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Implementation of Targeted Interventions to Decrease the Rate of Antiretroviral Related Medication Errors in Hospitalized Patients

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Abstract

Purpose—The implementation of targeted interventions aimed at decreasing the frequency of antiretroviral errors in hospitalized patients with human immunodeficiency virus (HIV) is described.

Summary—A prospective investigation conducted at our institution reported at least one error in the initial antiretroviral regimen in 49 out of 68 patients (72%). Since this analysis, several interventions aimed at decreasing this error rate have been instituted including computer alerts for incorrect doses and drug interactions added to the pharmacy entry system, an educational pocket card distributed among the staff, addition of commercially available combination antiretroviral products to the hospital formulary, computerized physician ordering system updates to include common dosing regimen defaults, involvement of the infectious diseases consult service to evaluate prescribed regimens of newly admitted patients with HIV, and daily review of newly initiated antiretroviral regimens by a clinical pharmacist trained in HIV care. A prospective follow up analysis was conducted after these interventions were in place to evaluate their effectiveness. A total of 78 patients were identified during the study period and were included in the analysis. Twelve (15%) of the patients experienced at least one error in their initial drug regimen compared to 49 (72%) of the control patients from the data collected prior to the interventions ($p < 0.001$).

Conclusion—A significant reduction in the frequency of antiretroviral medication errors among hospitalized patients with HIV was observed after the implementation of several interventions. The striking impact of these interventions supports a comprehensive and proactive approach to preventing antiretroviral medication errors in hospitalized patients with HIV.

Introduction

Drug therapy for human immunodeficiency virus (HIV) has substantially progressed over the past twenty years. Since the introduction of antiretroviral therapy, considerable reductions in the morbidity and mortality associated with HIV and AIDS have been observed.[1–3] HIV has now become a chronic disease managed primarily by HIV specialists in the outpatient setting.[4,5] Because of the potential for the emergence of resistance,

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adherence to the medication regimen is essential for successful treatment and sustained viral suppression.[6] In addition, the increasing complexity of HIV care and the rapidly evolving nature of medication management in this patient population have created an environment in which inpatient clinicians without extensive experience in the management of HIV are responsible for managing and initiating unfamiliar antiretroviral medications in patients admitted to the hospital.[4,5,7,8]

It is estimated that at least 1.5 million preventable adverse drug events occur each year in the United States due to medication errors.[9] Medication errors are common during all steps of the medication use process, including procurement, prescribing, transcribing, dispensing, administration, and monitoring. Several studies have demonstrated the prevalence of medication errors occurring during transitions between the outpatient and inpatient settings.[10–12] In hospitalized patients, prescribing and administration errors are the most common types of medication errors accounting for three-fourths of all medication errors.[13]

The widespread availability and increasing complexity of antiretroviral therapy have raised the concern for medication errors in hospitalized patients with HIV.[14–22] Prior studies in hospitalized patients with HIV have reported error rates between 5% and 30%.[15–18] Medication errors of omission could potentially have deleterious consequences for the long term care of patients with HIV through the development of resistance mutations rendering current available drug regimens ineffective. Furthermore, the many potential drug interactions associated with antiretroviral regimens could place patients at risk for drug toxicity or for drug-resistant infection.

Problem

A prospective investigation conducted at our institution revealed a high frequency of antiretroviral related medication errors occurring upon admission to the hospital and throughout hospital admission.[23] Prior to this investigation, there were no systematic processes in place at our institution to prevent, identify or resolve antiretroviral errors in a hospital-wide manner.

Background

The University of North Carolina Hospitals is an 803 bed academic medical center that provides acute inpatient adult and pediatric care. The frequency and severity of antiretroviral related medication errors were prospectively evaluated in a consecutive sample of HIV-infected patients admitted to our institution.[23] Patients were identified between January and April 2006 using a report generated from the inpatient pharmacy medication system. All antiretroviral medications of hospitalized patients were reviewed daily by either a pharmacist specialized in Infectious Diseases (ID) or an ID specialty pharmacy resident. Any antiretroviral errors present in the initial inpatient regimen and any subsequent errors occurring during hospitalization or upon discharge were described. Initial inpatient regimen was defined as the first antiretroviral regimen prescribed to a patient during hospitalization. Errors were classified based on the source of the error (attributable to prescribing, dispensing, clinic documentation, or acquisition) and severity. Severity was defined using the classification system described by Cornish and colleagues.[11] Class 1 errors were errors

that were unlikely to cause patient discomfort or clinical deterioration. Class 2 errors were those with the potential to cause moderate discomfort or clinical deterioration. Class 3 errors were those with the potential to cause severe discomfort or clinical deterioration. The severity of each error was discussed and agreed upon by a consensus of three ID-specialized clinical pharmacists. When errors were identified, the pharmacist was responsible for notifying the primary inpatient team caring for the patient to resolve the error.

