Effectiveness of Antiretroviral Therapy after Protease Inhibitor Failure: An Analytic Overview

Elena Losina, Runa Islam, Alison C. Pollock, Paul E. Sax, Kenneth A. Freedberg, and Rochelle P. Walensky

Departments of Biostatistics and Epidemiology, Boston University School of Public Health, Division of General Medicine and the Partners AIDS Research Center, Massachusetts General Hospital and Harvard Medical School, and Infectious Diseases Division, Brigham and Women's Hospital, Boston, Massachusetts

To examine effectiveness of subsequent antiretroviral therapy (ART), studies published during the period of 1 January 1997 through 31 May 2003 involving patients who had failed a protease inhibitor (PI)–containing regimen and were switched to another regimen were reviewed. Twelve studies describing 1197 patients were analyzed. A total of 38% of patients had human immunodeficiency virus (HIV) RNA levels of <500 copies/mL at 24 weeks. After adjustment for baseline HIV RNA level, the rate of virologic suppression ranged from 16% for patients switching drugs within previously failed classes to 54% for nonnucleoside reverse-transcriptase inhibitor (NNRTI)–naive patients switched to boosted PI- and NNRTI-containing regimens. ART regimens in patients who failed a PI-containing regimen provided virologic suppression only in a few patients. The best response was seen in NNRTI-naive patients receiving NNRTI- and boosted PI-containing regimens. New approaches are needed to achieve better suppression in pretreated HIV-infected patients.

Approximately 60%–90% of patients receiving antiretroviral therapy (ART) for the first time achieve and maintain undetectable HIV RNA levels for ≥1 year [1–4]. However, regimen failure rates of 10%–40% create the need for subsequent antiretroviral regimens, which are generally associated with diminished rates of virologic suppression [5, 6].

A decision to switch ART raises several questions: Which regimen should be next? How many drugs should it include? What are the most effective options available? The July 1993 guidelines state that “assessing and managing a patient with extensive prior antiretroviral experience and treatment regimen failure is complex” [7, p. 28]. Comparing published reports examining antiretroviral efficacy in subsequent regimens is challenging because studies have different designs and are limited by small sample sizes. In addition, patient diversity in terms of drug exposure and previous treatment duration further complicate measurement of subsequent ART efficacy.

Meta-analysis is the process of synthesizing results from multiple studies to attain stable estimates and more generalizable aggregate outcomes [8]. Despite some potential limitations from biases due to incomplete reporting of negative studies, changes in standards of care over time, and differences in entry criteria, meta-analytic techniques are considered important methods for synthesizing evidence in clinical research. They are particularly valuable for analysis of HIV/AIDS therapies because of the diversity in studies, the discrepant experiences among populations, and the volume of reported literature. Meta-analyses have been used successfully in HIV/AIDS epidemiology [9–11], for the evaluation of surrogate markers [12, 13], for expressing the impact of multiple antiretroviral drugs [14], and
for reporting the overall effectiveness of ART in treatment-naive patients [4]. Our objective was to use meta-analytic techniques to estimate the aggregate effectiveness of subsequent ART regimens in patients who failed a protease inhibitor (PI)-containing regimen.

MATERIALS AND METHODS

Literature search and inclusion criteria. We performed a systematic literature search by deriving 2 sets of keywords (group 1: “AIDS,” “HIV,” “antiretroviral therapy,” “protease inhibitor,” “nucleoside reverse transcriptase inhibitor,” and “non-nucleoside reverse transcriptase inhibitor”; group 2: “failure,” “virologic suppression,” “antiretroviral experienced,” “pretreated,” “non-naive,” “salvage,” “second line,” “efficacy,” and “viral load”) and using all 2-keyword combinations from these groups to perform searches of the MEDLINE database. When any single search yielded >500 results, we added in a third keyword from either group to narrow results. Analyses were limited to published studies, because conference abstracts often omitted necessary data. We defined “subsequent therapy” as any regimen received after failing ≥1 PI-containing regimen, and we measured its effectiveness as the percentage of patients with complete virologic suppression (i.e., HIV RNA level of <500 copies/mL).

