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

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Relationship between Contraindicated Drug-Drug Interactions and Subsequent Hospitalizations among Patients Living with HIV Initiating Combination Antiretroviral Therapy

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Running Title: Drug-Drug Interactions and Hospitalizations

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Abstract

People 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 2000-2013. Hospitalization was defined as an admission to an inpatient hospital facility for ≥ 24 hours. Of the 1329 patients evaluated, 149 (11.2%) patients were hospitalized within one year of ART initiation. A significantly higher proportion of patients with XDDIs were hospitalized compared to those who did not have XDDIs (20.3% versus 10.2%, Risk Ratio, RR: 1.98, 95% confidence interval, CI: 1.35–2.91, p=0.001). 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=0.05), after adjustment for CD4<242 cells/mm^3 (HR: 2.38; 95% CI: 1.72–3.33; p<0.001), protease inhibitor (PI)-based regimen (HR: 1.35; 95% CI: 0.97-1.89; p=0.08), recreational drug use (HR: 2.58, 95% CI: 1.85–3.58, p<0.001) and non-HIV medications ≥10 (HR: 1.62; 95% CI: 0.97–2.69; p=0.07). In this study an increased risk of hospitalization was observed among PLWH with XDDIs compared to 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.

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Introduction:

Due 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 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 virologic 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 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 (NRTIs) 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

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outcome of interest was hospitalization within one year of initiating ART. Additional data collected for the present study were time to hospitalization and admitting diagnosis. Only the first hospital admission of ≥24 hours was captured during the study period.

Data Analyses

Bivariate analyses were performed using Chi-square/Fisher's exact tests (categorical variables) or Mann-Whitney *U*/Student's t-tests (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 ($p<0.25$) with hospitalizations in the bivariate analyses were included at model entry and retained only if the resulting hazard ratio (HR) for XDDIs changed ≥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 male (91%) with a mean ± standard deviation (SD) age of 47.1 years ± 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 one 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 neurologic (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 ($p>0.05$ for each two-way comparison).

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In bivariate analyses (supplemental Table 1), 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/mm^3, comorbidities ≥10, number of non-HIV medications ≥12, and HIV RNA ≥143,000 copies/mL.

A significantly higher proportion of patients with XDDIs were hospitalized compared to those without XDDIs (20.3% versus 10.2%, Risk Ratio, RR: 1.98, 95% confidence interval, CI: 1.35–2.91, p=0.001). The relationship between XDDIs and hospitalization is displayed in Figure 1. The proportion of individuals remaining hospitalization-free significantly differed between those with and without XDDIs over the study period.

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=0.05), after adjustment for CD4 <242 cells/mm^3 (HR: 2.38; 95% CI: 1.72–3.33; p<0.001), PI-based regimen (HR: 1.35; 95% CI: 0.97-1.89; p=0.08), recreational drug use (HR: 2.58, 95% CI: 1.85–3.58, p <0.001) and non-HIV medications ≥10 (HR: 1.62; 95% CI: 0.97–2.69; p=0.07).

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% versus 10.2%, p = 0.001; 88.3% power). The number needed to harm, calculated using the inverse of the risk difference, was 9.9. This meant that approximately 1 in 10 patients with a XDDI were hospitalized within one 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, polypharmacy). It is important to note that drug interaction databases, such as Lexi-Interact, are frequently updated. Some of the XDDIs from the original paper by Jakeman et al[2] have been reclassified as lower-tiered

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interactions. In a *post-hoc* analysis, we re-assessed all of the XDDIs from the original paper and 72 patients still had a XDDI (December 2018). This did not alter our findings. The frequency of hospitalizations between those with and without re-assessed XDDIs remained significantly different (19.4% vs 10.7%, p=0.02). 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]

While 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 approximately 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. While 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 one 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. While 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 included patients taking NNRTI- and PI-based regimens. However, many contemporary

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regimens that are recommended for treatment naïve individuals involve an INSTI. While this could limit generalizability, there is considerable heterogeneity in drug-interaction potential within the INSTI class and future studies should assess the intra-class effect on hospitalizations. Additionally, there are emerging non-INSTI agents, such as the NNRTI doravirine, being considered for treatment-naïve patients. 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. While not causal, this study reinforces the importance of evaluating patients' medications for XDDIs to potentially prevent hospitalization.

