Short Communication: Relationship Between Contraindicated Drug–Drug Interactions and Subsequent Hospitalizations Among Patients Living with HIV Initiating Combination Antiretroviral Therapy

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Abstract

Persons living with HIV (PLWH) are at an increased risk of contraindicated drug–drug interactions (XDDIs), which may result in deleterious outcomes. Study objectives were to (1) compare the frequency of hospitalizations between patients with and without XDDIs and (2) determine if XDDIs are independently associated with hospitalizations in PLWH. A retrospective cohort study was performed among PLWH receiving care at the Upstate New York Veterans' Healthcare Administration or University of New Mexico Truman Health Services from 2000 to 2013. Hospitalization was defined as an admission to an inpatient hospital facility for ≥ 24 h. Of the 1329 patients evaluated, 149 (11.2%) patients were hospitalized within 1 year of antiretroviral therapy initiation. A significantly higher proportion of patients with XDDIs were hospitalized compared with those who did not have XDDIs (20.3% vs. 10.2%, risk ratio: 1.98, 95% confidence interval [CI]: 1.35–2.91, $p = .001$). In the multivariate Cox proportional hazards regression analyses, XDDIs were independently associated with hospitalizations (hazard ratio [HR]: 1.58; 95% CI: 1.00–2.48; $p = .05$), after adjustment for $CD4 < 242$ cells/mm³ (HR: 2.38; 95% CI: 1.72–3.33; $p < .001$), protease inhibitor (PI)-based regimen (HR: 1.35; 95% CI: 0.97–1.89; $p = .08$), recreational drug use (HR: 2.58, 95% CI: 1.85–3.58, $p < .001$), and non-HIV medications ≥ 10 (HR: 1.62; 95% CI: 0.97–2.69; $p = .07$). In this study an increased risk of hospitalization was observed among PLWH with XDDIs compared with those without XDDIs. This relationship persisted after adjustment for CD4 count, use of a PI-based regimen, recreational drug use, and number of non-HIV medications.

Keywords: HIV, antiretroviral therapy, drug interactions, hospitalization, polypharmacy

Introduction

OWING TO ADVANCES in antiretroviral therapy (ART), persons living with HIV (PLWH) are living longer and developing age-related comorbidities that require additional medication therapy. Polypharmacy, however, is associated with an increased risk of contraindicated drug–drug interactions (XDDIs) among PLWH.^{1–4}

Consequences of XDDIs in PLWH have not been thoroughly characterized in the literature, partly because XDDIs

can result in a multitude of varying effects and studying each individual XDDI would be difficult. Potential serious consequences include decreased ART exposure leading to incomplete virological suppression, emergence of drug resistance, disease progression, HIV transmission, as well as augmented non-HIV drug exposure resulting in medication-related toxicities with varying degrees of severity, potentially requiring hospitalization.^{5–7} Evaluating hospitalization as a consequence of XDDIs is a way to potentially capture the effect of multiple types of XDDIs. Hospitalizations are

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associated with considerable expenditures and are potentially avoidable when they are due to XDDIs.

Study objectives were to (1) compare the frequencies of hospitalization between PLWH with or without XDDIs and (2) determine if XDDIs are independently associated with hospitalizations in PLWH.

Materials and Methods

This was an analysis of PLWH evaluated in a previously published cohort study examining the relationship between ART regimen and XDDIs.² Patients were included if they received a traditional ART regimen and were seen at either the University of New Mexico Truman Health Services (UNM-THS) or Upstate New York Veterans' Healthcare Administration (VISN-2) between January 2000 and December 2013. Traditional ART regimen was defined as two nucleoside reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI).

Data collected are described in Jakeman *et al.* and, in brief, included sociodemographic characteristics, medications at time of ART initiation, comorbidities, and laboratory values.² For the current analyses, the primary exposure variable was XDDIs, defined as interactions with an X-rating (i.e., contraindicated) within Lexi-Interact.⁸ The outcome of interest was hospitalization within 1 year of initiating ART. Additional data collected for this study were time to hospitalization and admitting diagnosis. Only the first hospital admission of ≥ 24 h was captured during the study period.

Data analyses

Bivariate analyses were performed using chi-squared test/Fisher's exact test (categorical variables) or Mann-Whitney *U* test/Student's *t*-test (continuous variables). Classification and regression tree (CART) analyses were performed to identify breakpoints in continuous variables associated with hospitalizations. Kaplan-Meier plots were generated and survival distributions were compared using the log-rank test.