We included all studies that were published in the English language from 1 January 1997 through 31 May 2003; included HIV-infected adults (>18 years old) who had virologically failed ≥1 PI-containing regimen with ≥3 drugs from at least 2 different classes; included patients who received a subsequent regimen containing ≥3 drugs from at least 2 different antiretroviral classes; reported at least 24 weeks of follow-up; and reported the proportion of patients having HIV RNA levels of <500, <400, or <200 copies/mL by intent-to-treat analysis or included enough information to perform these calculations. We included single arms of a study in the analysis if one arm met inclusion criteria but the others did not. Two authors (R.I. and E.L.) screened all of the articles and independently determined inclusion criteria. Discrepancies in inclusion decisions were resolved by discussion with a third author (R.P.W.).

Data abstraction and outcome definition. Abstracted data from each study included baseline CD4 cell count and HIV RNA level; study design (observational/intervention); number of patients enrolled; threshold and assay for virus load; composition of current regimen; and previous nonnucleoside reverse transcriptase inhibitor (NNRTI) experience. In the main analyses, we distinguished among 4 regimen types (table 1): (1) remaining within already-failed classes (PI and/or NNRTI, depending on experience), (2) adding a boosted PI (i.e., with ritonavir), (3) adding an NNRTI (for NNRTI-naive patients), and (4) adding an NNRTI and boosted PI (for NNRTI-naive patients). To address the hypothesis that boosted PI regimens containing lopinavir may be superior to other boosted PIs, we performed a secondary analysis by stratifying regimens in type IV as lopinavir-containing or not. None of the type II regimens in our study contained lopinavir.

Because the primary goal was to examine the virologic effectiveness of subsequent ART regimens stratified by NNRTI experience, we focused on study subgroups on the basis of patients’ experience with NNRTIs. This sometimes led us to define the study groups slightly differently than in the primary published analyses. The implications were 2-fold: first, we created more homogenous groups with respect to virologic suppression; and second, we did not necessarily have baseline characteristics of patient subgroup by NNRTI experience because they were not all reported as such. We tried to contact the authors of 3 studies in which these data were not available in the original reports [15–17] and received the necessary data from the largest of these studies [16]. We compared baseline CD4 cell count and HIV RNA level by regimen type for studies for which these data were available. For baseline HIV RNA level, differences among regimen types were neither clinically important (at most, 0.3 log₁₀) nor statistically significant. On the basis of these analyses, we assigned overall baseline HIV RNA levels reported by the study authors for patients with and without NNRTI experience for the remaining 2 studies (6.6% Table 1. Description of regimen types under consideration.

<table>
<thead>
<tr>
<th>Regimen type</th>
<th>First-time NNRTI</th>
<th>Boosted PI</th>
<th>No. of study groups</th>
<th>No. of patients</th>
<th>Median no. of patients per group</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No</td>
<td>No</td>
<td>6</td>
<td>352</td>
<td>55</td>
</tr>
<tr>
<td>II</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
<td>110</td>
<td>55</td>
</tr>
<tr>
<td>III</td>
<td>Yes</td>
<td>No</td>
<td>10</td>
<td>473</td>
<td>26</td>
</tr>
<tr>
<td>IV</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
<td>262</td>
<td>36</td>
</tr>
</tbody>
</table>

NOTE. NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; type I, already-failed classes (PI or NNRTI, depending on experience); type II, boosted PIs without the addition of another drug class to which patients were previously naive; type III, addition of NNRTIs to subsequent regimens for patients who had been NNRTI naive; type IV, subsequent regimens containing both an NNRTI and a boosted PI administered to NNRTI-naive patients.
Table 2. Description of studies included in the review, grouped by regimen type.

