



Dexamethasone in hospitalised COVID-19 patients not on intensive respiratory support

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Although commonly used, dexamethasone within 48 h of admission was associated with increased 90-day mortality in patients hospitalised with COVID-19 not on oxygen and with no mortality benefit in patients on low-flow nasal cannula <https://bit.ly/3l2aqjb>

Cite this article as: Crothers K, DeFaccio R, Tate J, *et al.* Dexamethasone in hospitalised COVID-19 patients not on intensive respiratory support. *Eur Respir J* 2022; 60: 2102532 [DOI: 10.1183/13993003.02532-2021].

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This article has an editorial commentary: <https://doi.org/10.1183/13993003.03222-2021>

Received: 21 Sept 2021
Accepted: 17 Nov 2021

Abstract

Background Dexamethasone decreases mortality in coronavirus disease 2019 (COVID-19) patients on intensive respiratory support (IRS) but is of uncertain benefit if less severely ill. We determined whether early (within 48 h) dexamethasone was associated with mortality in patients hospitalised with COVID-19 not on IRS.

Methods We included patients admitted to US Veterans Affairs hospitals between 7 June 2020 and 31 May 2021 within 14 days after a positive test for severe acute respiratory syndrome coronavirus 2. Exclusions included recent prior corticosteroids and IRS within 48 h. We used inverse probability of treatment weighting (IPTW) to balance exposed and unexposed groups, and Cox proportional hazards models to determine 90-day all-cause mortality.

Results Of 19973 total patients (95% men, median age 71 years, 27% black), 15404 (77%) were without IRS within 48 h. Of these, 3514 out of 9450 (34%) patients on no oxygen received dexamethasone and 1042 (11%) died; 4472 out of 5954 (75%) patients on low-flow nasal cannula (NC) only received dexamethasone and 857 (14%) died. In IPTW stratified models, patients on no oxygen who received dexamethasone experienced 76% increased risk for 90-day mortality (hazard ratio (HR) 1.76, 95% CI 1.47–2.12); there was no association with mortality among patients on NC only (HR 1.08, 95% CI 0.86–1.36).

Conclusions In patients hospitalised with COVID-19, early initiation of dexamethasone was common and was associated with no mortality benefit among those on no oxygen or NC only in the first 48 h; instead, we found evidence of potential harm. These real-world findings do not support the use of early dexamethasone in hospitalised COVID-19 patients without IRS.

Introduction

Corticosteroids have emerged as an effective therapy for critically ill patients with coronavirus disease 2019 (COVID-19). The large UK RECOVERY randomised controlled trial of corticosteroids in COVID-19 patients demonstrated an overall 2.8% absolute decrease in mortality for patients treated with dexamethasone compared with usual care [1]. When stratified by respiratory support at randomisation,



dexamethasone was associated with greater benefit among those on invasive mechanical ventilation (IMV) *versus* supplemental oxygen (inclusive of noninvasive mechanical ventilation (NIV)); dexamethasone was not significantly associated with mortality in those not on oxygen. Dissemination of these and other results led to rapid uptake in the use of corticosteroids for COVID-19 patients, particularly those receiving more intensive respiratory support (IRS) such as high-flow nasal cannula (HFNC), NIV and IMV [2–6].

However, whether corticosteroids are beneficial in all patients with COVID-19 remains uncertain. The association between corticosteroids and outcomes among a wider group of patients with COVID-19, including a larger proportion without IRS than in the RECOVERY trial, has been mixed [7–11]. Variability in the effect of corticosteroids may be due to numerous factors. A recent Cochrane review concluded that systemic corticosteroids “probably reduce all-cause mortality slightly” but that there is an “urgent need for good-quality evidence for specific subgroups of disease severity, for which we propose level of respiratory support at randomisation” [12].

We determined the association between corticosteroids and 90-day all-cause mortality using real-world clinical data from the Dept of Veterans Affairs (VA), the largest integrated healthcare system in the US. In a racially and geographically diverse, national cohort of hospitalised COVID-19 patients, we first assessed patterns of corticosteroid receipt. As nearly all patients on IRS received corticosteroids, mainly dexamethasone, we focused on those who were without IRS. We used propensity score weighting to account for confounding by indication. We hypothesised that dexamethasone would not be associated with mortality benefit in patients without IRS.

