Antiretroviral Medication Errors among Hospitalized Patients with HIV Infection

Darius A. Rastegar, Amy M. Knight, and Jim S. Monolakis
Johns Hopkins Bayview Medical Center, Baltimore, Maryland

Background. Highly active antiretroviral therapy (HAART) has improved survival for persons living with human immunodeficiency virus (HIV) infection. However, effective therapy requires high levels of adherence over extended periods of time. Previous studies suggest that patients receiving long-term medication are at risk for unintended medication discrepancies at the time of hospital admission.

Methods. We retrospectively identified every HIV-infected patient admitted to our hospital over a 1-year period who received an antiretroviral agent. We collected information on medications and renal function from the hospital computerized provider order entry system. We reviewed the medical records for those admissions for which a potential error was identified. We defined errors using Department of Health and Human Services guidelines and included only those errors that were not corrected within 24 h after initial entry.

Results. There were a total of 209 admissions during a 1-year period in which an HIV-infected patient received antiretroviral therapy. After review of the medical records for 77 admissions with a potential error, 61 uncorrected errors from 54 admissions were identified (percentage of total admissions, 25.8%; 95% confidence interval, 20.1%–32.3%). The most common type of error was an error with respect to the amount or frequency of dosage, which occurred in 34 (16.3%) of the admissions; 18 of these errors were attributable to failure to appropriately adjust dosage for renal insufficiency. The next most common error was combining antiretroviral drugs with a contraindicated medication; this occurred in 12 (5.2%) of the admissions. Patients erroneously received 2 antiretroviral agents in 8 (3.8%) of the admissions and had an unexplained delay in continuing HAART in 7 (3.3%).

Conclusions. HIV-infected patients receiving HAART are at substantial risk for antiretroviral medication errors at the time of hospitalization. More needs to be done to ensure that these patients receive appropriate therapy during their inpatient stay.

Medication errors and drug-related adverse events are a common and serious problem for inpatient services [1, 2]. Many of these errors are in the form of unintended discrepancies in long-term medications at the time of admission [3]; these errors may then be carried over into the patient’s discharge instructions and outpatient treatment [4]. The use of computerized provider order entry (CPOE) systems may help to reduce medication errors [5], but errors and adverse drug reactions are still significant problems in institutions that adopt these systems [6], and certain systems may even facilitate errors [7].

HAART has significantly improved the survival and quality of life of HIV-infected individuals [8]. However, the regimens are complicated, and there are many potential drug interactions that place patients at risk for toxicity or for drug-resistant viral infection. Furthermore, physicians and other health care providers who are not experienced with antiretroviral management are often unfamiliar with these medications and their proper use [9]. With this in mind, we sought to determine the frequency and characteristics of errors in antiretroviral prescribing among hospitalized patients at our institution.

PATIENTS AND METHODS

Setting. Johns Hopkins Bayview Medical Center is a 354-bed hospital in Baltimore, Maryland. There are 7 general services in the hospital: surgery (which includes a surgical intensive care unit and a burn unit), psy-
chiary, obstetrics and gynecology, pediatrics, neurology, chemical dependency (a detoxification unit), and medicine. The medicine service includes general medical, cardiac intensive care, medical intensive care, and cardiac and pulmonary intermediate care services.

Johns Hopkins Bayview Medical Center implemented hospital-wide computerized order entry by pharmacists, nurses, and unit secretaries on 1 July 2003 using a client-server system provided by Meditech. CPOE was phased in from October 2003 to May 2004. Providers select medications by generic or brand name from a list of all formulary medications; they then select the desired dose of the medication from a list of doses compiled by Johns Hopkins Bayview Medical Center pharmacists. Providers receive a warning at the time of order entry if the dose is higher or lower than a range of acceptable doses maintained by First DataBank. Providers also receive a warning at order entry if a conflict is detected by the medication interaction checking system, which is also supported by First DataBank. This database is updated on a monthly basis. Providers have the option of overriding the warning and picking from a predefined list of reasons for the override, erasing the order that has generated the warning, or replacing it with a more suitable medication. The Meditech system calculates an estimated glomerular filtration rate for all patients >18 years old each time a Basic or Comprehensive Metabolic Panel is resulted, using the Modification of Diet and Renal Disease equation [10]. However, the CPOE system does not take creatinine level or estimated glomerular filtration rate into account when generating dose range warnings.

