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Polypharmacy, Drug-Drug Interactions, and Risk of Hospitalization among Veterans with HIV Taking 2-, 3-, and 4-Drug Antiretroviral Therapy Regimens

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Key Takeaways

- This analysis estimated KPDI Index scores, which quantify risk and severity of potential drug-drug interactions; people with HIV taking 3DRs and DTG/3TC ART regimens had the lowest median KPDI Index values.
- Where appropriate, selecting a simplified HIV treatment regimen with fewer ARVs may reduce the risk of drug-drug interactions and associated hospitalizations.

Introduction

- People aging with HIV face greater challenges with polypharmacy and an increased risk of drug-drug interactions.
- The approval of dolutegravir-based 2-drug regimens (dolutegravir/lamivudine [DTG/3TC] and dolutegravir/rilpivirine [DTG/RPV]) offers the option of effectively treating HIV with fewer overall agents.

Objectives

- This study estimates the association between antiretroviral (ARV) regimen, non-ARV medication count, and hospitalization using data from the Veteran Aging Cohort Study (VACS), an on-going multicenter, prospective cohort study of Veterans with and without HIV who receive care in the VA healthcare system [1].

Methods

Study Population

- Diagnosed with HIV-1 and prescribed >1 prescription for a 2-, 3-, or 4-drug regimen (DR) between 01OCT2020 and 30SEP2023.
  - 2-DR: DTG/3TC, DTG/RPV
  - 3-DR: integrase inhibitor, protease inhibitor, or non-nucleoside reverse transcriptase inhibitor plus 2 nucleoside reverse transcriptase inhibitors
  - 4-DR: 3-DR plus cobicistat or ritonavir
- Excluded individuals who had >15 non-ARV medications.

Known Pairwise Drug Interaction (KPDI) Index

- Identified overlapping prescriptions (≥1 day overlap) using pharmacy fill/refill data, and matched pairs of overlapping medications with KPDI from the DrugBank database [2].
- Created KPDI Index as an exposure-weighted sum of the average associations of individual KPDI with 1-year mortality [3].

Statistical Analysis

- VACS Index 2.0, a physiologic score that predicts the risk of all-cause mortality based on age, HIV biomarkers (CD4 and VL), and non-HIV biomarkers (hemoglobin, hepatitis C, fibrosis-4, eGFR, albumin, BMI, and white blood cell count), was used to measure frailty [4].
- The Cox regression model was used to estimate the association between non-ARV medication count and 1-year risk of hospitalization, adjusting for demographics, frailty, and KPDI Index.

Results

Table 1. Baseline characteristics, by regimen

	DTG/3TC (N=661)	DTG/RPV (N=866)	3-DR (N=15920)	4-DR (N=3214)
Age, years, n (%)				
18-49	164 (24.8)	105 (12.1)	4307 (27.1)	847 (26.4)
50-64	257 (38.9)	289 (33.4)	5690 (35.7)	1274 (39.6)
65+	240 (36.3)	472 (54.5)	5923 (37.2)	1093 (34.0)
Male, n (%)	624 (94.4)	841 (97.1)	15360 (96.5)	3111 (96.8)
Race & ethnicity, n (%)				
White, non-Hispanic	250 (37.8)	315 (36.4)	5715 (35.9)	1148 (35.7)
Black, non-Hispanic	296 (44.8)	419 (48.4)	7565 (47.5)	1605 (49.9)
Hispanic	69 (10.4)	85 (9.8)	1806 (11.3)	289 (9.0)
Other/Unknown[a]	46 (7.0)	47 (5.4)	834 (5.2)	172 (5.4)
Smoking, n (%)				
Current	129 (19.5)	157 (18.1)	3967 (24.9)	816 (25.4)
Former	211 (31.9)	262 (30.3)	4322 (27.1)	831 (25.9)
Never	276 (41.8)	334 (38.6)	5542 (34.8)	1103 (34.3)
Unknown	45 (6.8)	113 (13.0)	2089 (13.1)	464 (14.4)
Alcohol use and dependence, n (%)	128 (19.4)	142 (16.4)	3725 (23.4)	678 (21.1)
Drug use and dependence, n (%)	62 (9.4)	87 (10.0)	1987 (12.5)	383 (11.9)
Charlson Comorbidity Index[b], n (%)				
0	318 (48.1)	279 (32.2)	8256 (51.9)	1794 (55.8)
1-2	203 (30.7)	291 (33.6)	5284 (33.2)	1041 (32.4)
≥3	140 (21.2)	296 (34.2)	2380 (14.9)	379 (11.8)
VACS Index 2.0, median (IQR)	49.0 (39.0, 62.0)	60.0 (46.0, 74.0)	50.0 (39.0, 63.0)	48.0 (39.0, 61.0)
Non-ARV medication count, median (IQR)	5 (3, 9)	6 (3, 10)	5 (2, 9)	4 (2, 8)
KPDIs[c], median (IQR)	10 (3, 27)	14 (4, 31)	9 (2, 25)	11 (3, 26)
KPDI Index, median (IQR)	0.00 (-0.73, 2.03)	1.01 (0.00, 7.51)	0.06 (-0.55, 3.74)	0.98 (-0.12, 6.58)
All-cause mortality, 1-year, n (%)	10 (1.5)	34 (3.9)	386 (2.4)	62 (1.9)
Hospitalization, 1-year, n (%)	67 (10.1)	140 (16.2)	1857 (11.7)	344 (10.7)

