Incidence of Antiretroviral Drug Interactions During Hospital Course: The Role of a Pharmacist-Led Antiretroviral Stewardship Program

Journal of Pharmacy Technology
2014, Vol. 30(2) 48–53
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DOI: 10.1177/8755122513500919
pharmatech.sagepub.com

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Abstract

Background: Human immunodeficiency virus (HIV) providers are treating more comorbid conditions with additional pharmacologic agents, resulting in patients with HIV being disproportionately at risk for clinically significant drug–drug interactions (CSDDIs). There is a potential to overlook these interactions and ultimately place patients at risk for drug toxicity, resistance, and virologic failure. **Objective:** To assess the burden of CSDDIs among patients receiving antiretroviral therapy (ART) within 24 hours of admission and to evaluate the effect of a clinical pharmacist operating through an antiretroviral stewardship (ARVSP) program in identifying and correcting potential drug interactions. **Methods:** Adult HIV-positive patients receiving ART who were admitted to The Brooklyn Hospital Center from November 2010 through January 2012 were included in the analysis. Drug interactions were categorized according to time frame (ie, within 24 hours of admission vs after 24 hours of admission) and type (ie, contraindicated combinations, dosage modifications, and frequency alterations). The Liverpool HIV drug reference, Micromedex drug database, and the Department of Health and Human Services Guidelines were used as comprehensive tools for identification of antiretroviral drug errors. **Results:** Eighty-four CSDDIs were identified from 252 admissions among 158 patients receiving ART during the study period. Of the identified CSDDIs, 61 (73%) occurred within 24 hours of admission and 23 (27%) later in the hospital course. Forty-eight drug interactions (57%) represented contraindicated drug combinations. Protease inhibitor–based regimens were associated with the highest percentage of CSDDIs (98%). Of all CSDDIs, the most common interacting drug class was acid-suppressive therapy (63%). Clinical pharmacists identified and intervened in 80% of the CSDDIs that occurred on patient admission with all interventions accepted. **Conclusions:** CSDDIs are common among patients receiving ART at the time of admission and throughout the hospital course. Interventions including medication review by clinical pharmacists are critical in the prevention of CSDDIs on admission.

Keywords

HIV, drug interactions, medication errors, pharmacist interventions

Introduction

Over the past 2 decades, the availability of combination antiretroviral therapy (ART) has greatly decreased acquired immunodeficiency syndrome (AIDS)–related mortality and the incidence of opportunistic infections.^{1,2} It has been projected that more than half of all human immunodeficiency virus (HIV)–infected patients will be ≥50 years of age by 2015.³ As a result of prolonged survival, the rate of comorbid conditions such as cardiovascular disease, non-HIV-related cancers, metabolic disorders, psychiatric disorders, osteoporosis, and renal and hepatic insufficiencies is increasing.⁴ Consequently, clinicians are prescribing more

medications with one study reporting HIV-infected patients on ART taking an average of 6 to 10 medications daily.⁵ Given the increased number of comorbid conditions, complexity of antiretroviral regimens, and poor clinician familiarity and experience with ART, patients living with HIV

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are disproportionately at risk for clinically significant drug–drug interactions (CSDDIs).

Antiretroviral medication errors that are commonly attributed to unrecognized drug–drug interactions may place patients at risk for drug resistance as incomplete regimens may result in functional monotherapy. In addition, increased levels of concomitant medications may result in adverse drug reactions. Previous studies suggest that medication errors occur frequently in hospitalized patients and have increased over the years.^{5–10} A retrospective study detected an error rate of 25.8% of hospital admissions among patients receiving antiretrovirals.⁶ Furthermore, contraindicated combinations with ART represent a common error classification, recently reported as high as 33%.¹¹ Despite advances in technology, improved medication administration recording, and drug interaction alerts implemented to minimize prescribing errors, drug interactions remain a significant problem.

Antiretroviral medication errors most often occur within the first 24 hours of admission. Yehia and colleagues identified 145 ART medication errors on the first day of hospitalization versus 22 errors later in the hospital course. Furthermore, patients admitted to a non-HIV/AIDS service were at increased risk of ART medication errors. The authors conclude that interventions are warranted to safeguard patients from potential ART medication errors within the first 24 hours of hospitalization.¹² Consequently, a multidisciplinary approach including a clinical pharmacy review of medication orders within the first 24 hours of admission may be warranted to identify, correct, and ultimately prevent antiretroviral drug interactions.

