was achieved by 47% of patients at a median follow-up of 335 days. The median CD4+ cell count increase and HIV-RNA level decrease were $0.10 \times 10^9/L$ (100 cells/µL) and greater than $1.3 \log_{10}$ in patients who achieved virological success, and $0.010 \times 10^9/L$ and $0.32 \log_{10}$ for those who did not. In multivariate analysis the likelihood of virological success was diminished in women ($P = .02$) and in patients who missed 2 or more clinic visits in the prior year ($P = .001$), and decreased when the regimen was started earlier ($P = .04$). Patients with a lower nadir CD4+ cell count ($P = .04$) and higher peak plasma HIV-RNA levels ($P < .001$) also had a decreased likelihood of virological success.

Conclusions: More than half the patients who started a regimen that included protease inhibitors in an academic clinical practice failed to achieve durable suppression of viral replication and also experienced a poorer immunologic outcome as determined by CD4+ cell count increase. Missed clinic visits, more advanced disease, and higher plasma HIV-RNA levels may predict failure.

Arch Intern Med. 1999;159:1771-1776

THE PROGNOSIS for patients infected with the human immunodeficiency virus (HIV) has improved substantially with the use of protease inhibitors (PIs). This improvement is evident by the resolution of previously untreatable infections and recent decreases in mortality and hospitalization rates, and it has been confirmed in controlled trials using both surrogate markers and clinical end points.

Plasma HIV-RNA levels are independent predictors of acquired immunodeficiency syndrome (AIDS) risk and death, and therapy-induced changes in plasma HIV-RNA levels partly explain the clinical benefit of PIs. For these reasons, guidelines for treating HIV-infected subjects include administration of antiretroviral regimens that reduce and maintain plasma HIV-RNA levels below the limit of detection of currently available assays for as long as possible.

Plasma HIV-RNA levels have remained below the limits of detection for up to 2 years in most patients participating in clinical trials of combination antiretroviral therapies that include a PI. To ascertain whether comparable results are achieved in clinical practice, and to identify factors associated with durable viral suppression, we reviewed the use of PIs at our clinic.

RESULTS

The baseline characteristics of 366 patients treated with PI regimens are given in Table 1. The median follow-up was 335 days (interquartile range [IQR], 158-503 days). At least 1 plasma HIV-RNA level
was available for 310 patients (84.7%) after initiation of PI regimens, and these patients made up the group for analysis. Overall, 145 (46.8%) of 310 patients experienced virological success. These patients were more likely to be older (P<.03), male (P<.03), and white (P<.02). In addition, the highest ever plasma HIV-RNA level, lower CD4+ cell counts at the time of starting a PI regimen, and the lowest ever CD4+ cell count were associated with virological failure (P<.001 for each). Charts were reviewed to ensure the accuracy of the antiviral treatment history. Confirmation of accuracy was possible for 239 patients (77%). Patients were more likely to achieve virological success if PIs were added to their regimens in conjunction with other antiretrovirals. The number of antiretrovirals added in conjunction with the PIs was significantly associated with virological success, even after allowing for the highest plasma HIV-RNA level (Table 2). Patients exposed to fewer antiretrovirals prior to starting the PI regimen were also more likely to achieve virological success (P<.001) (Figure 1).

To permit a more detailed examination of virological outcome, patients were further divided into 5 virological response groups (Figure 2): those with plasma HIV-RNA levels (1) consistently below the limit of detection; (2) below the limit of detection at least twice and subsequently above; (3) only once below the limit of detection and the last HIV-RNA level above the limit of detection; (4) never below the limit of detection, but decreasing at least 0.5 log10; and (5) never decreasing 0.5 log10. The median decrease in plasma HIV-RNA levels from the start of a PI regimen to the last visit was greater than 1.3 log 10 for patients with virological success (group 1) and 0.32 log10 for patients with virological failure (groups 2-5) (P<.001).

The degree of immunologic restoration as measured by the CD4+ cell count tended to vary with the degree of virological success (Figure 3). The mean increases in the number of circulating CD4+ cells from the start of the PI regimens to the last visit in patients experiencing virological success (group 1) and failure (groups 2-5) were 0.083 (range, –0.14 to 0.57) and 0.044 (range, –0.32 to 0.67) × 10⁹/L, respectively (P<.01).