<table>
<thead>
<tr>
<th>Study, group</th>
<th>Year</th>
<th>Design</th>
<th>Level of detection of HIV RNA test, copies/mL</th>
<th>Sample size</th>
<th>Regimen</th>
<th>Baseline HIV RNA level, log10 copies/mL</th>
<th>Baseline CD4 cell count, cells/mm³</th>
<th>Mean duration of previous PI regimen, months</th>
<th>Regimen type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benson et al. [21]</td>
<td>2002</td>
<td>I</td>
<td>400</td>
<td>36</td>
<td>Lopinavir-ritonavir, nevirapine, and NRTI</td>
<td>4.1</td>
<td>348</td>
<td>NA</td>
<td>IV</td>
</tr>
<tr>
<td>Group 1</td>
<td>34</td>
<td>Lopinavir-ritonavir, nevirapine, and NRTI</td>
<td>4.0</td>
<td>349</td>
<td>NA</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deeks et al. A [22]</td>
<td>1999</td>
<td>O</td>
<td>500</td>
<td>27</td>
<td>PI to which patient was naive, NRTI, NNRTI</td>
<td>4.5</td>
<td>196</td>
<td>&lt;2</td>
<td>I</td>
</tr>
<tr>
<td>Group 2</td>
<td>72</td>
<td>PI to which patient was naive, NRTIs</td>
<td>4.5</td>
<td>196</td>
<td>&lt;2</td>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>10</td>
<td>Nelfinavir, saquinavir, abacavir, nevirapine</td>
<td>4.2</td>
<td>288</td>
<td>16.6</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duval et al. [23]</td>
<td>2002</td>
<td>I</td>
<td>200</td>
<td>7</td>
<td>Amprenavir, efavirenz or nevirapine, 1 or 2 PIs</td>
<td>4.9</td>
<td>120</td>
<td>27</td>
<td>III</td>
</tr>
<tr>
<td>Group 2</td>
<td>11</td>
<td>Amprenavir-ritonavir, efavirenz or nevirapine, 1 or 2 PIs</td>
<td>4.5</td>
<td>200</td>
<td>39</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gulick et al. [24]</td>
<td>2000</td>
<td>I</td>
<td>500</td>
<td>47</td>
<td>Saquinavir-ritonavir, delavirdine</td>
<td>4.5</td>
<td>228</td>
<td>13</td>
<td>IV</td>
</tr>
<tr>
<td>Group 2</td>
<td>47</td>
<td>Saquinavir-ritonavir, delavirdine</td>
<td>4.5</td>
<td>230</td>
<td>12.2</td>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>45</td>
<td>Saquinavir-ritonavir, delavirdine, adefovir dipivoxil</td>
<td>4.6</td>
<td>242</td>
<td>14.3</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>48</td>
<td>Saquinavir, nevirapine, delavirdine</td>
<td>4.4</td>
<td>202</td>
<td>15.5</td>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 5</td>
<td>45</td>
<td>Saquinavir, neflavinavir, adefovir dipivoxil</td>
<td>4.5</td>
<td>193</td>
<td>15.1</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 6</td>
<td>45</td>
<td>Saquinavir, neflavinavir, delavirdine, adefovir dipivoxil</td>
<td>4.4</td>
<td>258</td>
<td>15.4</td>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammer et al. [16]</td>
<td>2002</td>
<td>I</td>
<td>200</td>
<td>147</td>
<td>Amprenavir, abacavir, efavirenz, adefovir dipivoxil, (another PI)</td>
<td>4.8</td>
<td>212</td>
<td>&gt;4</td>
<td>I</td>
</tr>
<tr>
<td>Group 2</td>
<td>64</td>
<td>Amprenavir, abacavir, efavirenz, adefovir dipivoxil, (another PI)</td>
<td>4.8</td>
<td>192</td>
<td>&gt;4</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>93</td>
<td>Amprenavir, abacavir, efavirenz, adefovir dipivoxil</td>
<td>4.7</td>
<td>227</td>
<td>&gt;4</td>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>177</td>
<td>Amprenavir, abacavir, efavirenz, adefovir, another PI</td>
<td>4.6</td>
<td>214</td>
<td>&gt;4</td>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katner et al. [25]</td>
<td>2002</td>
<td>O</td>
<td>400</td>
<td>63</td>
<td>Indinavir-ritonavir, adefovir dipivoxil</td>
<td>3.8</td>
<td>202</td>
<td>NA</td>
<td>II</td>
</tr>
<tr>
<td>Kempf et al. [26]</td>
<td>2002</td>
<td>I</td>
<td>400</td>
<td>57</td>
<td>Lopinavir-ritonavir, efavirenz, and NRTIs</td>
<td>4.5</td>
<td>245</td>
<td>NA</td>
<td>IV</td>
</tr>
<tr>
<td>Khanna et al. [27]</td>
<td>2000</td>
<td>O</td>
<td>500</td>
<td>23</td>
<td>Abacavir, NRTI, NNRTI, PI</td>
<td>5.2</td>
<td>89</td>
<td>41</td>
<td>III</td>
</tr>
<tr>
<td>Lafeuillade et al. [28]</td>
<td>2002</td>
<td>I</td>
<td>200</td>
<td>24</td>
<td>Stavudine, didanosine, efavirenz, abacavir</td>
<td>4.2</td>
<td>457</td>
<td>&gt;3</td>
<td>III</td>
</tr>
<tr>
<td>Piketty et al. [29]</td>
<td>1999</td>
<td>O</td>
<td>500</td>
<td>32</td>
<td>Saquinavir-ritonavir, efavirenz, NRTIs</td>
<td>4.3</td>
<td>258</td>
<td>19</td>
<td>IV</td>
</tr>
<tr>
<td>Shulman et al. [17]</td>
<td>2000</td>
<td>O</td>
<td>500</td>
<td>14</td>
<td>Efavirenz, adefovir dipivoxil, other ART</td>
<td>5.1</td>
<td>102</td>
<td>NA</td>
<td>I</td>
</tr>
<tr>
<td>Group 2</td>
<td>19</td>
<td>Efavirenz, adefovir dipivoxil, other ART</td>
<td>5.1</td>
<td>102</td>
<td>NA</td>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** ART, antiretroviral therapy; I, interventional study; NA, not applicable; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; O, observational study; PI, protease inhibitor; type I, already-failed classes (PI or NNRTI, depending on experience); type II, boosted PIs without the addition of another drug class to which patients were previously naive; type III, addition of NNRTIs to subsequent regimens for patients who had been NNRTI naive; type IV, subsequent regimens containing both an NNRTI and a boosted PI administered to NNRTI-naive patients.