Methods

Study design and population

We conducted an observational cohort study of 27 168 patients admitted to a VA hospital within 14 days after a positive PCR or antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between 7 June 2020 and 31 May 2021 (to allow 90-day follow-up on all) [13, 14]. Before 7 June 2020, corticosteroids were mostly initiated after 48 h. Index date was defined as date of presentation, including emergency room and time under observation status if not admitted directly. We determined length of stay by concatenating episodes of care separated by <24 h, with first episode on the index date as day 1. Due to changes in COVID-19 incidence and treatment protocols over time, we divided the observation period into seven time phases (table 1). Additional methodological details are provided in the supplementary material.

Our study was approved by the Institutional Review Boards of VA Puget Sound Health Care System (Seattle, WA, USA), and VA Connecticut Healthcare System and Yale University (New Haven, CT, USA), all of whom granted waivers of consent.

Exclusions

Of 27 168 patients, we excluded 7195, yielding a cohort of 19 973 patients (figure 1 and supplementary material). The most common exclusion was length of stay <48 h as these patients had insufficient time to receive dexamethasone, followed by any systemic corticosteroid exposure prior to the index date. This was defined as any corticosteroids within 14 days or receipt of corticosteroids for ≥ 14 days in the preceding 45 days. For mortality analyses, we further excluded 454 patients because they were at sites where no or all patients received dexamethasone (n=277), received hydroxychloroquine (n=89) or received vasopressors in the first 48 h (n=90), as these patients may have had an alternative indication for corticosteroids.

Exposures, outcomes and covariates

All data came from VA electronic health record extracts, which provide directly analysable demographics, comorbidities, medications, vital signs and laboratory results as well as notes that require text processing.

Dexamethasone exposure

Exposure was defined as at least one dose of oral or parenteral dexamethasone within 48 h after the index date as determined from barcode medication administration data. We also determined administration of other systemic corticosteroids (prednisone, prednisolone, methylprednisolone and/or hydrocortisone).

Outcome

The primary outcome was 90-day all-cause mortality, ascertained using inpatient records and VA death registry data to capture deaths outside of hospitalisation.

TABLE 1 Characteristics of patients[#] stratified by highest oxygen support during the first 48 h of hospitalisation for COVID-19