The Brooklyn Hospital Center, a 416-bed tertiary care facility located in Brooklyn, New York, established an antiretroviral stewardship program in 2005 to identify and prevent complications from antiretroviral medication errors. The program receives requests for an average of 360 to 400 antiretroviral approvals annually. Under this program, pharmacy consultation is required prior to entry of any antiretroviral order with the exception of those placed by an infectious diseases attending. Computerized provider order entry alerts via Eclipsys Sunrise Clinical Manager prompt the health care provider to contact the ARVSP for verification. Consultations are reviewed and recommendations are provided within 2 hours of receipt of the consult. All antiretroviral medication orders must receive prior approval from our antiretroviral stewardship program prior to dispensing from the general pharmacy.

On consultation, the clinical pharmacist subsequently interviews each HIV-positive patient to assess adherence and appropriateness of ART and opportunistic infection prophylaxis. This consult service is available 24 hours a day through our post-graduate year 1 and 2 residency on call program. A certified HIV pharmacist oversees all approvals performed by pharmacy residents. The antiretroviral regimens are also screened by the clinical pharmacist for dosage adjustments, antiretroviral medication errors, and

drug–drug interactions on patient admission. The antiretroviral regimens are reconciled with an internal database containing medical records of patients followed by the facility's HIV outpatient clinic called the Program for AIDS Treatment and Health (PATH) Center. Regimens that matched outpatient clinic records are deemed accurate, and regimens of patients not seen at the PATH center are reconciled against national guidelines, retail pharmacy records, and communications with primary care physicians.

All antiretroviral approvals and denials are documented in the medical record and an internal clinical pharmacy database. A standardized form is completed by pharmacy residents and clinical pharmacists documenting the recommendations in the hospital computerized provider order entry (CPOE) system. Our study aims to provide a current estimate of CSDDIs among patients receiving ART and assess the impact of a clinical pharmacist operating through an antiretroviral stewardship (ARVSP) program in identifying and correcting potential drug interactions.

Methodology

Study Population and Setting

A single-center, retrospective study was conducted for adult inpatients receiving antiretrovirals at The Brooklyn Hospital Center. Patients admitted to an inpatient medicine service from November 2010 through January 2012 were eligible for inclusion if all of the following were met: (a) age 18 years and older, (b) diagnosed with HIV or AIDS, and (c) receiving treatment with antiretrovirals. If patients had multiple hospital admissions within the study period, all encounters were included in the analysis. All patients were randomly identified by searching for antiretroviral consultations through our institution's clinical pharmacy database (MedKeeper), an internal documentation system used only by pharmacists to document consults and interventions. The Brooklyn Hospital Institutional Review Board approved the study with a waiver of informed consent.

Data Collection

For each patient, data collected included age, sex, race/ethnicity, selected comorbid conditions (cardiac disease states, lung disease, opportunistic infections, malignancy, psychiatric disorders, diabetes mellitus, renal/hepatic insufficiencies, and hematologic disorders), serum creatinine on admission, CD4 lymphocyte count and HIV-1 RNA level within 6 months, body mass index (BMI), and full medication lists (name, dose, route, frequency, and start/end date). For all patients, the creatinine clearance was calculated using the Cockcroft Gault equation if BMI <30 kg/m² or >40 kg/m² or alternatively using the Salazar-Corcoran equation if BMI 30 to 40 kg/m².

Definitions and Medication Error Identification

A clinically significant drug–drug interaction was defined as an interaction involving antiretrovirals that resulted in a dosage or frequency modification or the use of an alternative agent due to one agent being contraindicated. During the retrospective review, all treatment regimens were triple screened using the Liverpool HIV drug reference, Micromedex drug database, and the Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. These databases are generally regarded as comprehensive tools for identification of antiretroviral medication errors.

For each inpatient admission, the total number of CSDDIs, the types of CSDDIs, interacting pharmacologic drug classes, and interventions performed by a clinical pharmacist were quantified and evaluated. CSDDIs were categorized as (a) contraindicated combination, (b) lack of drug dosage modification, or (c) lack of frequency modification. Results were expressed as percentages and frequencies according to descriptive analyses.

Drug–drug interactions were classified according to concomitant interacting drug classes based on the Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, and subgrouping was performed based on time of occurrence (ie, on admission vs during hospitalization). CSDDIs occurring within 24 hours of hospitalization were considered “on admission,” and those occurring after 24 hours of hospitalization were considered “during hospitalization.” The primary endpoint was quantification of CSDDIs among patients receiving ART and clinical pharmacist interventions operating through an antiretroviral stewardship (ARVSP) program within 24 hours of admission. Secondly, the goal of this analysis was to quantify the number of CSDDIs occurring after the first 24 hours of hospital admission and determine pharmacologic drug classes associated with the most frequent drug interactions.

Results

Patient Characteristics

During the study period, 252 admissions were identified among 158 HIV-infected patients receiving antiretroviral therapy. The majority of hospitalized patients were male, ≥ 50 years of age, and did not have virologic suppression within the past 6 months (Table 1). Sixty-nine percent of the study cohort received either a protease inhibitor–based regimen or a non-nucleoside reverse transcriptase inhibitor–based regimen. Chronic cardiac diseases including hypertension and heart failure represented the most frequent comorbidity shared among all patients. Forty-eight percent of the patient population had a total of 2 or more of the selected comorbidities.