* Mean time was not reported, so the maximum time that patients received a PI regimen is listed.
* For the purposes of this study, patients from Hammer et al. [16] were grouped on the basis of NNRTI experience, not study medication as published.
* Mean time was not reported, so the minimum time that patients received a PI regimen is listed.
* Two arms of Lafeuillade et al. [28] were excluded from this study because treatment regimens included hydroxyurea.
We analyzed data for 1197 HIV-infected patients from 2 studies (2 study groups), regimens contained boosted PIs in 5 studies (6 study groups) remained within already-failed classes (PI or NRTI). Regimens for patients in 5 studies (6 study groups) examined the effectiveness of adding NNRTIs to sequential regimens containing both an NNRTI and a boosted PI administered to NNRTI-naive patients (type IV) [21, 23, 24, 26, 29].

Baseline study and participant characteristics are shown in table 2. For the 1197 patients from the 25 study groups included (median, 45 patients per study group), median baseline HIV RNA levels were 3.8–5.2 log_{10} copies/mL, and median baseline CD4 cell counts were 89–457 cells/mm^3. Of the 12 studies, 6 used 500 copies/mL, 3 used 400 copies/mL, and 3 used 200 copies/mL as the HIV RNA detection threshold.

**RESULTS**

**Included Studies**

**Identification of eligible studies.** We screened 154 studies and eliminated 85 on the basis of abstract review. The most common reasons for exclusion were that not all patients met the definition of virologic failure, there was no 24-week follow-up data, or virologic suppression to <500 copies/mL was not reported (see Appendix). Sixty-nine articles were retrieved for more detailed evaluation; 57 of these were excluded because, upon more complete review, we found that they did not meet the inclusion criteria. The remaining 12 studies were used for the analysis.

**Description of included studies, patients, and treatment regimens.** We analyzed data for 1197 HIV-infected patients from 7 clinical trials and 5 observational studies (2 retrospective cohort studies and 3 prospective cohort studies) (table 2). The studies included 25 different patient groups, which were based on NNRTI experience and use of boosted PIs. We defined 4 regimen types (table 1). Regimens for patients in 5 studies (6 study groups) remained within already-failed classes (PI or NNRTI, depending on experience) (type I) [15–17, 22, 24]. In 2 studies (2 study groups), regimens contained boosted PIs without the addition of another drug class to which patients were previously naive (type II) [24, 25]. Seven studies (10 study groups) examined the effectiveness of adding NNRTIs to subsequent regimens for patients who had been NNRTI naïve (type III) [15, 17, 22–24, 27, 28]. Five studies (7 study groups) investigated subsequent regimens containing both an NNRTI and a boosted PI administered to NNRTI-naive patients (type IV) [21, 23, 24, 26, 29].