[a] Other includes American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander.
[b] A weighted index of 16 conditions, with weights indicated in parentheses: myocardial infarction (1), congestive heart failure (1), peripheral vascular disease (1), cerebrovascular disease (1), dementia (1), chronic pulmonary disease (1), rheumatic disease (1), diabetes without chronic complications (1), diabetes with chronic complications (2), hemiplegia or paraplegia (2), mild to moderate renal disease (1), severe renal disease (3), malignancy (2), mild liver disease (1), moderate to severe liver disease (3), and metastatic solid tumor (6).
[c] Includes non-ARV/ARV KPDIs and non-ARV/non-ARV KPDIs.
Abbreviations: IQR=interquartile range.

Figure 1. Non-ARV medication count, VACS Index 2.0 score, and all-cause mortality rates by KPDI Index quintile for each regimen

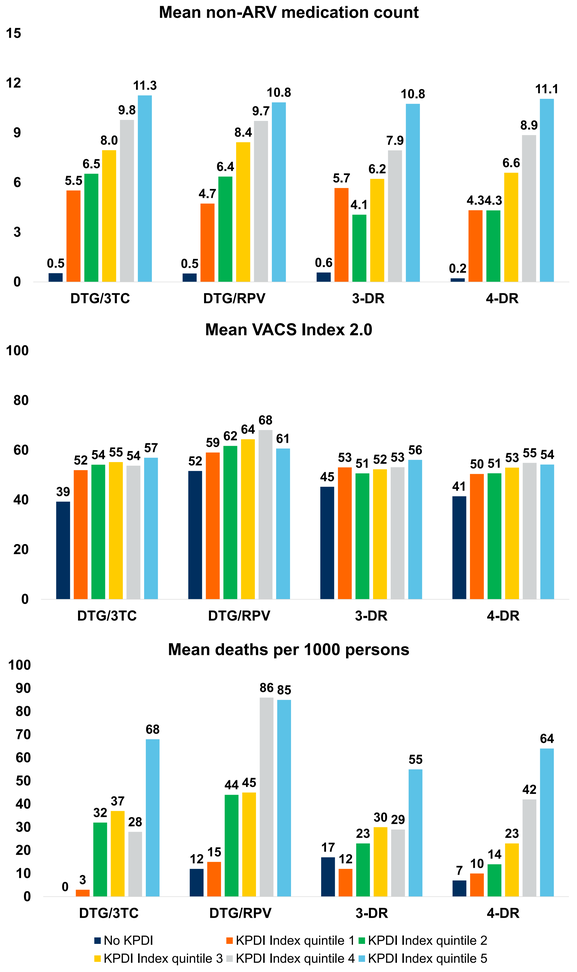

Table 2. Survival models of non-ARV medication count and 1-year risk of hospitalization