The time of observation was divided into six 6-month periods. Patients started on PI regimens earlier in the observation period were more likely to fail virologically than patients started later (P<.001). Patients experiencing virological success had a median follow-up of 364 days (IQR, 228-520 days); those experiencing failure had a median follow-up of 287 days (IQR, 117-481 days) (P<.001).

We attempted to evaluate adherence to treatment regimens by asking physicians to rate their patients’ adherence to the recommended regimens. Sixty-three percent of patients judged by their physicians as adherent experienced virological success; conversely, only 13% of patients judged by their physicians as nonadherent experienced virological success (P<.001). In addition, patients judged by their physicians to be using illicit drugs were less likely to achieve virological success than were patients thought to be drug free (28% vs 53%; P<.003). Physicians’ judgment of adherence was related to clinic attendance; patients were more likely to be considered nonadherent if they missed a greater number of clinic visits during the previous year (P<.001). More importantly, however, a greater number of missed clinic visits during the year preceding the evaluation was associated with virological failure (P<.001).

When multivariate analysis was performed, male sex, missing fewer than 2 clinic visits the year preceding the analysis, starting PI regimens at a later date, a higher CD4+ cell nadir, and lower peak plasma HIV-RNA levels were independently predictive of virological success (Table 3). Age, race, CD4+ cell count at the time of starting a PI regimen, the number of antiretroviral treatments started prior to starting a PI regimen were not significantly associated with virological outcome in the backward conditional logistic regression model. To avoid introduction of bias, physicians’ estimates of adherence and drug use were not included in the regression model.

In this large cohort of patients with HIV infection treated at a teaching hospital with PI regimens, we found that after a median follow-up of 341 days, only 47% achieved virological success, defined as a plasma HIV-RNA level...
of PIs, or are just a reflection of short follow-up, after experienced significant CD4+ cell count increases. It is patients with incomplete viral suppression often experienced significant CD4+ cell count increases. It is uncertain whether the patients who made up group 5 (no significant decrease in plasma HIV-RNA levels after starting a PI regimen) were actually taking their medication. Kaufmann et al have shown recently that CD4+ cell count increases may persist in patients who were predictive of virological outcome. To our knowledge, this is the first report describing a poorer virological outcome in women. Although biological differences in antiviral responses cannot be excluded, we suspect that social factors such as access to information and competing priorities account for differential outcomes in women.22 Adherence to treatment regimens is a critical predictor of a successful antiviral effect.15 In this study we did not have access to direct measurements of adherence and so used the number of missed clinic visits in the past year as a potential indicator of adherence. This

Table 1. Baseline Characteristics of the 366 Patients Who Began Protease Inhibitor–Containing Regimens*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 366)</th>
<th>Success (n = 145)</th>
<th>Failure (n = 185)</th>
<th>Unknown† (n = 38)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>37 (17-68)</td>
<td>39 (17-68)</td>
<td>37 (19-65)</td>
<td>36 (24-63)</td>
<td>.03</td>
</tr>
<tr>
<td>Men/women</td>
<td>305 (83)/61 (17)</td>
<td>128 (42)/27 (18)</td>
<td>130 (43)/55 (57)</td>
<td>47 (15)/9 (15)</td>
<td>.03</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>White</td>
<td>184 (50)</td>
<td>90 (49)</td>
<td>74 (40)</td>
<td>20 (11)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>167 (46)</td>
<td>51 (31)</td>
<td>81 (49)</td>
<td>35 (20)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15 (4)</td>
<td>4 (27)</td>
<td>10 (67)</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>Mean lowest CD4+ cell count, ×10⁹/L (range)§</td>
<td>0.14 (0-0.68)</td>
<td>0.18 (0-0.60)</td>
<td>0.10 (0-0.68)</td>
<td>0.17 (0-0.51)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean CD4+ cell count at start of regimen, ×10⁹/L (range)§</td>
<td>0.21 (0-1.08)</td>
<td>0.21 (0-0.93)</td>
<td>0.21 (0-1.08)</td>
<td>0.196 (0-0.59)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean highest log₁₀ plasma viral load (range)¶</td>
<td>4.81 (2.38-6.4)</td>
<td>4.45 (2.38-6.11)</td>
<td>5.14 (3.51-6.4)</td>
<td>4.76 (3.31-5.88)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as number (percentage) of patients.
†Patients without sufficient virological data to determine outcome.
‡P value for the association of baseline variable with virological outcome (success vs failure).
§n = 337 patients.
†n = 362 patients.
¶n = 352 patients.