Baseline study and participant characteristics are shown in table 2. For the 1197 patients from the 25 study groups included (median, 45 patients per study group), median baseline HIV RNA levels were 3.8–5.2 log_{10} copies/mL, and median baseline CD4 cell counts were 89–457 cells/mm^3. Of the 12 studies, 6 used 500 copies/mL, 3 used 400 copies/mL, and 3 used 200 copies/mL as the HIV RNA detection threshold.

**Virologic Suppression**

**Virologic suppression and regimen type.** The overall rate of virologic suppression to <500 copies/mL at 24 weeks was 38% (95% CI, 27%–48%). Figure 1 illustrates the aggregate suppression rate for each of the 4 regimen types as well as individual suppression rates for each study group. Patients receiving type I regimens had the lowest suppression rate (16%; 95% CI, 0%–31%). The estimated suppression rates for regimen types II and III were 27% (95% CI, 0%–53%) and 39% (95% CI, 27%–51%). NNRTI-naive patients switching to a regimen with an NNRTI and boosted PI (type IV) had the highest suppression rate (54%; 95% CI, 40%–69%).

Pairwise differences in suppression rates among regimen groups are listed in table 3. With respect to virologic suppression, addition of both a boosted PI and an NNRTI to NNRTI-naive patients (type IV regimen) was superior to other regimen types.

**Virologic suppression, baseline CD4 cell count, and HIV RNA level.** We examined the relationship between baseline HIV RNA level, CD4 cell count, and HIV RNA suppression at 24 weeks by correlation analyses. Baseline CD4 cell count exhibited a moderate positive correlation (r = 0.46; P = .020) with viral suppression to <500 copies/mL at 24 weeks, whereas baseline HIV RNA level showed a moderate negative correlation (r = −0.53; P = .007). These suggest a linear trend in the relationship between baseline CD4 cell count and HIV RNA level and virologic suppression. However, results of multivariate regression examining the independent effect of baseline CD4 cell count, HIV RNA level, and regimen type on virologic suppression at 24 weeks revealed that, after adjusting for baseline HIV RNA and regimen type, baseline CD4 cell count was no longer a statistically significant predictor of viral suppression (P = .4578). Baseline HIV RNA (P = .016) and regimen type (P < .0001) were both independently predictive of 24-week viral suppression.
Figure 1. Suppression rates, by individual study arms and by regimen type. Type I (green circles) indicates regimens composed of drugs within already-failed classes (protease inhibitor [PI] and/or nonnucleoside reverse-transcriptase inhibitor [NNRTI], depending on experience). Type II (blue circles) indicates regimens consisting of boosted PIs but otherwise remaining within ART drug classes to which patients already had some prior experience with. Type III (yellow circles) indicates regimens where NNRTIs were added in NNRTI-naive patients. Type IV (red circles) indicates regimens include both NNRTIs and boosted PIs in NNRTI-naive patients. The size of each circle is directly proportional to the sample size of the arm of the study included in the current review. Aggregate virologic suppression for each regimen type stratum and overall suppression across all regimen types are denoted by bolding the circumference. Overall virologic suppression is shown in purple.

Change in CD4 Cell Count from Baseline
Data on the change in CD4 cell count were available for 1144 patients (all but 2 studies). On average, CD4 cell counts increased by 42 cells/mm³ (95% CI, 27–57 cells/mm³) at 24 weeks. CD4 cell count increased for type I regimens by 19 cells/mm³ (95% CI, −15 to 52 cells/mm³), for type II regimens by 55 cells/mm³ (95% CI, 7–102 cells/mm³), for type III regimens by 39 cells/mm³ (95% CI, 15–62 cells/mm³), and for type IV regimens by 56 cells/mm³ (95% CI, 31–81 cells/mm³). None of the pairwise comparisons were statistically significant at .05 level.