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Conflicts of Interests/Disclosures

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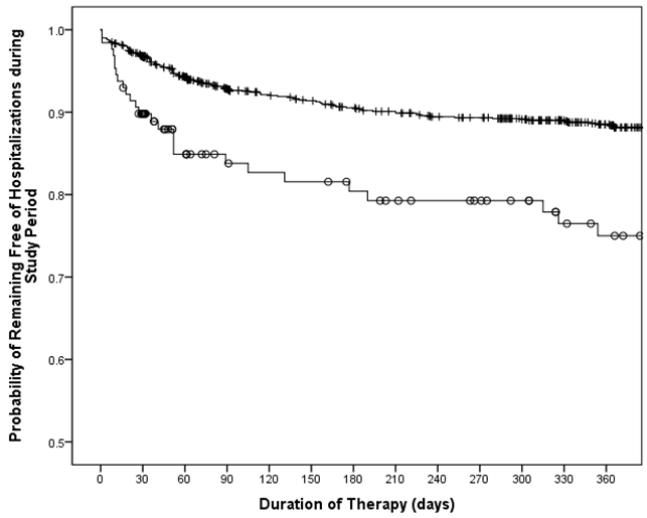

Figure title: Kaplan Meier Plot of Probability of Remaining Free of Hospitalizations during Study Period between Patients with and without Contraindicated Drug-Drug Interactions

Figure legend: Patients with no contraindicated drug-drug interactions are denoted by + and patients with contraindicated drug-drug interactions are denoted by ○ with censoring occurring each time a symbol appears. Log-rank p-value < 0.001.

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Supplemental Table 1: Clinical and Demographic Characteristics between Hospitalized and Non-Hospitalized Patients.

Covariate	No hospitalization (n = 1180)	Hospitalization (n = 149)	P-value
Sex, male (%)	1072 (90.8)	138 (92.6)	0.48
Age in years, mean ± SD	46.7 ± 11.5	49.9 ± 10.2	<0.001
• Age ≥ 44 years* (%)	744 (63.1)	117 (78.5)	<0.001
Race (%) • Black • Hispanic • Caucasian • Other	 212 (18.0) 46 (3.9) 494 (41.9) 428 (36.3)	 53 (35.6) 5 (3.4) 58 (38.9) 33 (22.1)	<0.001
CD4 count, median (interquartile range, IQR)	428 (260 – 657)	284 (117 – 502)	<0.001
• CD4 < 242*	315 (26.7)	73 (49)	<0.001
HIV RNA, median (IQR)	57 (49 – 11873)	77 (49 – 11705)	0.07
• HIV RNA ≥ 143,000*	50 (4.2)	12 (8.1)	0.04
Comorbidities, median (IQR)	5 (3 – 7)	6 (4 – 8)	0.002
• Comorbidities ≥ 10*	121 (10.3)	30 (20.1)	<0.001
Alcoholism	287 (24.3)	49 (32.9)	0.03
Bipolar/Mood Disorder	119 (10.1)	22 (14.8)	0.08

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Cancer	130 (11.0)	30 (20.1)	0.001
Chronic kidney disease	39 (3.3)	12 (8.1)	0.004
Chronic obstructive pulmonary disease	60 (5.1)	21 (14.1)	<0.001
Coronary artery disease	57 (4.8)	18 (12.1)	0.001
Dyslipidemia	407 (34.5)	33 (22.1)	0.003
Hepatitis C	227 (19.2)	46 (30.9)	0.001
Hypertension	335 (28.4)	55 (36.9)	0.03
Recreational Drugs	327 (27.7)	76 (51.0)	<0.001
Schizophrenia/Psychosis	42 (3.6)	12 (8.1)	0.009
Non-HIV Medications, Median (IQR)	2 (1 – 5)	4 (2 – 7)	<0.001
• Non-HIV Medications ≥ 10*	69 (5.8)	19 (12.8)	0.001
Medications			
Antiretroviral Medication Class			
• NNRTI	547 (46.4)	61 (40.9)	0.21
• PI	387 (32.8)	68 (45.6)	0.002
• INSTI	246 (32.8)	68 (45.6)	0.03
Alpha Blockers	42 (3.6)	13 (8.7)	0.003
Antiepileptic Medications	41 (3.5)	10 (6.7)	0.05

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Antifungals	94 (8.0)	24 (16.1)	0.001
Antipsychotic Medications	53 (4.5)	22 (14.8)	<0.001
Antiulcer Medications	130 (11.0)	28 (18.8)	0.006
Asthma Medications	137 (11.6)	30 (20.1)	0.003
Benzodiazepine	78 (6.6)	18 (12.1)	0.02
Beta Blockers	83 (7.0)	19 (12.8)	0.01
Narcotic Analgesics	152 (12.9)	37 (24.8)	<0.001
Non-ACEi/ARB Blood Pressure Medications	91 (7.7)	22 (14.8)	0.004
Non-Steroidal Anti-Inflammatory Drugs	116 (9.8)	27 (18.1)	0.002
Serotonin Antagonist and Reuptake Inhibitor	112 (9.5)	23 (15.4)	0.02
Selective Serotonin Reuptake Inhibitor/ Serotonin-Norepinephrine Reuptake Inhibitor	152 (12.9)	28 (18.8)	0.05

*Classification and regression tree (CART) – derived breakpoint

No statistical significant differences were found for the following comorbidities: anxiety, asthma, benign prostatic hyperplasia, bipolar disorder, cardiovascular disease, depression, diabetes, epilepsy/seizure, erectile dysfunction, insomnia, neurologic disorders, post-traumatic stress disorder

No statistical significant differences were found for the following medications/classes: antihistamine medications, oral antidiabetic medications, angiotensin converting enzyme inhibitors, and HMG-CoA reductase inhibitors.

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