	Overall	Oxygen support first 48 h				
		None	NC only	Other/NIV	HFNC	IMV
Overall cohort	19973	9450	5954	2103	2051	415
Demographics						
Age, years						
<50	1760 (9)	1013 (11)	459 (8)	138 (7)	120 (6)	30 (7)
50–59	2361 (12)	1205 (13)	691 (12)	204 (10)	216 (11)	45 (11)
60–69	4677 (23)	2194 (23)	1340 (23)	490 (23)	536 (26)	117 (28)
70–79	7230 (36)	3155 (33)	2235 (38)	833 (40)	837 (41)	170 (41)
≥80	3945 (20)	1883 (20)	1229 (21)	438 (21)	342 (17)	53 (13)
Male	18993 (95)	8948 (95)	5651 (95)	2002 (95)	1991 (97)	401 (97)
Race						
White, non-Hispanic	11033 (55)	5019 (53)	3387 (57)	1253 (60)	1161 (57)	213 (51)
Black, non-Hispanic	5449 (27)	2854 (30)	1522 (26)	498 (24)	481 (23)	94 (23)
Hispanic	1738 (9)	773 (8)	526 (9)	167 (8)	216 (11)	56 (13)
Other	1144 (6)	510 (5)	330 (6)	134 (6)	134 (7)	36 (9)
Unknown	609 (3)	294 (3)	189 (3)	51 (2)	59 (3)	16 (4)
Phase (admission date)						
1 (7 June–11 July 2020)	1505 (8)	590 (6)	592 (10)	115 (5)	161 (8)	47 (11)
2 (12 July–15 Aug 2020)	1688 (8)	602 (6)	714 (12)	148 (7)	190 (9)	34 (8)
3 (16 Aug–31 Oct 2020)	2724 (14)	931 (10)	1145 (19)	254 (12)	319 (16)	75 (18)
4 (1 Nov–30 Nov 2020)	2842 (14)	891 (9)	1215 (20)	273 (13)	405 (20)	58 (14)
5 (1 Dec–31 Dec 2020)	4052 (20)	2204 (23)	866 (15)	519 (25)	387 (19)	76 (18)
6 (1 Jan–31 Jan 2021)	3588 (18)	2045 (22)	749 (13)	428 (20)	300 (15)	66 (16)
7 (1 Feb–31 May 2021)	3574 (18)	2187 (23)	673 (11)	366 (17)	289 (14)	59 (14)
Selected conditions						
Dementia	2357 (12)	1290 (14)	659 (11)	240 (11)	137 (7)	31 (7)
CHF	4356 (22)	1981 (21)	1339 (22)	555 (26)	401 (20)	80 (19)
COPD/asthma	5903 (30)	2433 (26)	1978 (33)	738 (35)	636 (31)	118 (28)
Charlson Comorbidity Index						
0	3718 (19)	1885 (20)	1034 (17)	316 (15)	407 (20)	76 (18)
1–2	6336 (32)	2939 (31)	1897 (32)	627 (30)	718 (35)	155 (37)
3–4	4622 (23)	2102 (22)	1457 (24)	520 (25)	457 (22)	86 (21)
≥5	5297 (27)	2524 (27)	1566 (26)	640 (30)	469 (23)	98 (24)
Medication use						
Corticosteroid, any systemic						
First 48 h	11970 (60)	3514 (37)	4627 (78)	1521 (72)	1923 (94)	385 (93)
Later than 48 h	1607 (8)	870 (9)	467 (8)	202 (10)	47 (2)	21 (5)
None	6396 (32)	5066 (54)	860 (14)	380 (18)	81 (4)	9 (2)
Dexamethasone						
First 48 h	11361 (57)	3198 (34)	4472 (75)	1447 (69)	1871 (91)	373 (90)
Later than 48 h	1586 (8)	833 (9)	473 (8)	201 (10)	55 (3)	24 (6)
None	7026 (35)	5419 (57)	1009 (17)	455 (22)	125 (6)	18 (4)
Remdesivir						
First 48 h	9533 (48)	2716 (29)	3706 (62)	1197 (57)	1637 (80)	277 (67)
Later than 48 h	1607 (8)	768 (8)	532 (9)	188 (9)	88 (4)	31 (7)
None	8833 (44)	5966 (63)	1716 (29)	718 (34)	326 (16)	107 (26)
Prophylactic anticoagulant						
First 48 h	14708 (74)	6820 (72)	4502 (76)	1576 (75)	1514 (74)	296 (71)
Later than 48 h	1752 (9)	842 (9)	463 (8)	183 (9)	212 (10)	52 (13)
None	3513 (18)	1788 (19)	989 (17)	344 (16)	325 (16)	67 (16)
Therapeutic anticoagulant						
First 48 h	4550 (23)	1815 (19)	1446 (24)	516 (25)	647 (32)	126 (30)
Later than 48 h	13921 (70)	6627 (70)	4220 (71)	1478 (70)	1333 (65)	263 (63)
None	1502 (8)	1008 (11)	288 (5)	109 (5)	71 (3)	26 (6)
Vasopressors						
First 48 h	391 (2)	55 (1)	35 (1)	22 (1)	42 (2)	237 (57)
Later than 48 h	1197 (6)	272 (3)	272 (5)	132 (6)	417 (20)	104 (25)
None	18385 (92)	9123 (97)	5647 (95)	1949 (93)	1592 (78)	74 (18)

Continued

TABLE 1 Continued

	Overall	Oxygen support first 48 h				
		None	NC only	Other/NIV	HFNC	IMV
Intensive care						
First 48 h	4143 (21)	1172 (12)	884 (15)	427 (20)	1275 (62)	385 (93)
Later than 48 h	1468 (7)	465 (5)	554 (9)	211 (10)	221 (11)	17 (4)
None	14362 (72)	7813 (83)	4516 (76)	1465 (70)	555 (27)	13 (3)
Intubation						
First 48 h	415 (2)	0 (0)	0 (0)	0 (0)	0 (0)	415 (100)
Later than 48 h	1078 (5)	257 (3)	259 (4)	121 (6)	441 (22)	0 (0)
None	18480 (93)	9193 (97)	5695 (96)	1982 (94)	1610 (78)	0 (0)
Hospital length of stay, days						
<7	10604 (53)	5633 (60)	3316 (56)	1098 (52)	501 (24)	56 (13)
7–13	5365 (27)	2248 (24)	1613 (27)	602 (29)	788 (38)	114 (27)
≥14	4004 (20)	1569 (17)	1025 (17)	403 (19)	762 (37)	245 (59)
Mortality (unadjusted, cumulative incidence)						
30 days	2587 (13)	724 (8)	648 (11)	351 (17)	648 (32)	210 (51)
60 days	3125 (16)	939 (10)	799 (13)	421 (20)	731 (36)	234 (56)
90 days	3340 (17)	1041 (11)	857 (14)	448 (21)	752 (37)	241 (58)

Data are presented as n or n (%). NC: nasal cannula; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease. #: the 19973 patients stratified by respiratory support in figure 1, prior to additional exclusions for mortality analyses among those on no intensive respiratory support.