To determine if XDDIs were independently associated with hospitalizations during the study period, multivariate Cox proportional hazards regression analyses were performed. Variables associated ($p < .25$) with hospitalizations in the bivariate analyses were included at model entry and retained only if the resulting hazard ratio (HR) for XDDIs changed $\geq 10\%$ when removed. All analyses were performed using CART (Salford Systems, San Diego, CA) and SPSS v24.0 (IBM Corp., Armonk, NY).

Results

There were 1,329 PLWH meeting inclusion criteria. Most were men (91%) with a mean $\pm$ standard deviation age of 47.1 ± 11.4 years. The median (interquartile range [IQR]) number of comorbidities was 5 (3–7). Patients were using a median (IQR) of 3 (1–5) non-HIV medications and 128 patients (9.6%) had ≥ 1 XDDIs present.

Within 1 year of ART initiation, 149 patients (11.2%) were hospitalized. Admitting diagnoses were psychiatric/substance abuse (26.4%), infectious disease (18.9%), cardiac

(9.9%), gastrointestinal (9.4%), other (8.5%), respiratory (6.6%), orthopedic (6.1%), renal (4.7%), hepatitis (4.2%), cancer (2.8%), and neurological (2.4%) processes. Only four (13.3%) of infectious diseases-related admissions were due to opportunistic infections. The median (IQR) time to hospitalization from ART initiation was 52 (20–139) days. The median (IQR) times to hospitalization by regimen type were NNRTI: 44 (17–126), PI: 52 (18–139), and INSTI: 67 (39–171) days ($p > .05$ for each two-way comparison).

In bivariate analyses (Supplementary Table S1), several covariates were associated with hospitalization, including age, race, number of non-HIV medication, certain medication classes, and comorbidities. Among the continuous variables assessed, there were several CART-derived breakpoints identified where patients had a significant increase in likelihood of hospitalization. These included age ≥ 44 years, $CD4 < 242$ cells/mm³, comorbidities ≥ 10 , number of non-HIV medications ≥ 12 , and HIV RNA $\geq 143,000$ copies/mL.

A significantly higher proportion of patients with XDDIs were hospitalized compared with those without XDDIs (20.3% vs. 10.2%, risk ratio: 1.98, 95% confidence interval [CI]: 1.35–2.91, $p = .001$). The relationship between XDDIs and hospitalization is displayed in Figure 1. The proportion of individuals remaining free of hospitalization significantly differed between those with and without XDDIs for the study period.

In the multivariate Cox proportional hazards regression analyses, XDDIs were independently associated with hospitalizations (HR: 1.58; 95% CI: 1.00–2.48; $p = .05$), after adjustment for $CD4 < 242$ cells/mm³ (HR: 2.38; 95% CI: 1.72–3.33; $p < .001$), PI-based regimen (HR: 1.35; 95% CI: 0.97–1.89; $p = .08$), recreational drug use (HR: 2.58, 95% CI: 1.85–3.58, $p < .001$), and non-HIV medications ≥ 10 (HR: 1.62; 95% CI: 0.97–2.69; $p = .07$).

FIG. 1. Kaplan-Meier plot of probability of remaining free of hospitalizations during study period between patients with and without XDDIs. Patients with no XDDIs are denoted by + and patients with XDDIs are denoted by o with censoring occurring each time a symbol appears. Log-rank *p* value $< .001$. XDDI, contraindicated drug-drug interaction.

Discussion

We observed a high frequency (11.2%) of individuals who were hospitalized within the first year of starting ART. Patients with XDDIs had a higher likelihood of hospitalization than those without XDDIs (20.3% vs. 10.2%, $p = .001$; 88.3% power). The number needed to harm, calculated using the inverse of the risk difference, was 9.9. This meant that ~ 1 in 10 patients with an XDDI were hospitalized within 1 year of ART initiation. XDDIs were independently associated with hospitalization in the multivariable analyses after adjusting for several important confounders. Collectively, this would suggest that risk is multifactorial with an interplay between disease severity and medication regimen complexities (i.e., XDDIs, type of ART, and polypharmacy).

It is important to note that drug interaction databases, such as Lexi-Interact, are frequently updated. Some of the XDDIs from the original article by Jakeman *et al.*² have been reclassified as lower-tiered interactions. In a *post hoc* analysis, we reassessed all of the XDDIs from the original article and 72 patients still had an XDDI (December 2018). This did not alter our findings. The frequency of hospitalizations between those with and without reassessed XDDIs remained significantly different (19.4% vs. 10.7%, $p = .02$). We chose to present data on the initial population with XDDIs since those are the patients that would have been considered at risk of becoming hospitalized at the time of the original publication.²

Although HIV-related morbidity has decreased in PLWH due to highly effective ART, risk of hospitalization remains a concern. Within the literature, reported hospitalization rates are as high as 26.6 patients per 100 persons in PLWH.⁹ Consistent with our study, current literature suggests $\sim 7\%$ of patients on ART are prescribed a medication that is contraindicated.¹⁰ Clinicians can potentially reduce hospitalizations by addressing XDDIs.