	Unadjusted HR (95% CI)	Adjusted for demographics HR (95% CI)	Additionally adjusted for frailty HR (95% CI)	Additionally adjusted for KPDI Index HR (95% CI)
Non-ARV medication count				
DTG/3TC	1.06 (1.01-1.12)	1.05 (1.00-1.11)	1.03 (0.97-1.09)	1.01 (0.95-1.08)
DTG/RPV	1.11 (1.07-1.16)	1.11 (1.07-1.15)	1.08 (1.04-1.12)	1.06 (1.02-1.11)
3-DR	1.09 (1.08-1.10)	1.08 (1.07-1.09)	1.07 (1.06-1.08)	1.06 (1.04-1.07)
4-DR	1.09 (1.07-1.12)	1.09 (1.06-1.11)	1.08 (1.05-1.10)	1.06 (1.03-1.09)
ART regimen (ref = DTG/3TC)				
DTG/RPV	1.46 (1.06-2.01)	1.37 (1.00-1.89)	1.16 (0.83-1.63)	1.14 (0.81-1.59)
3-DR	1.15 (0.89-1.49)	1.14 (0.88-1.47)	1.08 (0.82-1.42)	1.03 (0.78-1.36)
4-DR	1.10 (0.83-1.45)	1.08 (0.82-1.42)	1.09 (0.81-1.46)	1.02 (0.76-1.37)
Age per 10 years		1.10 (1.06-1.13)	0.77 (0.74-0.81)	0.78 (0.74-0.81)
Sex (ref = Female)				
Male		1.39 (1.09-1.79)	1.35 (1.05-1.74)	1.38 (1.07-1.77)
Race and ethnicity (ref = White, non-Hispanic)				
Black, non-Hispanic		1.28 (1.17-1.40)	1.15 (1.05-1.26)	1.17 (1.07-1.29)
Hispanic		1.14 (0.99-1.31)	1.12 (0.97-1.29)	1.13 (0.98-1.31)
Other/Unknown		0.99 (0.81-1.22)	0.93 (0.75-1.15)	0.94 (0.76-1.17)
VACS Index 2.0 per 5 points			1.17 (1.16-1.19)	1.17 (1.15-1.19)
Charlson Comorbidity Index (ref = 0)				
1-2			1.20 (1.08-1.33)	1.19 (1.07-1.32)
≥3			1.39 (1.23-1.57)	1.38 (1.22-1.56)
KPDI Index (ref = No KPDIs)				
Quintile 1				1.10 (0.92-1.32)
Quintile 2				1.35 (1.12-1.62)
Quintile 3				1.48 (1.21-1.80)
Quintile 4				1.44 (1.16-1.78)
Quintile 5				1.23 (0.95-1.59)

* A Wald test indicated no statistically significant difference in the effect of non-ARV medication count on the risk of hospitalization across regimens (p-value = 0.564).

Discussion

- Drug-drug interactions among people with HIV can significantly increase risk of hospitalization, particularly among older people and those with more comorbidities and polypharmacy.
- KPDI Index scores, estimating risk and severity of potential drug-drug interactions, varied by ART regimen (Table 1):
  - Individuals on 4-DR ART regimens had higher median KPDI than individuals on 3DRs and DTG/3TC.
  - Individuals on DTG/RPV also had higher median KPDI values, but this was potentially influenced by the older age, greater frailty (VACS Index 2.0), and more comorbidities in this group.
- Higher KPDI Index values were associated with greater risk of hospitalization (Table 2).
- After adjusting for demographics, frailty, and KPDI index, there was a statistically significant increase in hospitalization for each additional non-ARV prescribed for all regimens except DTG/3TC (Table 2). A simplified 2-DR of DTG/3TC may decrease the potential for drug-drug interactions as polypharmacy increases.
- Providers should collect comprehensive lists of medications when treating people with HIV and select ART regimens and non-ART medications to minimize polypharmacy and potential drug-drug interactions.
- Where appropriate, selecting a simplified HIV treatment regimen with fewer ARVs may help minimize the risk of drug-drug interactions and associated hospitalizations.

Acknowledgments: This research was sponsored by ViiV Healthcare. This study was supported by the Veterans Aging Cohort Study, which is a CHAART Cooperative Agreement funded by National Institutes of Health NIAAA (P01 AA029545, U24-AA020794, U01-AA020790, U24-AA022001, U01-AA026224, U10 AA013566-completed) and in kind by the US Department of Veterans Affairs. The VACS study was approved by the institutional review boards of Yale University (ref Yale: 0309025943) and VA Connecticut Healthcare System (ref VA: AJ0001). It has been granted a waiver of informed consent and is compliant with the Health Insurance Portability and Accountability Act. **Disclaimer:** The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

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