Respiratory support

We stratified patients by highest level of respiratory support during the initial 48 h of hospitalisation into the following categories: 1) no oxygen support; 2) low-flow oxygen *via* nasal cannula (NC) that was not identified as a high-flow or other delivery device; 3) other supplemental oxygen/NIV, including face mask, nonrebreather mask or other delivery not identifiable as low-flow NC or high-flow; 4) high-flow oxygen/HFNC; and 5) IMV. When no evidence of oxygen supplementation was found, patients were classified as without oxygen (category 1). IMV was identified by structured data sources (International Classification of Diseases, 10th Revision procedure and Current Procedural Terminology codes). Categories 2–4 were assessed from unstructured text notes using natural language processing, validated with manual chart review to identify key terms indicative of respiratory support (supplementary material).

Covariates

We obtained age, race, ethnicity, sex, comorbidities, additional medications, vital signs and laboratory results. We calculated the Charlson Comorbidity Index (CCI) [15] and the Veterans Health Administration COVID-19 (VACO) Index (table 2 and supplementary table E1) [16]. We focused on routinely collected laboratory tests that have been associated with increased mortality in COVID-19 [17], including albumin, liver function, lactate, white blood cell count and creatinine (table 2 and supplementary table E1). We selected the worst laboratory tests, temperature, blood pressure and pulse oximetry within the initial 48 h. To account for potential effects of co-prescribed medications, we included use of remdesivir and prophylactic anticoagulants within the initial 48 h [14]. Intensive care unit (ICU) admission was determined using VA bedsection codes [14, 18]. As there was generally very little missing data (<5%), an explicit level for missingness was used for selected covariates.

Statistical analysis

We first compared COVID-19 patients by the five respiratory support categories using summary statistics (table 1). Because nearly all patients on IMV or HFNC received dexamethasone, there was insufficient variability to allow generation of propensity score weights. Category 3 (other/NIV) was heterogeneous with respect to respiratory support used and illness severity. For these reasons, as well as the greater clinical equipoise, we restricted our analysis to patients without IRS (specifically, no oxygen or low-flow NC support only).

In those without IRS, we compared mortality by exposure to dexamethasone overall and stratified by NC. To account for confounding by indication, we generated propensity scores for the probability of receiving dexamethasone in the first 48 h using logistic regression. Models included covariates associated with dexamethasone exposure and mortality: comorbidities, laboratory results, vital signs, site utilisation