**Patient identification.** We identified all adult inpatients at Johns Hopkins Bayview Medical Center for whom an order for antiretroviral medication was placed into our CPOE system from 1 April 2004 to 31 March 2005. We recorded the age of the patient and the service in which they were hospitalized when the error occurred (medicine, surgery, psychiatry, obstetrics and gynecology, chemical dependence, or neurology). For those patients admitted to the medical service, we recorded whether they were admitted to the intensive or intermediate care unit or to the general medical service.

**Error identification.** Errors were identified with a 2-step process. First, we reviewed the electronic medication list and laboratory data for all patients who had been prescribed an antiretroviral medication for potential dosing and drug interaction errors. Patients at our hospital are prohibited from taking their own medications unless an adequate substitute is unavailable from our pharmacy; in this event, orders for the patients’ own medications are still placed into our CPOE system and, therefore, would also have been captured in our review. Errors that were corrected before the patient received a dose of medication were not recorded. Second, we reviewed the paper records for all admissions with a potential error to determine whether an error had actually occurred. Outpatient records, when available, were also reviewed to see whether there was a discrepancy with the patient’s outpatient regimen. We categorized errors using the most recent Department of Health and Human Services guidelines for the period studied [11], as follows.

1. Delay in continuing outpatient regimen (>24 h after admission). If the patient initiated antiretroviral therapy during their hospitalization, this was not considered to be an error. If antiretroviral medications were deliberately withheld because of possible toxicity or because the patient could not take oral medications, this was also not counted as an error.

2. Inadequate regimen (i.e., ≤2 antiretroviral agents). Ritonavir was not counted as a separate agent when used to boost another protease inhibitor. If review of inpatient and outpatient records demonstrated that the regimen corresponded with the patient’s outpatient regimen at the time of admission, this was not counted as an error.

3. Error with respect to the amount or frequency of antiretroviral drug dosage, including failure to adjust for renal failure or antiretroviral drug interaction. If the error was corrected within 24 h or the patient had an increase in serum creatinine level that resolved within 24 h and the dosage was appropriate for subsequent renal function, these were not counted as errors.

4. Use of other medications that are contraindicated for use with specific antiretrovirals (e.g., proton pump inhibitors used in conjunction with atazanavir or simvastatin or lovastatin used in conjunction with ritonavir).

We also conducted chart reviews for evidence of adverse reactions from drug interactions identified as having the potential to cause toxicity (e.g., coadministration of simvastatin and ritonavir) or from failure to adjust antiretroviral dosage for renal insufficiency. We also interrogated the CPOE system to determine whether a warning was generated for the contraindicated combinations or the incorrect dosages (those not attributable to failure to correct for renal insufficiency). The initial data collection was conducted by the 3 authors individually, and the findings were reviewed as a group to decide which were potential errors; the review of paper records was also conducted as a group, and decisions were made by consensus. Use of this retrospective data was approved by the institutional review board of Johns Hopkins Bayview Medical Center.

**Data analysis.** We calculated the total number of errors, types of errors, and error rates by service. We used stepwise binary logistic regression analysis to examine the association between medication errors and demographic factors (age and sex), length of stay, renal insufficiency, and the service in which the patient was hospitalized. Statistical analysis was performed using SPSS software, version 10.0 (SPSS).
RESULTS

A total of 215 admissions were identified in which an order for an antiretroviral medication was entered into the CPOE system from 1 April 2004 to 31 March 2005. Four of these were orders for lamivudine for treatment of hepatitis B; 2 were orders entered for non–HIV-infected patients and were cancelled within a few minutes of entry. The remaining 209 admissions were included in our analysis.

A total of 160 patients were included in this analysis; 32 of them were admitted more than once during the time period that was studied. The mean age of these patients was 43.7 years, and 91 (56.9%) of the patients were male.

The distribution of these admissions by service was as follows: 96 admissions (45.9%) were to the general medical service, 29 admissions (13.9%) were to the medical and/or cardiac intensive or intermediate units, 32 admissions (15.3%) were to the chemical dependence service, 15 admissions (7.2%) were to the surgery service, 15 admissions (7.2%) were to the psychiatry service, and 3 admissions (1.4%) were to the neurology service. During this same time period, there were a total of 9660 admissions to the medical service (including the medical and/or cardiac intensive or intermediate care units), 2850 admissions to the chemical dependence service, 1822 admissions to the obstetrics and gynecology service, 845 admissions to the psychiatry service, and 642 admissions to the neurology service. Patients had renal insufficiency (estimated glomerular filtration rate, <60 mL/min) in 51 (24.4%) of the admissions. The length of stay ranged from 0 to 33 days; the median duration of hospital stay was 4 days.