At least one error in the initial antiretroviral regimen occurred in 49 out of 68 patients (error rate=72%) (95% CI, 60%–82%). In 38 of these patients (56%), the error had the potential to cause moderate or severe discomfort or clinical deterioration. With all errors combined from the initial regimens and throughout the patients' hospitalizations, 57 patients (84%) experienced at least one medication error with 44 patients (64%) experiencing at least one Class 2 or 3 error. Of the 87 errors identified in the initial inpatient drug regimens, 37 (45%) were attributable to prescribing errors, 27 (33%) were attributable to dispensing errors, and 18 (22%) were attributable to outpatient clinic documentation errors. The majority of errors occurring during hospitalization or upon discharge were the result of clinically significant drug interactions with the patient's antiretroviral regimen. From this study, the use of atazanavir during hospitalization was identified as a predictor of the occurrence of errors, due to common errors arising from the interaction between atazanavir and gastric acid suppressant drugs. Furthermore, the receipt of a combination antiretroviral drug requiring hospital formulary conversion was identified as a risk factor in patients in which more than one class 2 or 3 error occurred.[23]

The high frequency of errors revealed in this analysis emphasized the need for targeted interventions aimed at preventing these errors before they occur and at quickly identifying and resolving errors that do occur.

Analysis and Resolution

Interventions

Since this initial investigation, several interventions have been employed with the purpose of decreasing this medication error rate. Because of the multi-factorial nature of antiretroviral medication errors found in our investigation, we chose a comprehensive approach to decreasing the error rate. Our goal was to target the most common sources of error which included drug interactions, general prescribing errors, and errors due to hospital formulary conversions.

An educational pocket card was produced and distributed among the hospital's staff of health professionals including physicians, pharmacists, and nurses. This educational card, which is shown in Figure 1, was short and informative providing common doses, frequencies, and dosage forms of all available antiretroviral medications.

Several alerts were added to the pharmacy entry system in order to notify pharmacists of drug interactions and incorrect doses of antiretroviral medications at the point of order verification. The pharmacy entry system alerts also included information regarding the necessary components of an antiretroviral drug regimen in order to decrease the occurrence

of errors of omission. The computerized physician ordering system was also updated to include the most common dosing regimen as its default for each antiretroviral drug. These ordering defaults suggested appropriate doses and frequencies of antiretroviral drugs in order to facilitate accurate physician prescribing.

All commercially available combination antiretroviral agents were added to the hospital formulary due to the finding that combination non-formulary antiretroviral medications were associated with a greater incidence of errors. Prior to this, if a patient had been on Epzicom® (abacavir/lamivudine), either the pharmacist or the physician was required to convert this drug into its individual components which were on formulary. The same was true for other commercially available combination antiretroviral drugs. Truvada® (tenofovir/emtricitabine) also required an additional conversion of emtricitabine to its formulary equivalent lamivudine because emtricitabine was also not available on formulary. Conversions frequently resulted in omissions or dosage errors. Adding all combination antiretroviral medications to the hospital formulary eliminated this conversion step and therefore, decreased the likelihood of errors occurring.

In general, it has been the practice of our institution to avoid the addition of combination medication products to the hospital formulary for various reasons. Storage space is limited both in the central inpatient pharmacy and on the floors. Titrating combination medications can be problematic. For example, when titrating a combination antihypertensive medication, both active ingredients contained in the product are titrated simultaneously. In the acute care setting it is often advantageous to titrate these medications individually in order to achieve the desired response. Because antiretrovirals are not titrated, this factor was not a concern. Finally, combination products can lead to confusion because of the names they are given in computerized systems. In our system, when using generic medication names, the user would need to know which medication contained in the combination was listed first in its title in order to obtain the correct result from a search. A search for “zidovudine” would produce only a result of the individual zidovudine products, whereas a search for “lamivudine” would produce both the individual product lamivudine as well as the combination product named “lamivudine/zidovudine” because in the combination product, lamivudine was listed first. The incorrect search could lead to selection of the incorrect product. To avoid this confusion, combination antiretroviral products were named by their proprietary names in both the computerized physician order entry system and the pharmacy system.