Table 2. Virological Success According to Peak Plasma Human Immunodeficiency Virus (HIV)–RNA Level and Number of Antiretrovirals Added at the Time of Starting the Protease Inhibitor–Containing Regimen*

<table>
<thead>
<tr>
<th>Plasma HIV-RNA Level, log₁₀ copies/mL</th>
<th>0</th>
<th>1</th>
<th>≥2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.60</td>
<td>3/100</td>
<td>2/100</td>
<td>5/100</td>
<td>10/100 (100)</td>
</tr>
<tr>
<td>2.6-3.10</td>
<td>3/100</td>
<td>2/100</td>
<td>2/100</td>
<td>7/100 (70)</td>
</tr>
<tr>
<td>3.11-3.60</td>
<td>5/71</td>
<td>6/100</td>
<td>0/10</td>
<td>11/4 (79)</td>
</tr>
<tr>
<td>3.61-4.10</td>
<td>4/11 (36)</td>
<td>8/12 (67)</td>
<td>1/2 (50)</td>
<td>13/25 (52)</td>
</tr>
<tr>
<td>4.11-4.60</td>
<td>13/26 (50)</td>
<td>10/16 (63)</td>
<td>5/7 (71)</td>
<td>28/49 (57)</td>
</tr>
<tr>
<td>4.61-5.10</td>
<td>7/22 (32)</td>
<td>8/19 (42)</td>
<td>7/14 (50)</td>
<td>22/55 (40)</td>
</tr>
<tr>
<td>5.11-5.60</td>
<td>11/31 (35)</td>
<td>4/11 (36)</td>
<td>7/13 (54)</td>
<td>22/55 (40)</td>
</tr>
<tr>
<td>≥5.60</td>
<td>1/11 (0)</td>
<td>2/8 (25)</td>
<td>4/10 (40)</td>
<td>7/29 (24)</td>
</tr>
</tbody>
</table>

*By logistic regression analysis both the lower peak plasma HIV-RNA level (P < .001) and the number of antivirals changed at the time of initiation of protease inhibitor treatment (P < .02) correlated with virological success. All data are given as number of successes/total number of patients (percentage).
evaluation was highly predictive of virological outcome. Since treatment of HIV infection is lifelong and success is dependent on adherence,10,23 and since there is seldom a need to begin treatment emergently, the number of missed clinic visits may constitute a useful aid in predicting the likelihood of adherence to antiretroviral therapies. Other tools like blood levels,24 pill counts, MEMS caps,25 and 3-day diaries have been used to assess adherence, but some are expensive, and all require administration of therapy (and consequent risk of failure). Better tools and strategies for predicting and increasing adherence are needed.

Patients starting on PI regimens soon after the availability of these agents had a worse virological success for a longer period than those who did not. It may be explained by several other factors: the hard-gel formulation of saquinavir, which has low bioavailability, was the first available PI, and suboptimal exposures may have resulted in the emergence of cross-resistance to other PIs.26,27 Although patients with more advanced disease, higher levels of viral replication, and/or more extensive pretreatment histories may have been the first to receive these agents, timing of therapy remained an independent predictor of outcome in this analysis. In addition, there has been a “learning curve” for the use of PIs. In univariate analysis, it was found that patients who added only a single PI to their regimen had a lower likelihood of success than patients who had more than 1 drug added, a finding similar to that of previous studies.13,14 This variable did not remain significantly associated with a favorable virological outcome on multivariate analysis, probably because we were not able to differentiate between use of a new nucleoside and “recycling” of previously used nucleosides. The practice of adding a single drug to a failing regimen is now

Figure 1. Percentage of patients (n = 246) achieving either virological success (below 400 copies/mL) or failure (above 400 copies/mL) according to the number of antiviral drugs used prior to starting their first treatment regimen that included protease inhibitors.