Table 1. Demographic Characteristics of All Hospital Admissions Including Duplicated Patients.

Baseline Patient Demographics (N = 252)	
Age, years (mean $\pm$ SD)	51 $\pm$ 12.67
Female, n (%)	98 (39)
ICU admission, n (%)	20 (8)
Creatinine clearance, mL/min (mean $\pm$ SD)	78.2 $\pm$ 29.83
CD4 count, cells/mm ³ , n (%)	
≥ 200	160 (64)
< 200	61 (24)
Unknown	31 (12)
Viral load, copies/mL, n (%)	
Detectable (> 20 -75)	129 (52)
Undetectable (< 20 -75)	89 (35)
Unknown	34 (13)
Medical service, n (%)	
Infectious diseases/HIV AIDS	122 (48)
Other	130 (52)
Comorbidities, n (%)	
Cardiac disease states	107 (42)
Lung disease	76 (30)
Opportunistic infection	35 (14)
Malignancy	32 (13)
Psychiatric disorders	30 (12)
Diabetes mellitus	20 (8)
Renal insufficiency	19 (8)
Hepatic insufficiency	4 (2)
Hematologic disorders	2 (1)
Antiretroviral classes	
PI-based regimen	127 (50)
Integrase-based regimen	56 (22)
NNRTI-based regimen	48 (19)
Nucleoside sparing regimen	8 (3)
CCR5 or fusion inhibitor–based regimen	7 (3)
Triple nucleoside regimen	6 (2)

Abbreviations: ICU, intensive care unit; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Patient Outcomes

A total of 84 potential drug–drug interactions were identified as clinically significant, indicating an incidence rate of 1 in every 3 patient admissions. The types of CSDDIs and interacting pharmacologic drug classes are outlined in Table 2. Analysis of CSDDIs revealed that 95% occurred with protease inhibitors and 4% involved non-nucleoside reverse transcriptase inhibitors (NNRTIs). Atazanavir was the antiretroviral most frequently involved in drug errors. The CSDDIs observed in our population involved a variety of pharmacologic classes; however, the combination of atazanavir and acid-suppressive therapy was the most common contra-indicated drug–drug interaction followed by the combination of HMG CoA reductase inhibitors and protease inhibitors.

Table 2. Characterization of CSDDIs and Concomitant Medications Identified in These Interactions (N = 84).

Type of CSDDI, n (%)	
Contraindicated drug combinations	48 (57)
Lack of drug dosage modification	13 (16)
Lack of drug schedule modification	23 (27)
Drug classes, n (%)	
Acid-suppressive therapy	53 (63)
HMG-CoA reductase inhibitors	13 (15)
Anti-mycobacterials	4 (5)
Anti-gout therapy	3 (4)
Cardiac medications	3 (4)
Benzodiazepines	3 (4)
Antiretrovirals	2 (2)
Corticosteroids	1 (1)
Antifungals	1 (1)
Anticonvulsants	1 (1)

Abbreviation: CSDDI, clinically significant drug–drug interaction.

Of the 84 CSDDIs identified, 61 (73%) occurred within 24 hours of admission and among patients without virologic suppression (Figure 1). Clinical pharmacists identified and intervened on majority of the CSDDIs that occurred on patient admission through the institution's antiretroviral stewardship program. However, fewer than half of the CSDDIs that occurred after the initial screening process was performed were identified. All interventions made by clinical pharmacists were documented and communicated to the corresponding primary care team with an acceptance rate of 100%. Overall, 25 (30%) CSDDIs were missed by any health care provider and were administered to the patient. Forty-eight percent of the drug interactions occurred in patients with 2 or more of the selected comorbidities. Although acid-suppressive therapy remained the most common drug class associated with CSDDIs on admission and during the hospital course, cardiac medications, anti-gout therapy, and benzodiazepines represented a significant portion as well.

Discussion

With the advent of improved antiretroviral therapy, HIV has become a chronic manageable illness.¹ Consequently, patients require additional pharmacologic agents for comorbid conditions, resulting in the increased potential for complex drug interactions. Previous studies have revealed that antiretroviral errors and drug interactions are common in hospitalized patients with rates as high as 41%.⁵⁻¹¹ Furthermore, a retrospective study estimating the current burden associated with inpatient antiretroviral prescribing errors reported that 13% of 110 hospitalized patients with HIV were receiving a nonrecommended drug–drug combination.¹² Our findings support these observations as our

Figure 1. Timing of CSDDIs and the impact of clinical pharmacists. A total of 84 errors were identified.

incidence rate for CSDDIs was 33%, of which 57% were composed of a contraindicated drug combination.