Another advantage of adding combination antiretroviral medications to formulary is improved drug interaction monitoring for many patients. It is the policy of our institution that patients may bring in their own supply of medications if the medication is not available on the hospital formulary, provided certain procedures are followed. These nonformulary home medications are entered into the system using “free-text” methods which are not recognized by the pharmacy system and therefore require manual screening for drug interactions. The addition of all combination antiretroviral drugs available on formulary circumvented this problem.

Physicians were requested by the Department of ID to notify the Adult ID Consult Service of all HIV-infected patients who were admitted to their services to evaluate the prescribed

antiretroviral regimen when the patients were admitted. Instead of a full consult for these patients, the ID Consult Service elected to provide cursory reviews, without documentation in the medical records, unless a full consult was specifically requested by the primary inpatient team caring for the patient. Finally, a clinical pharmacist from existing staff, trained in HIV care, began reviewing all newly initiated antiretroviral regimens for appropriateness, accuracy, and continuity. This clinical pharmacist was either an ID specialized clinical pharmacist or an ID specialty pharmacy resident.

These interventions were employed in a staggered manner over the course of one year following the initial analysis.

Evaluation of Interventions

Beginning seven months after the complete implementation of our interventions, we began a post-intervention follow-up prospective analysis to determine the prevalence and severity of antiretroviral related medication errors in order to evaluate the effectiveness of our interventions. Patients in the post-intervention group were identified using a daily computer-generated report from the inpatient pharmacy medication system from November 8, 2007 to April 1, 2008. Men and women over 18 years old were included if they were HIV-positive, were admitted to an inpatient service, were receiving at least one antiretroviral for the treatment of HIV through the pharmacy system, and if they received primary HIV care at the hospital-based ID clinic. This study was approved by the institution's Human Research Ethics Biomedical Institutional Review Board.

The medication profiles of the patients included were reviewed on admission, daily, and at discharge, by either a specialized ID clinical pharmacist or by an ID specialty pharmacy resident who had been trained in HIV management. The ID clinical pharmacist was available to the resident if there was any need for confirmation or assistance. The accuracy of the regimen was confirmed by consulting the patient's ID clinic medical record. Appropriateness of the regimen was assessed using the most current update of the Department of Health and Human Services Guidelines on HIV/AIDS. Given the rapidly evolving nature of HIV management, deviations from the guidelines were expected. If the clinical pharmacist deemed that there was inadequate justification for the regimen, the HIV physician was contacted for clarification before recording these variances as errors. All errors occurring on admission and throughout hospitalization were documented and described. Initial inpatient regimen errors were defined as errors occurring in the first antiretroviral regimen prescribed during the hospitalization. Errors throughout hospitalization were defined as errors which occurred at any point after the initial inpatient regimen was prescribed, including errors occurring in discharge instructions. Errors were classified based on the source of the error (attributable to prescribing, dispensing, clinic documentation, or acquisition) and severity. Severity was defined using the classification system described by Cornish and colleagues.[11] The severity of each error was discussed and agreed upon by a consensus of three ID-specialized clinical pharmacists. When errors were identified, the pharmacist was responsible for notifying the primary inpatient team caring for the patient to resolve the error.

The intervention group consisted of the patients identified and included in the follow-up study after the implementation of interventions aimed at decreasing the error rate. The control group consisted of the patients included in the initial prospective study conducted at our institution prior to the implementation of these interventions.[23]

The primary endpoint of this study was the difference in the error rate, occurring at initial admission, between the original error rate obtained from the pre-intervention initial study (control group) and the error rate found in the post-intervention follow-up study (intervention group). Secondary endpoints included the percentage of errors classified as Class 2 or 3, the total number of errors occurring among all patients throughout hospitalization and the types of errors that occurred. Secondary endpoints were also compared between pre and post intervention groups.

The original error rate of 72 % which was obtained from the initial analysis was used for the sample size calculation. Using a 2-tailed proportions test ($\alpha = 0.05$), we calculated a total of 78 patients in the follow-up study needed along with the 68 patients in the initial study to have 80% power to detect a 24% absolute reduction in the error rate. The error rates were compared using a 2-tailed Fisher's Exact test.

A total of 78 patients were identified during the study period and included in the intervention group of this analysis. Baseline characteristics of the study groups are shown in Table 1.

