

Nucleoside Reverse-Transcriptase Inhibitor Dosing Errors in an Outpatient HIV Clinic in the Electronic Medical Record Era

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Information on antiretroviral dosing errors among health care providers for outpatient human immunodeficiency virus (HIV)-infected patients is lacking. We evaluated factors associated with nucleoside reverse-transcriptase inhibitor dosing errors in a university-based HIV clinic using an electronic medical record. Overall, older age, minority race or ethnicity, and didanosine use were related to such errors. Impaired renal function was more common in older patients and racial or ethnic minorities and, in conjunction with fixed-dose combination drugs, contributed to the higher rates of errors in nucleoside reverse-transcriptase inhibitor dosing. Understanding the factors related to nucleoside reverse-transcriptase inhibitor dosing errors is an important step in the building of preventive tools.

Antiretroviral prescribing errors can contribute to HIV treatment failure, the development of drug resistance, and increased toxicity when drugs are inappropriately dosed [1]. The use of an increasingly complex arsenal of drugs by non-HIV-infection specialists is postulated to contribute to antiretroviral dosing errors among HIV-infected inpatients [2–6], but little is known about the frequency of and factors related to dosing errors by specialists treating outpatients, particularly with newer coformulated nucleoside reverse-transcriptase inhibitors (NRTIs).

The advent of fixed-dose NRTI combination tablets with similar efficacy and a lower pill burden have led to the increased selection of these agents as dual-NRTI backbones for contem-

porary HIV therapy [7–9]. Combination NRTI preparations that are dose-adjusted for renally impaired patients are not currently available, creating the potential for dosing errors.

The present study assessed the frequency of and factors related to NRTI dosing errors in a university-based outpatient HIV clinic. Medications were prescribed by HIV-infection specialists using a locally programmed electronic medical record (EMR). We hypothesized that dosing errors would be more common among renally impaired patients and that the use of combination NRTIs would increase the risk for dosing errors in such patients.

Methods. The University of Alabama at Birmingham 1917 HIV/AIDS Clinic (Birmingham, AL) currently cares for >1400 HIV-infected patients. In 2004, the clinic deployed its own client-server-based point-of-care EMR, which was developed within the clinic to its own specifications. This system allows for real-time collection of medication, laboratory, clinical, and health care use data. The EMR contains readily accessible drug prescription information supplied by the Clinical Pharmacology Database from Gold Standard Multimedia. This information is used to process drug-drug interactions for new prescriptions as they are added to the EMR by primary health care providers. Health care providers have access to data needed to calculate creatinine clearance (using the Cockcroft-Gault equation) in the EMR, but at present, the EMR neither performs this calculation nor offers dosing recommendations [10].

Most uninsured patients fill antiretroviral prescriptions at our clinic pharmacy; other patients often choose to use outside pharmacies. University of Alabama at Birmingham 1917 Clinic pharmacists do not have access to renal function and weight data when filling prescriptions and, therefore, are not able to evaluate dosing errors in antiretroviral prescriptions on the basis of these parameters.

All new NRTI medication records added to the EMR system from 1 August 2004 through 15 September 2006 were identified. NRTIs were included in the analysis if data needed to calculate creatinine clearance by the Cockcroft-Gault equation were available to providers prior to the date of prescription. Only erroneous NRTI prescriptions not corrected within 24 h of the original entry in the EMR were included; errors corrected in less time were excluded from the analysis.

Two reviewers independently examined all NRTI prescriptions for dosing errors. Four categories of NRTI dosing errors were defined: (1) weight errors, defined as failure to adjust the dosage to a patient's weight; (2) renal errors, defined as failure to adjust the dosage to the patients' creatinine clearance value

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Table 1. Factors associated with dosing errors for 907 new nucleoside reverse-transcriptase inhibitor (NRTI) prescriptions at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic, August 2004–September 2006.

Variable	OR (95% CI)	
	Univariate analysis	Multivariable analysis
Drug administered, didanosine vs. other NRTI	10.11 (5.50–18.61)	11.51 (5.99–22.08)
Age, per 10 years	1.50 (1.13–1.98)	1.75 (1.28–2.38)
Sex, female vs. male	1.38 (0.75–2.53)	1.16 (0.58–2.31)
Health care provider, physicians vs. nurse practitioners/others	1.33 (0.76–2.33)	1.58 (0.85–2.94)
Race, black/other vs. white	2.68 (1.45–4.94)	2.69 (1.37–5.26)

NOTE. Analyses was performed using generalized estimated equations to account for nesting of multiple prescriptions within individual patients.

(calculated using the Cockcroft-Gault equation); (3) failure to adjust the didanosine dosage when used in conjunction with tenofovir; and (4) the use of nonstandard dosages (i.e., dosages not approved for use in the United States).

The primary outcome measure, presence of an NRTI dosing error, was a dichotomous measure. Study variables were evaluated using descriptive statistics to evaluate distributions and to ensure that the assumptions of statistical tests were met. Univariate and multivariable logistic regression models were used to evaluate the relationships between dosing errors among all NRTI prescriptions and demographic factors (age, sex, and race), provider type (physicians, including infectious-diseases fellows and attendings, vs. nurse practitioners), and the use of didanosine. To estimate the mediating effect of renal impairment (defined as a creatinine clearance <60 mL/min) on the statistically significant variables, an additional multivariable logistic regression model containing renal impairment was fit.

All analyses were performed at the level of the prescription and used generalized estimating equations for binary outcomes with a logit link for the analysis of correlated data to account for the nesting of multiple NRTI prescriptions within individual patients [11]. Using an exchangeable correlation structure generalized estimating equation provided standard errors adjusted for multiple prescriptions per patient (907 new NRTI prescriptions among 603 patients). The use of generalized estimating equations addresses problems associated with clustered data and yields consistent parameter estimates and robust standard errors [12].