Underrecognition of drug interactions by clinicians can place patients at risk for drug toxicity, and virologic failure. Drug resistance can develop as a consequence of drug errors especially if patients are being treated with NNRTIs, which tend to have a low genetic barrier to resistance.¹³ Arshad and colleagues conducted a survey composed of clinical scenarios based on antiretroviral prescribing errors, revealing a correct response rate of 37% among non-ID/HIV physicians and 93% for ID/HIV physicians.¹⁴ Furthermore, one study reported physician awareness of CSDDIs through correction of errors as 36%, suggesting an overall low rate of clinical vigilance.¹⁵ A pharmacist-based survey was also conducted to assess antiretroviral medication knowledge of pharmacists licensed in New York State, an urban area with a high prevalence of HIV and revealed a correct response rate of 60%.¹⁶ Failure to recognize drug interactions in the HIV patient population may be multifactorial, including lack of clinician knowledge of interactions, alert fatigue from computerized systems, and the complexity of antiretroviral therapy in general.

Clinical pharmacists play an essential role in medication error prevention, thereby improving patient outcomes and reducing health care–related costs.¹⁷⁻²⁰ Carcelero and colleagues revealed that the pharmacist made interventions in all of the 60 errors detected in hospitalized HIV-infected patients, in whom 92% of the interventions were accepted.¹¹ Additionally, medication reconciliation of ART by a pharmacist within 24 hours of admission reduced the error rate from 52% to 5% in a recent trial.¹⁸ Our study demonstrated that clinical pharmacists identified and intervened in 80% of CSDDIs on patient admission as a result of our institution's antiretroviral stewardship program. The majority of CSDDIs that were not identified on admission were atazanavir and acid-suppressive therapy of antacids automatically embedded into a detoxification order set.

Antiretroviral medication orders were only screened by a clinical pharmacist on admission as there was no continuous monitoring process in place by a specialized pharmacist during the hospital course. The lack of a clinical pharmacist continuing to follow all patients on ARVs coupled with the poor clinician familiarity with antiretroviral regimens in general may account for 57% of drug interactions that were missed during the hospitalization. Because our CPOE system has drug interaction alerts, one may argue that this should serve as a continuous review after the initial medication reconciliation for any addition of interacting medication orders. However, our study is consistent with literature suggesting knowledge gaps among health care providers and the additional need for educational modules as majority of errors were missed by all providers. To capture the full potential of the pharmacist and the antiretroviral stewardship program, a continuous clinical pharmacy review of medication orders should be developed. Interestingly, all the interventions made during hospitalization were attributed to clinical pharmacists rounding with other medical teams such as critical care, internal medicine, and family medicine opposed to other health care providers.

Some limitations of our study should be considered when interpreting our results and further extrapolating the clinical implications to other institutions. First, this is a single-center analysis and results may be representative of our institution only and not have generalizability to other hospital settings. Second, the lack of documentation by clinical pharmacists may have resulted in underreporting of interventions actually made. Our study did not capture information on the duration of the drug interaction, the time taken to correct the error, and interventions made by other health care providers.

Future directions to safeguard patients and prevent medication errors involve a multidisciplinary approach. Institutions should consider implementation of the following strategies to reduce the large number of antiretroviral-related medication errors occurring: (a) provider and staff pharmacist education modules on ART with a focus on common inpatient drug interactions, (b) increase the availability of reputable drug information resources including smart phone applications, (c) inclusion of ART drug interaction and intervention forms in computerized physician order entry systems, (d) regular audits of prescribing patterns, (e) encouragement of specialized services or teams for HIV/AIDS patients regardless of admitting diagnosis, and (f) continuous review of medication orders by specialized pharmacists especially during evening and weekend hours, which may be prone to more frequent drug errors due to limited staff.^{21,22}

In conclusion, CSDDIs are common among hospitalized HIV-infected individuals and occur most often on admission. Contraindicated combinations of medications related to protease inhibitor-based regimens represent the majority of the identified interactions. Results of our study indicate

that clinical pharmacists are critical in the prevention of CSDDIs on admission; however, additional strategies are warranted to reduce medication errors throughout the hospital course. Expansion of hospital-based antiretroviral stewardship programs may assist in the identification and ultimately prevention of antiretroviral medication errors.

Authors' Note

Tiffany E. Bias was a PGY-2 Infectious Diseases Pharmacy Resident at The Brooklyn Hospital Center, Brooklyn, New York, at time of the case. Data from this study were presented at the American Conference for the Treatment of HIV 2012; Denver, Colorado.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Agnes Cha is a consultant for Janssen Therapeutics. All other authors have nothing to disclose.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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