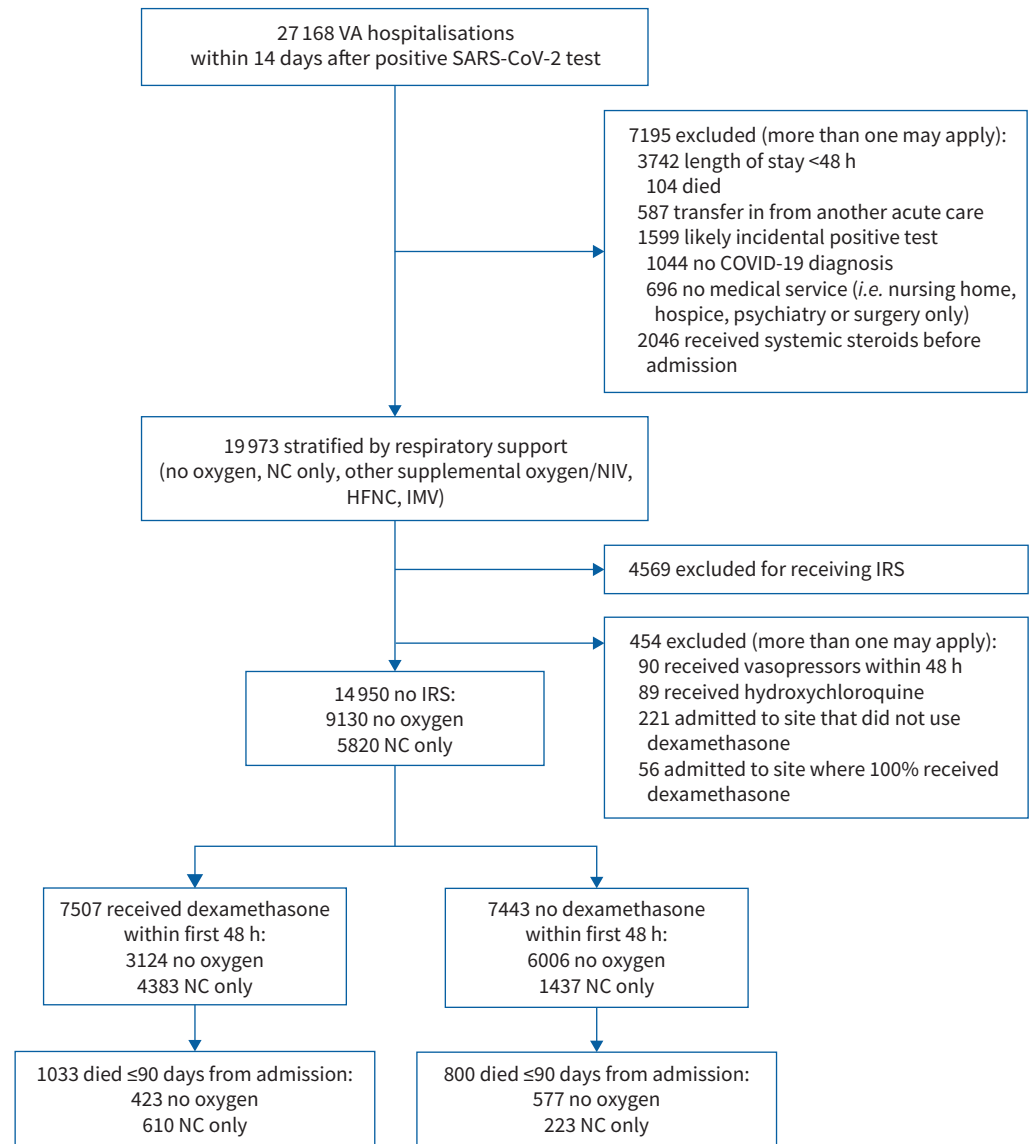


FIGURE 1 Derivation of the study population. Time period of admission from 7 June 2020 through 31 May 2021. VA: Veterans Affairs; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; IRS: intensive respiratory support; NC: nasal cannula; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation.

patterns, co-medications and the time phases (table 2 and supplementary table E1). We constructed inverse probability of treatment weights from propensity scores for each patient to create pseudo-populations with balanced distributions of covariates [19]. In our primary analysis, we used average treatment effect (ATE) weights, reflecting the overall population from which the sample was taken. We used stabilised weights and trimmed from analysis the 10 patients with the most extreme high and low weights [20]. We calculated standardised mean differences between treatment groups and considered ≤ 0.2 as balanced. Using days since index date as the time scale, we compared differences in survival using weighted Kaplan–Meier plots [21] and estimated the ATE using Cox proportional hazards models to generate hazard ratios (HR) and 95% confidence limits using a robust variance estimator. We included the VACO Index in outcome models to further account for residual confounding [16].

Subgroup and sensitivity analyses

In subgroup analyses, we excluded patients admitted to the ICU within the first 48 h and restricted to those aged ≥ 70 years. In sensitivity analyses, we limited the window between a positive SARS-CoV-2 test to

TABLE 2 Characteristics of the combined cohort of patients without oxygen or on nasal cannula only after inverse probability of treatment weighting for estimating the average treatment effect in the total population (ATE models)