There were limitations to this study. First, association is not causation. Although we observed a statistical association between XDDIs and hospitalizations, causality cannot be confirmed given the study design. Larger prospective studies that assess factors leading to hospitalizations would be needed to provide a stronger basis for causality. Second, a detection bias could have been present. Hospitalizations that occurred outside of UNM-THS or VISN-2 networks were not captured. Given the closed nature of VISN-2 and the association between UNM-Hospital and UNM-THS, the only comprehensive HIV clinic in Albuquerque during the evaluation period, we anticipate that this occurred at a low frequency and is unlikely to substantively change the results. Third, patients were followed for 1 year after starting ART. Our *a priori* assumption was that most adverse effects requiring hospitalization would have occurred within this time frame. We observed most hospitalizations occurring ≤ 180 days. However, adverse effects resulting from XDDIs may be a function of duration and intensity of exposure and the optimal observation window is unknown. Fourth, the admitting diagnoses may not have been associated with XDDIs. Although this study demonstrates that patients who have XDDIs have an increased risk of hospitalization, the cause for hospitalization may not align with XDDIs. Hospitalizations due to XDDIs are difficult to capture since the exact mechanisms are generally not fully known and adverse effects of XDDIs can be underappreciated. Fifth, the long study period in-

cluded patients taking NNRTI- and PI-based regimens. However, many contemporary regimens that are recommended for treatment-naïve individuals involve an INSTI. Although this could limit generalizability, there is considerable heterogeneity in drug-interaction potential within the INSTI class and future studies should assess the intraclass effect on hospitalizations. In addition, there are non-INSTI agents, such as the NNRTI doravirine, that can be used as initial treatment in certain clinical situations. Finally, XDDIs were only assessed upon initiation of ART. If a patient were to change medications after initiating ART or hospitalization, our analyses would not have captured these changes. Given the Joint Commission's Hospital National Patient Safety Goals and medication reconciliation performance elements, it is possible that these XDDIs were mitigated at the time of hospitalization.

We observed a statistical association between PLWH with XDDIs and hospitalizations. This relationship persisted after adjustment for several important confounders. Although not causal, this study reinforces the importance of evaluating patients' medications for XDDIs to potentially prevent hospitalization.

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Supplementary Material

Supplementary Table S1

References

1. Tseng A, Szadkowski L, Walmsley S, Salit I, Raboud J: Association of age with polypharmacy and risk of drug interactions with antiretroviral medications in HIV-positive patients. *Ann Pharmacother* 2013;47:1429–1439.
2. Jakeman B, Nasiri M, Ruth L, Morse C, Mahatme S, Patel N: Comparing the frequencies of contraindicated drug–drug interactions between differing antiretroviral regimens in HIV-infected patients. *Ann Pharmacother* 2017;51:365–372.
3. Marzolini C, Back D, Weber R, *et al.*: Ageing with HIV: Medication use and risk for potential drug–drug interactions. *J Antimicrob Chemother* 2011;66:2107–2111.

4. Patel N, Abdelsayed S, Veve M, Miller CD: Predictors of clinically significant drug–drug interactions among patients treated with nonnucleoside reverse transcriptase inhibitor-, protease inhibitor-, and raltegravir-based antiretroviral regimens. *Ann Pharmacother* 2011;45:317–324.
5. Okulicz JF, Grandits GA, French JA, *et al.*: Virologic outcomes of HAART with concurrent use of cytochrome p450 enzyme-inducing antiepileptics: A retrospective case control study. *AIDS Res Ther* 2011;8:18.
6. von Wyl V, Yerly S, Böni J, *et al.*: Factors associated with the emergence of k65r in patients with HIV-1 infection treated with combination antiretroviral therapy containing tenofovir. *Clin Infect Dis* 2008;46:1299–1309.
7. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA: Drug–drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* 2003;289:1652–1658.
8. *Lexicomp Online, Interactions Online. Clinical Drug Information*. Wolters Kluwer, Hudson, OH, 2013.
9. Bachhuber MA, Southern WN: Hospitalization rates of people living with HIV in the united states, 2009. *Public Health Rep* 2014;129:178–186.
10. Holtzman C, Armon C, Tedaldi E, *et al.*: Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. *J Gen Intern Med* 2013;28:1302–1310.

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