The results of the review process are illustrated and summarized in figure 1. On initial review of medication lists and renal function, a total of 89 potential errors were identified in 77 of the 209 admissions. Antiretroviral therapy was started >24 h after admission for 17 (8.1%) of these admissions. In 15 (7.1%) of the admissions, the patient received ≤2 antiretroviral agents; in 44 (21.1%) of the admissions, a dosage error occurred (of these errors, 24 were attributable to failure to correct for renal insufficiency). Finally, in 13 (6.2%) of these admissions, the patient received a drug that was contraindicated for administration in combination with 1 of the antiretroviral agents in their regimen. After review of the inpatient charts for the 77 admissions with a potential error, as well as the outpatient records for 46 of these admission, 28 (31.5%) of the 89 potential errors were judged to not be errors. The most common type of error was an error in the amount or frequency of the dosage, which occurred in 34 (16.3%) of the admissions; 18 of these errors were attributable to a failure to appropriately adjust dosage for renal insufficiency. We were able to find documentation of the outpatient regimen for patients associated with 28 of the 34 admissions involving an error of dosage; in 16 cases, we found a discrepancy with the patient’s earlier outpatient regimen, but in 12 cases, the dosage was consistent with the patient’s outpatient regimen. After error of dosage, the next most common error was combining antiretrovirals with a contraindicated medication; this occurred in 12 (5.2%) of the admissions; 6 of these errors were attributable to the combination of simvastatin and a protease inhibitor, and the other 6 errors were attributable to the combination of a proton pump inhibitor with atazanavir. Patients erroneously received ≥3 antiretroviral agents in 8 (3.8%) of the admissions and had an unexplained delay in continuing antiretroviral therapy in 7 (3.3%). One potential drug-related adverse reaction was identified for medications. For the remaining 7 admissions, there was no explanation for the delay. For 7 of the 15 admissions in which patients were given ≤2 antiretroviral medications, we found documentation that the regimen corresponded with the patient’s outpatient regimen. Of the remaining 72 errors, 11 were corrected within 24 h of admission to the hospital, including 10 of the 45 errors in which an incorrect dose was given and 1 of the 17 errors in which a contraindicated drug combination was given.

The characteristics of the 61 uncorrected errors from 54 (25.8%) of the admissions are summarized in table 1, and table 2 describes a few representative errors. The most common type of error was an error in the amount or frequency of the dosage, which occurred in 34 (16.3%) of the admissions; 18 of these errors were attributable to a failure to appropriately adjust dosage for renal insufficiency. We were able to find documentation of the outpatient regimen for patients associated with 28 of the 34 admissions involving an error of dosage; in 16 cases, we found a discrepancy with the patient’s earlier outpatient regimen, but in 12 cases, the dosage was consistent with the patient’s outpatient regimen. After error of dosage, the next most common error was combining antiretrovirals with a contraindicated medication; this occurred in 12 (5.2%) of the admissions; 6 of these errors were attributable to the combination of simvastatin and a protease inhibitor, and the other 6 errors were attributable to the combination of a proton pump inhibitor with atazanavir. Patients erroneously received ≥3 antiretroviral agents in 8 (3.8%) of the admissions and had an unexplained delay in continuing antiretroviral therapy in 7 (3.3%).
Table 1. Characteristics of antiretroviral prescribing errors.

<table>
<thead>
<tr>
<th>Error</th>
<th>No. (%) of total hospital admissions in which antiretroviral drugs were prescribed (n = 209)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in continuing therapy for &gt;24 h</td>
<td>7 (3.3)</td>
<td>...</td>
</tr>
<tr>
<td>Insufficient regimen (&lt;3 antiretrovirals)</td>
<td>8 (3.8)</td>
<td>In 7 other admissions, patients received &lt;3 antiretrovirals, but this corresponded with their outpatient regimen.</td>
</tr>
<tr>
<td>Incorrect amount or frequency of dosage</td>
<td>34 (16.7)</td>
<td>In 18 of these admissions, errors were caused by failure to correctly adjust for renal insufficiency.</td>
</tr>
<tr>
<td>Contraindicated drug combination</td>
<td>12 (5.2)</td>
<td>In 6 of these admissions, patients received a combination of simvastatin and protease inhibitor. In the other 6 admissions, patients received a combination of proton pump inhibitor and atazanavir.</td>
</tr>
<tr>
<td>Total</td>
<td>54 (26.3)</td>
<td>...</td>
</tr>
</tbody>
</table>