Secondary Analyses
We performed a subgroup analysis by further stratifying patients receiving type IV regimens with and without lopinavir. Three groups (124 patients) examined the effectiveness of saquinavir-based [24, 29] and amprenavir-based [23] boosted PI regimens (type IVa) [24, 23, 29]. Four study groups (138 patients) examined lopinavir-based boosted PI regimens (type IVb) [21, 26]. After adjusting for baseline HIV RNA level, the virologic suppression rates for types IVa and IVb were 37% and 70% (a 33% difference; \( P = .009 \)).

DISCUSSION
In this systematic overview, we examined rates of virologic suppression and CD4 cell response associated with subsequent ART after failure of a PI-containing regimen. The estimated aggregate HIV RNA suppression rate of \( \leq 500 \) copies/mL at 24 weeks was 38%. This indicates modest virologic effectiveness of ART for pretreated HIV-infected patients when compared with first-line 24 week efficacies of 75%–95% [1–4]. For patients who failed a PI-containing regimen, the use of a new regimen without adding drugs from another class provided the lowest suppression rate, ~16% at 24 weeks. These rates were nearly doubled (to ~30%) when regimens included a boosted...
PI or drugs from a new class (NNRTI). The highest rates of viral suppression (54%) were studied in articles examining regimens containing both a boosted PI and an NNRTI for patients without previous NNRTI experience. Virologic suppression among boosted PI regimens with NNRTIs in patients without previous NNRTI experience varied greatly on the basis of whether regimens did (70%) or did not (37%) contain lopinavir. The cohorts who received lopinavir-ritonavir had what appear to be higher baseline CD4 counts and thus may represent earlier and less heavily pretreated patients.

Although no published meta-analysis has examined virologic suppression for subsequent ART regimens after failure of a PI-containing regimen, there have been 2 meta-analytic reviews examining the impact of first-line therapy [4, 30]. Our results differed from these studies in 2 important ways. In an analysis of first-line regimens, Skowron et al. [30] found that baseline CD4 cell counts were a significant predictor of viral suppression. In our analysis of subsequent regimens, this relationship was statistically significant only in bivariate analysis, not in multivariate analysis. Results from Bartlett et al. [4] suggested that, for treatment-naive patients, suppression rates were similar across all regimen types. In contrast, we found that virologic outcomes in patients who failed a PI-containing regimen depend on the content of the subsequent regimen and the availability of a new class of agents. The addition of a new drug class (e.g., NNRTI) doubled the response, compared with that for a subsequent regimen that used only drugs from classes with which patients had previous experience. Furthermore, the use of a boosted PI with lopinavir also improved virologic suppression when joined by a drug from a new class (NNRTI); in this case, viral suppression rates were similar to those for first-line therapy. The question remains whether to use lopinavir-containing regimens as first-line agents or whether to reserve them for patients who fail a first regimen [7].

With current HIV therapy, a narrowly focused clinical trial of subsequent therapy will be difficult to design because of the diversity of patients’ treatment histories. This study is the first to systematically aggregate data from the many small studies on outcomes of subsequent therapy. Strengths of this analysis are the inclusion of various study designs, use of an intent-to-treat approach, and adjustment for interstudy variability by means of random-effect models.

Because we were unable to include patient-level data, we compiled outcomes on the basis of regimen type. Differences in reporting styles limited the number of included studies; however, we have presented cumulative data on 1197 patients, making this the largest analysis of subsequent therapy to date. The lack of information regarding the number of regimens previously failed in most articles limited our ability to distinguish between studies of second-line regimens and studies of patients who failed >2 regimens. A general reporting standard for including information on number of previous ART regimens in the description of future study populations would help in comparing different studies or in performing meta-analysis and selecting more homogeneous groups. Many studies assessed results of resistance testing retrospectively, without tailoring the subsequent regimen on the basis of these tests. Thus, despite the reported association between the results of resistance tests and the virological response of subsequent regimens, in very few of these published studies was choice of a subsequent regimen informed by resistance tests results.

Although NNRTIs are currently used widely as first-line regimens in the United States, these results are very useful for patients who initiated therapy in the years before the extensive use of NNRTIs, as well as for patients in less developed countries where the number of available antiretroviral agents may be limited. Similarly, although resistance tests are used extensively in the United States and Europe, these tests are not available in many other countries with a high prevalence of HIV infection. Results of these analyses may provide important information to physicians and patients faced with the challenge of finding the next best regimen after PI failure.