A subanalysis involving patients with impaired renal function (creatinine clearance, <60 mL/min, according to Cockcroft-Gault equation) evaluated relationships between dosing errors and coformulated NRTIs, demographic factors (i.e., age, sex, and race), and provider type (physicians vs. nurse practitioners) using univariate and multivariable generalized estimating equation logistic regression. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute).

Results. During the study period, 922 NRTI prescription records were generated. Fifteen records were excluded (14 for discontinuation within <24 h and 1 for adefovir), and 907 NRTI records for 603 patients were analyzed. Patient characteristics were as follows: median age, 40 years; white race, 51%; male sex, 76%; uninsured, 28%; cared for by nurse practitioners, 49%; impaired renal function (creatinine clearance, <60 mL/min), 12%; median CD4 cell count, 256 cells/mm³; and median viral load, 4.0 log₁₀ copies/mL (CD4 and viral load values obtained ± 180 days from study initiation).

Overall, 53 (6%) of a total of 907 NRTI prescriptions and 41 (31%) of 132 prescriptions in renally impaired patients were dosed incorrectly. Among the 53 prescriptions overall that were dosed incorrectly, several had multiple flaws, and 63 total errors were detected. Among flawed prescriptions in the overall group, renal dosing errors were most common (40 [75%] of 53 errors). The NRTI most frequently misdosed was didanosine; 22 (28%) of 78 didanosine prescriptions were misdosed. Clinical consequences of incorrect dosing were observed in only 2 patients, including 1 patient with acute renal failure (which subsequently reversed) and 1 patient with nonfatal lactic acidosis syndrome.

In generalized estimating equation–adjusted multivariable logistic regression analysis, didanosine use (OR, 11.51; 95% CI, 5.99–22.1), advancing age (OR, 1.75 per 10 years; 95% CI, 1.28–2.38 per 10 years), and minority race or ethnicity (OR, 2.69; 95% CI, 1.37–5.26) were associated with dosing errors (table 1).

We postulated that the increased risk of dosing errors seen in older patients and racial or ethnic minorities was associated with worse renal function in these groups [13]. To evaluate this hypothesis, renal dysfunction (creatinine clearance, <60 mL/min) was added to the multivariable model. Using this model, the effects of age and race or ethnicity were attenuated and were no longer statistically significant, supporting our postulate (data not shown).

To test whether dosing errors were associated with the use of coformulated NRTIs in patients with renal impairment (cre-

atinine clearance, <60 mL/min), a subanalysis of both single and coformulated NRTI agents was performed. In multivariable analysis, coformulated NRTIs (OR, 3.73; 95% CI, 1.46–9.48) and race or ethnicity (OR, 8.12; 95% CI, 1.96–33.66) were associated with dosing errors.

Discussion. This study of NRTI prescriptions at a university-based HIV clinic using an EMR found errors in 6% of prescriptions overall and in 31% of prescriptions for patients with renal impairment. Previous studies, conducted among HIV-infected inpatients, have identified nonstandard dosing (i.e., overdosing, underdosing, or incorrect frequency of dosing) as the most common error type and have identified lamivudine as the NRTI most frequently associated with prescribing errors [2–6], compared with the findings in our study that a lack of dose adjustment for patients with renal impairment was the most common error and that didanosine was the NRTI most frequently associated with prescribing errors. Because didanosine was the only NRTI for which all 4 defined error types could occur, the complexity of didanosine dosing, relative to dosing with other NRTIs, might explain the higher risk of errors associated with this drug.

Use of coformulated NRTIs has increased over time, because they are associated with a reduced pill burden and provide the ability to simplify a patient's drug regimen. Compared with individual dosing of their constituent drugs, dosing of coformulated NRTIs was associated with nearly a 4-fold risk of dosing errors among renally impaired patients. Because formulations of coformulated NRTIs for patients with impaired renal function are not currently available, this is an important finding for providers prescribing these agents in clinical practice. Renal function should be monitored carefully, and caution must be exercised in treating patients with impaired renal function.

Incorrectly dosed antiretrovirals may lead to increased toxicity and accentuated adverse effects, which contribute to non-compliance, drug resistance, virologic failure, and clinical deterioration [1, 2, 4, 6, 14]. In our study, 2 patients experienced clinical adverse outcomes possibly related to incorrect dosing. In addition, prescription errors can lead to increased costs of care. Avoidance of the dosing errors observed in this study would have resulted in savings of \$80,884 from drug costs alone had accurately dosed NRTIs been used for the same duration, without taking into account the costs associated with treatment of any clinical sequelae of improper dosing.

These findings should be interpreted with respect to the limitations of this study. This study was conducted in a single academically affiliated HIV clinic; therefore, these findings might not be generalizable to other clinical settings or regions of the country. It is important to note that we detected dosing errors as recorded by providers in the EMR, but we cannot confirm that all erroneous prescriptions were filled by patients. We were

unable to link dosing errors to all adverse outcomes in the current study, although a future evaluation of the sequelae of dosing errors is planned.

Overall, our findings highlight the importance of renal impairment in NRTI dosing errors and identify the demographic groups at greatest risk for dosing errors. Coformulated NRTIs must be used carefully among renally impaired patients. Software that generates NRTI dosing recommendations on the basis of renal function, weight, coadministered drugs, and standard dosage recommendations may greatly reduce NRTI dosing errors in the health care system. Such software is currently under development at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic.

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