* No. of admissions in which an error occurred; >1 type of error was found in 7 admissions.

a patient receiving lopinavir and ritonavir who was prescribed simvastatin and had increasing liver enzyme levels until the simvastatin therapy was discontinued, after which the liver enzymes returned to previous levels.

The distribution of errors by service is shown in table 3. The error rate ranged from 0% for the obstetrics and gynecology service to 41.4% for the medical intensive and intermediate care units; in absolute terms, the largest number of errors involved the general medical service (31 errors). In multivariate analysis, the only factor that was independently associated with an antiretroviral medication error was renal insufficiency (estimated glomerular filtration rate, <60), with an OR of 5.18 (95% CI, 2.61–10.28).

On interrogation of the CPOE system for warnings, we found that the system generated a warning for 1 of the 6 contraindicated combination errors and for 5 of the 16 dosage errors that were not attributable to failure to correct for renal insufficiency.

DISCUSSION

With the advent of HAART, HIV infection has become a chronic illness that can be managed effectively with proper medical care. However, unlike errors associated with the treatment of other chronic illnesses, antiretroviral medication errors—even if they are corrected after a short period of time—may have serious long-term implications. Patients must be receiving appropriate regimens and maintain high levels of adherence for many years [12]; receiving insufficient regimens or improper dosages of medication places patients at risk for developing drug-resistant infection or toxicity. Ideally, patients receiving HAART who are admitted to the hospital should have a seamless transition in which their outpatient regimen is continued with no missed doses. However, our study shows that hospitalization can place these patients at substantial risk for gaps in effective therapy. Even when using a fairly conservative definition of an error (i.e., allowing for 24-h gaps in medication and correction of initial errors) we found errors associated with approximately one-quarter of all admissions. Furthermore, there may have been other errors that our review did not detect. Our review would not have captured errors involving patients who should have continued to receive HAART but did not receive any antiretrovirals; likewise, patients who were receiving >3 antiretrovirals as outpatients but were administered only 3 antiretrovirals after admission to the hospital would not have been identified. Another consideration is the timing of medication; some antiretroviral drugs must be given with food, and others must be given on an empty stomach; our review did not capture these kinds of errors, but a previous report suggests that they are common [13]. Our study does not provide outcome data for these patients, and it is likely that many were not harmed by the errors, but it is clear that the care provided was less than optimal.

Although our study was limited to a single hospital, it is likely that these types of errors occur in other institutions. Previous research has found that unintended medication discrepancies are common; in 1 study involving patients who were receiving at least 4 long-term medications who were admitted to a general medical service, at least 1 unintended discrepancy was found for approximately one-half of the admissions [3]. A study of antiretroviral prescribing errors among hospitalized patients reported rising rates of errors from 1996 (when HAART was first introduced) to 1998, when errors were detected for 12% of admissions; most of these were errors of dosage [14].

We found a significant rate of medication errors despite the use of CPOE and clinical-decision support. CPOE systems have...
Table 2. Examples of antiretroviral prescribing errors.