A total of 17 errors were observed throughout the study period. Twelve of these errors occurred in initial regimens, and 5 occurred at discharge as inaccurate documentation in discharge instruction notes in the patients' medical records. All 17 of the errors observed in the intervention group were classified as either Class 2 or 3 errors. All of the errors were resolved by pharmacists' recommendations to the primary clinical services. Twelve (15%) of the intervention patients had at least one error in their initial drug regimen, compared to 49 (72%) of the control patients ($p < 0.001$). Initial regimens included at least one Class 2 or 3 error in 12 (15%) of the intervention patients compared to 38 (56%) of the control patients ($p < 0.001$). At least one error occurred throughout hospitalization in 5 (6%) of intervention patients and in 57 (84%) of control patients ($p < 0.001$). At least one Class 2 or 3 error occurred throughout hospitalization in 5 (6%) of intervention patients and in 44 (67%) of control patients ($p < 0.001$) (Table 2).

Fourteen errors in the intervention group were classified as Class 2 errors and 3 errors in intervention group were classified as Class 3 errors. Class 2 errors included incorrect dosing of antiretrovirals (5 errors), antiretrovirals held due to raltegravir inavailability on formulary soon after its approval (2 errors), omission of prophylactic antibiotics which were part of the patients' home regimens (1 error), incorrect dosing of prophylactic antibiotics (2 errors), and omission of part of a regimen (4 errors). There were a total of 3 class 3 errors in the intervention group. Two of these errors were due to drug interactions between atazanavir and gastric acid suppressants and one error was due to incorrect dosing of zidovudine/ lamivudine.

A comparison of the types of errors occurring in the control group and the intervention groups are shown in Table 3. Inpatient prescribing errors accounted for 70% of all errors in the intervention group. Dispensing errors accounted for 24% of all errors. The remaining errors (6%) were attributable to inaccurate outpatient clinic documentation. A decrease in all types of errors was seen in the intervention group compared to the control group, with the exception of errors due to delays in acquisition (resulting in at least one missed day of therapy) in which a small increase was seen (1 error in the control group compared to 3 errors in the intervention group). The three errors due to delays in acquisition occurred with raltegravir soon after its approval, as it had not yet been added to the hospital formulary.

Discussion

In our evaluation, the percentage of patients in which at least one antiretroviral error occurred on initial admission decreased from 72% to 15% after the implementation of several targeted interventions. Our comprehensive approach to decreasing the antiretroviral error rate creates some uncertainty when evaluating the effects of the interventions because it is difficult to determine which of the interventions ascribed the greatest effect. We believe that the combined effect of several of our interventions including the educational pocket card, the addition of combination antiretroviral medications to formulary, the computerized physician order entry defaults, and the pharmacy system alerts led to the significant reduction in the error rate.

The educational pocket card was an important component to our intervention. The finding that converting combination, non-formulary agents to formulary equivalents was associated with a higher frequency of errors reflects the lack of familiarity among physicians and pharmacists with antiretroviral medications. The educational pocket card was specifically targeted toward this deficit. For a period of time, the pocket card also served to raise awareness of the high rate of antiretroviral errors which had been occurring. This heightened awareness may have influenced the decrease in error rate which was observed in this study as well.

Educational interventions aimed at reducing medication errors have been shown to be transiently effective but may lack sustained effects.[24] In addition, due the academic nature of our institution, new inexperienced physician residents arrive intermittently throughout each year. This continual influx of inexperience requires that educational efforts be continual. For these reasons, we did not expect education alone to be adequate to reduce our error rate for an extended period of time. It was essential to focus as well on our systems to reduce the error rate.

Likely, changes in our systematic processes such as the pharmacy entry alerts, the physician ordering default updates, and the addition of combination products to formulary contributed the greatest effect in decreasing errors. It is important, however, to routinely and frequently update these systems to mirror changes in practice, especially in the face of rapidly evolving fields of medicine such as HIV care. At our institution, the ID clinical pharmacy specialist is now responsible for reviewing these defaults and alerts on a regular basis to ensure that they reflect the most current standards of practice. The educational pocket card is now updated by

the ID specialty pharmacy resident twice annually and whenever new antiretroviral drugs are approved.

The impact of the review of antiretroviral medications by the ID consult service and by the ID-specialized clinical pharmacist was not evaluated in our analysis since the primary endpoint of our analysis was the error rate occurring upon initial admission before the medications were evaluated. These services likely do have value, however, as even after the interventions, we found a 15% antiretroviral error rate occurring on admission. Evaluation of newly initiated antiretroviral medications by the ID consult service and by the ID specialized pharmacist provides greater continuity of care and ensures optimized therapy throughout hospitalization. Because of the concern for drug interactions, adverse effects, and the development of resistance, daily medication profile reviews are essential in order to prevent and resolve errors in this population of hospitalized patients.