In summary, we have demonstrated by meta-analytic techniques that addition of a new drug class and addition of a drug

![Table 3. Pairwise difference in HIV RNA suppression rates at 24 weeks among different regimen groups.](https://academic.oup.com/cid/article-abstract/38/11/1613/285635)
from the same class capable of overcoming in-class resistance (e.g., lopinavir-ritonavir) are most effective for subsequent therapy in patients who fail a PI-containing regimen. Baseline HIV RNA was independently associated with virologic suppression after adjusting for regimen type, whereas baseline CD4 cell count at the time of switching had only a small influence on outcomes from subsequent regimens. These results suggest that switching regimens while HIV RNA levels are low may lead to better suppression with subsequent regimens. One possible explanation for this is that ongoing viral replication at higher levels may select for further drug resistance mutations, diminishing the efficacy of new drugs within the same class [7].

The use of a drug class to which the patient has not been exposed, such as an NNRTI and a novel PI designed to overcome PI resistance, appears to be the most effective treatment strategy, although how this will apply to patients who fail a boosted PI regimen is unclear. The availability of another new drug class, the fusion inhibitors (such as enfuvirtide), may also provide improved virologic suppression in patients who fail PIs and other regimens [31]. The judicious use of new drugs and new drug classes provides an opportunity for more effective and longer-lasting virologic suppression of HIV replication.

APPENDIX

Table A1. Reasons for exclusion of studies in a meta-analysis of the effectiveness of antiretroviral therapy after protease inhibitor failure.

<table>
<thead>
<tr>
<th>Outcomes of interest were not reported</th>
</tr>
</thead>
</table>
| Asboe et al., 2003 [32]; Baldanti et al., 2000 [33]; Boffito et al., 2002 [34]; Call et al., 2001 [35]; Casado et al., 2000 [36]; Casado et al., 2002 [37]; Chavarette et al., 2001 [38]; De Mendoza et al., 2002 [39]; Dionisio et al., 2001 [40]; Fatkenheuer et al., 1999 [41]; Falloon et al., 2002 [42]; Grodesky et al., 2001 [43]; Kitchen et al., 2001 [44]; Ledergerber et al., 1999 [45]; Lorenzi et al., 1999 [46]; Manfredi et al., 2001 [47]; Manfredi et al., 2001 [48]; Manfredi et al., 2003 [49]; Mocroft et al., 2001 [50]; Montaner et al., 2001 [6]; Olivieri, 2002 [51]; Paolucci et al., 2000 [52]; Romano et al., 2002 [53]; Rusconi et al., 2001 [54]; Saah et al., 2003 [55]; Smith et al., 2001 [56]; Valer et al., 2002 [57]; Walmsley et al., 2001 [58]; Wasmuth et al., 2002 [59]; and Youle et al., 2002 [60].
| Inclusion criteria were not met |
| Arvieux et al., 2002 [61]; Cingolani et al., 2002 [62]; Eron et al., 2000 [63]; Gulick et al., 2001 [64]; Haas et al., 2001 [65]; Haas et al., 2003 [66]; Hartmann et al., 2001 [67]; Lalezari et al., 2003 [31]; Lazzarin et al., 2003 [68]; Miller et al., 2000 [69]; Nadler et al., 2003 [70]; Pellegrin et al., 2002 [71]; Roge et al., 2003 [72]; Seminari et al., 1999 [73]; Sullivan et al., 2000 [74]; Walmsley et al., 2001 [58]; and Yozviak et al., 2001 [75].
| Inadequate detail on composition of study regimen |
| Barreiro et al., 2002 [76]; Baxter et al., 2000 [77]; Baxter et al., 2002 [78]; Clevenbergh et al., 2000 [79]; Durant et al., 2000 [80]; Mallon et al., 2003 [81]; Mazzotta et al., 2003 [82]; and Quiros-Roldan et al., 2001 [83].
| Outcomes of interest were reported in another study already included in our analysis |
| Gulick et al., 2002 [84]; and Parkin et al., 2000 [85].