<table>
<thead>
<tr>
<th>Error category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in continuing therapy</td>
<td>Patient was admitted to the hospital for treatment of an infected aortic graft. Lopinavir-ritonavir therapy was resumed 7 days after surgery; lamivudine and zidovudine therapy was resumed 10 days after surgery. Patient was admitted to the hospital for treatment of depression; HAART was resumed 2 days after admission. No reason was given for the delay.</td>
</tr>
<tr>
<td>Insufficient regimen (≤3 antiretrovirals)</td>
<td>Patient receiving indinavir and combivir (zidovudine and lamivudine) was admitted to the hospital with acute renal failure; zidovudine and lamivudine were withheld because of renal failure, and the patient continued to receive indinavir alone for 4 days. Attending physician gave verbal order for patient to be prescribed lopinavir-ritonavir, stavudine, and lamivudine at admission; this was correctly written by the nurse, but lamivudine was never entered into the system and was omitted on the hospital discharge instructions 12 days later.</td>
</tr>
<tr>
<td>Error in amount or frequency of dosage</td>
<td>Patient receiving hemodialysis was administered a regimen of zidovudine at a dosage of 100 mg daily instead of the recommended dosage of 300 mg daily; patient received the correct dosage as an outpatient. Patient was prescribed lopinavir-ritonavir at a dosage of 3 caps 3 times daily instead of the recommended dosage of 3 caps twice daily; the patient received the twice-daily regimen as an outpatient. Patient receiving ritonavir-boosted atazanavir was administered a subtherapeutic dosage of atazanavir 300 mg daily alone; this was continued on the hospital discharge instructions. Patient with normal renal function was prescribed tenofovir 300 mg twice daily (the frequency of dosage should have been daily), lamivudine 150 mg daily, and zidovudine 300 daily (both lamivudine and zidovudine should have been administered twice daily).</td>
</tr>
<tr>
<td>Contraindicated combination</td>
<td>Patient receiving lopinavir-ritonavir therapy was administered the hospital-formulary simvastatin instead of his outpatient atorvastatin; he was instructed to take simvastatin at discharge from the hospital. Patient receiving atazanavir therapy was prescribed pantaprazole therapy; he was not receiving a proton pump inhibitor at the time of admission to the hospital.</td>
</tr>
</tbody>
</table>

been shown to reduce general dosage errors, dosage errors in patients with renal insufficiency, and drug-drug interactions [5, 15, 16]. The system in use at Johns Hopkins Bayview Medical Center checks for appropriate dosages and contraindicated drug combinations. However, warnings are frequently ignored; we found that this occurred in at least 6 cases. Moreover, our system currently does not adjust dosage ranges for patients with renal insufficiency; providing dosage range input that adjusts for renal function may help to prevent some of these errors. However, these modifications cannot guard against errors of omission or delays in the continuation of therapy. Care maps, clinical pathways, or order sets that provide options in the form of commonly used combinations (with advice on adjustments for renal insufficiency) may help to reduce some of these errors. However, given the complexity of regimens and the many potential drug interactions, relying on automated systems may not be sufficient, and expert review by a pharmacist or physician who is familiar with these complicated regimens may be the best solution.

There are a number of interventions beyond CPOE that may help to reduce these errors. Improved information systems that facilitate the transfer of information on long-term medications from one care setting to another is one such measure; although there has been some research on a variety of interventions to improve adherence to medications after discharge from the hospital [17], there has been comparatively little attention paid to preventing treatment discontinuity at the time of admission. Providing guidance and supervision by health care providers (physicians or pharmacists) with experience and expertise in antiretroviral management may also help to prevent these errors [18, 19].

In summary, among HIV-infected patients who received antiretroviral therapy during hospitalization, we found errors in

Table 3. Hospital admissions associated with errors, by service.

<table>
<thead>
<tr>
<th>Service</th>
<th>Total no. of admissions</th>
<th>No. of errors</th>
<th>Error rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine</td>
<td>96</td>
<td>31</td>
<td>32.3</td>
</tr>
<tr>
<td>Intermediate and intensive care</td>
<td>29</td>
<td>12</td>
<td>41.4</td>
</tr>
<tr>
<td>Chemical dependence</td>
<td>32</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Surgery</td>
<td>19</td>
<td>4</td>
<td>21.1</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>15</td>
<td>4</td>
<td>26.7</td>
</tr>
<tr>
<td>Obstetrics and gynecology</td>
<td>15</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Neurology</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>Total</td>
<td>209</td>
<td>54</td>
<td>25.8</td>
</tr>
</tbody>
</table>

*No. of admissions of patients who were prescribed antiretroviral therapy.

bNo. of admissions associated with at least 1 uncorrected error.
the prescribing of antiretroviral medications for approximately one-quarter of these admissions, despite the use of a computerized order entry system. Many of these errors were in the form of unintended discrepancies with outpatient regimens. Patients with renal insufficiency are at particularly high risk for such errors. More needs to be done to develop systems of care to prevent such errors and to ensure optimal care for hospitalized patients with HIV infection.

Acknowledgments
We thank Peter K. Lindenauer, for his review of an earlier version of the manuscript, and Donald R. Jasinski, for his help in data analysis.

Potential conflicts of interest. All authors: no conflicts.

References