Figure 2. Responses in 310 patients were classified into 5 groups with plasma human immunodeficiency virus–RNA levels (1) below 400 copies/mL at least twice and below 400 copies/mL at last clinic visit (n = 146); (2) below 400 copies/mL at least twice but above 400 copies/mL at last visit (n = 14); (3) below 400 copies/mL only once (n = 24); (4) decreasing more than 0.5 log10, but never falling below 400 copies/mL; and (5) never decreasing more than 0.5 log10 (n = 31).

Table 3. Factors Associated With Virological Outcome Among 216 Patients Prescribed a Protease Inhibitor–Containing Regimen, Multivariate Analysis*

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>OR (95% CI) for Virological Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>&lt;.02</td>
<td>0.27 (0.1-0.74)</td>
</tr>
<tr>
<td>Early protease inhibitor start date (for every 6 mo earlier)</td>
<td>&lt;.04</td>
<td>0.70 (0.5-0.98)</td>
</tr>
<tr>
<td>≥2 Missed clinic visits during previous year</td>
<td>&lt;.001</td>
<td>2.12 (1.39-3.25)</td>
</tr>
<tr>
<td>CD4+ cell nadir (for every cell/µL lower)</td>
<td>&lt;.04</td>
<td>0.99 (0.99-0.999)</td>
</tr>
<tr>
<td>Peak plasma HIV-RNA level (for each log10 copies/mL lower)</td>
<td>&lt;.001</td>
<td>12 (1.39-3.25)</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; and HIV, human immunodeficiency virus.
recognized as suboptimal. Multidrug-resistant viral strains will probably be transmitted in the community, and recent infection may be associated with an unfavorable virological outcome.

In this study, both higher peak plasma HIV-RNA levels and lower nadir CD4+ cell counts were independent predictors of virological failure. These findings are in agreement with the results of other studies. In a controlled clinical trial, up to 40% of patients with a greater degree of immunosuppression and HIV replication had detectable virus in plasma after 24 weeks of therapy with indinavir and 2 nucleosides. As plasma HIV-RNA levels reflect production rates, the relationship between plasma HIV-RNA levels and outcome may be a consequence of the increased likelihood of selection for resistant mutants, the failure of the regimen to decrease replication sufficiently at the outset, and the interaction between these factors. It is appealing to propose that a "more potent" regimen, for example, a regimen that includes 2 nucleoside analogs and 2 PIs, or 2 nucleoside analogs, a PI, and a non-nucleoside reverse transcriptase inhibitor, might result in more sustained suppression of viral replication in subjects with more advanced HIV disease. Whether more potent but more complex regimens will improve virological and clinical outcomes is a question that needs to be addressed in controlled clinical trials.

The relationship between virological outcome and CD4+ cell nadir is less apparent, but it is consistent with previous observations. These patients may be more advanced and more likely to have been exposed to antiretrovirals in the past, but this relationship was not supported by multivariate analysis. Conceivably, patients with more advanced immunosuppression (lower CD4+ cell counts) have diminished endogenous immune mechanisms for controlling HIV replication. Consequently, a failure of host defenses to collaborate with antiviral drugs may account for the failure to achieve a profound and durable suppression of HIV replication. This hypothesis is supported by the the AIDS Clinical Trials Group Protocol 32 findings: after 24 weeks of treatment with indinavir, lamivudine, and zidovudine, patients starting therapy with more than 0.050 \times 10^9/L CD4+ cells achieved a reduction in plasma HIV-RNA levels close to 1 log_{10} greater than those starting with fewer than 0.050 \times 10^9/L CD4+ cells. In conclusion, we found that more than half of patients started on PI regimens at an academic medical center did not achieve sustained suppression of viral replication. Administration of PI regimens early after infection that include simpler treatment regimens, more active and non-cross-resistant therapies, and strategies to enhance endogenous antiviral activities are needed.

Accepted for publication January 11, 1999.

This study was supported by grants AI 25879 and AI 36219 from the National Institutes of Health, Bethesda, Md.

Reprints: Hernan Valdez, MD, 2061 Cornell, Room 301B, Cleveland, OH 44106 (e-mail: valdez.hernan@clevelandcu.org).

REFERENCES