There were several limitations of our assessment of our interventions. Errors of omission may not have been identified since patients were identified only if they had at least one antiretroviral drug included in the pharmacy computer system. Errors occurring during the administration process may not have been fully identified due to the fact that these records are maintained as paper records and are not electronic. Additionally, the severity scale used in this study was highly subjective and dependent upon the evaluation of three investigators.

It should also be highlighted that the recommendations for combining gastric acid suppressants with atazanavir changed twice in the Department of Health and Human Services Guideline for the Use of Antiretroviral Agents over the course of our evaluations.[25–27] Because of this, errors which occurred during the two different studies were judged using a different standard. During the first evaluation, it was recommended to separate histamine 2 receptor antagonsists and atazanavir by at least 12 hours and to not coadminister proton pump inhibitors with atazanavir.[25] In October 2006, the guidelines were updated to include more detail regarding histamine 2 receptor antagonists. In this update it was recommended to differentiate between treatment naïve patients and treatment experienced patients. For treatment naïve patients it was recommended to give atazanavir at least 10 hours after or 2 hours before the histamine 2 receptor antagonist or to boost the atazanavir with ritonavir. In treatment experienced patients, it was recommended to separate the doses and to boost the atazanavir.[26] Finally, in 2008, amidst the second evaluation, the guidelines were updated again to include more detail regarding both histamine receptor antagonists and proton pump inhibitors. In this update, it was recommended that histamine 2 receptor antagonists should not be given with unboosted atazanavir. The guideline also provided dosing guidance for histamine 2 receptor antagonists if given in combination with atazanavir. A recommendation was also added to include a higher dose of atazanavir when tenofovir and histamine 2 receptor antagonists were coadministered. The recommendations were also changed to allow for proton pump inhibitors at specified doses to be combined with boosted atazanavir in treatment naïve patients if properly separated.[27] These changes may have led to more proton pump inhibitor related errors found in the initial study compared to the follow-up study and may have influenced the rate of histamine 2 receptor antagonist related errors in both studies.

We believe that antiretroviral medication errors occurring in hospitalized patients with HIV are not uncommon. Hospitals should seek to characterize the causes of these errors in order to identify targets for interventions with the goal of decreasing the occurrence of errors.

Conclusion

A significant reduction in the frequency of antiretroviral medication errors among hospitalized patients with HIV was observed after the implementation of several targeted interventions. The striking impact of these interventions supports a comprehensive and proactive approach to preventing medication errors in hospitalized patients.

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Table 1

Baseline characteristics.

Characteristic	Control	Intervention
Total, N	68	78
Age (years), median (IQR)	45 (39–52)	44 (38–49)
Women, n (%)	20 (29)	24 (30)
Race, n (%)		
• AA	53 (78)	56 (72)
• Caucasian	12 (18)	17 (22)
• Hispanic	2 (3)	2 (2)
• Native American	1 (1)	3 (4)
CD4+ cell count (cells/mm^3), median (IQR)	304 (109–561)	189 (62–488)
CD4+ cell count < 200 (cells/mm^3), n (%)	27 (40)	40 (51)
HIV RNA (log_{10} copies/mL), median (IQR)	1.7 (1.7–4.3)	1.7 (1.7–4.4)
Undetectable HIV RNA, n (%)	37 (54)	39 (50)

IQR—inter-quartile range

Table 2

Antiretroviral medication errors before (control) and after (intervention) interventions.

Outcome Measure	Control (n=68)	Intervention (n=78)	p
Initial regimen, n (%)			
• At least one error	49 (72)	12 (15)	<0.0001
• At least one Class 2 or 3 error	38 (56)	12 (15)	<0.0001
Throughout hospitalization, n (%)			
• At least one error	57 (84)	17 (22)	<0.0001
• At least one Class 2 or 3 error	44 (65)	17 (22)	<0.0001

Table 3

Types of errors in control and intervention groups.

Description of Errors	Control	Intervention
Total Errors, n	119	17
Prescribing, n (%)	62 (52)	12 (70)
• Incorrect dose/frequency, n	15	3
• Incorrect drug, n	9	0
• Incomplete entry, n	14	3
• Drug interaction, n	11	1
• Discharge summary, n	13	5
Dispensing, n (%)	39 (33)	4 (24)
• Incorrect dose/frequency, n	1	0
• Incorrect administration time, n	22	1
• Incorrect drug, n	14	0
• Incomplete entry, n	1	0
• Delay in acquisition, n	1	3
Outpatient Documentation, n (%)	18 (15)	1 (6)