	Dexamethasone		SMD
	No	Yes	
Cohort	11 963.6	12 887.0	
Age, years			
<50	1082.7 (9.0)	1142.0 (8.9)	-0.002
50–59	1367.3 (11.4)	1551.5 (12.0)	0.006
60–69	2800.3 (23.4)	2959.5 (23.0)	-0.004
70–79	4206.0 (35.2)	4662.9 (36.2)	0.010
≥80	2507.4 (21.0)	2571.2 (20.0)	-0.010
Male	11 323.9 (94.7)	12 237.6 (95.0)	0.003
Race			
White, non-Hispanic	6430.7 (53.8)	7170.0 (55.6)	0.019
Black, non-Hispanic	3567.0 (29.8)	3507.0 (27.2)	-0.026
Hispanic	940.7 (7.9)	1120.5 (8.7)	0.008
Other	666.5 (5.6)	673.5 (5.2)	-0.003
Unknown	358.7 (3.0)	416.1 (3.2)	0.002
Phase (admission date)			
1 (7 June–11 July 2020)	1112.0 (9.3)	865.6 (6.7)	-0.026
2 (12 July–15 Aug 2020)	1063.1 (8.9)	1074.1 (8.3)	-0.006
3 (16 Aug–31 Oct 2020)	1764.3 (14.7)	1784.1 (13.8)	-0.009
4 (1 Nov–30 Nov 2020)	1567.9 (13.1)	1894.9 (14.7)	0.016
5 (1 Dec–31 Dec 2020)	2347.1 (19.6)	2693.3 (20.9)	0.013
6 (1 Jan–31 Jan 2021)	1998.7 (16.7)	2315.6 (18.0)	0.013
7 (1 Feb–31 May 2021)	2110.5 (17.6)	2259.4 (17.5)	-0.001
Site dexamethasone prescribing			
Low	3173.2 (26.5)	2421.9 (18.8)	-0.077
Medium	7115.5 (59.5)	7480.7 (58.0)	-0.014
High	1674.9 (14.0)	2984.5 (23.2)	0.092
Smoking status			
Unknown	384.8 (3.2)	384.5 (3.0)	-0.002
Never-smoker	4080.9 (34.1)	4491.1 (34.8)	0.007
Ex-smoker	4576.0 (38.2)	5277.6 (41.0)	0.027
Current smoker	2921.8 (24.4)	2734.0 (21.2)	-0.032
AUDIT-C score			
Unknown	441.7 (3.7)	431.4 (3.3)	-0.003
0	7978.6 (66.7)	8489.5 (65.9)	-0.008
1–3	2456.4 (20.5)	2962.0 (23.0)	0.025
4–7	734.5 (6.1)	719.6 (5.6)	-0.006
≥8	352.5 (2.9)	284.6 (2.2)	-0.007
Comorbidities			
Myocardial infarction	1078.8 (9.0)	1096.0 (8.5)	-0.005
CHF	2678.1 (22.4)	2865.7 (22.2)	-0.001
CVD	2113.7 (17.7)	2094.2 (16.3)	-0.014
Dementia	1748.8 (14.6)	1448.8 (11.2)	-0.034
COPD	3131.2 (26.2)	3760.1 (29.2)	0.030
Rheumatoid arthritis	186.2 (1.6)	206.8 (1.6)	0.000
Peptic ulcer	272.0 (2.3)	270.9 (2.1)	-0.002
Liver disease, mild	1504.2 (12.6)	1452.8 (11.3)	-0.013
Diabetes, uncomplicated	5683.8 (47.5)	6182.6 (48.0)	0.005
Diabetes, complicated	3873.3 (32.4)	3969.4 (30.8)	-0.016
Hemi- or paraplegia	341.0 (2.9)	285.3 (2.2)	-0.006
Renal disease	3228.2 (27.0)	3422.0 (26.6)	-0.004
Liver disease, moderate–severe	226.5 (1.9)	205.6 (1.6)	-0.003
Metastatic cancer	293.0 (2.4)	256.2 (2.0)	-0.005
HIV	153.5 (1.3)	150.8 (1.2)	-0.001
Charlson Comorbidity Index			
0	2212.6 (18.5)	2412.7 (18.7)	0.002
1–2	3634.1 (30.4)	4065.3 (31.5)	0.012

Continued

TABLE 2 Continued			
	Dexamethasone		SMD
	No	Yes	
3–4	2780.0 (23.2)	3018.6 (23.4)	0.002
≥5	3336.9 (27.9)	3390.4 (26.3)	−0.016
Number of doctors (prior year)			
0	4815.2 (40.2)	5033.7 (39.1)	−0.012
1	3240.7 (27.1)	3585.3 (27.8)	0.007
2–4	3564.9 (29.8)	3946.2 (30.6)	0.008
≥5	342.8 (2.9)	321.8 (2.5)	−0.004
Speciality clinics attended			
Cardiology	3108.1 (26.0)	3528.6 (27.4)	0.014
Coagulation	192.2 (1.6)	214.1 (1.7)	0.001
Pacemaker	428.2 (3.6)	424.7 (3.3)	−0.003
Dialysis	206.6 (1.7)	218.6 (1.7)	0.000
Gastroenterology	1147.9 (9.6)	1277.5 (9.9)	0.003
Hepatology	426.1 (3.6)	359.0 (2.8)	−0.008
Homeless	817.4 (6.8)	596.1 (4.6)	−0.022
Co-medications			
Prophylactic anticoagulants, first 48 h	8665.8 (72.4)	9589.0 (74.4)	0.020
Remdesivir, first 48 h	3664.1 (30.6)	6050.4 (46.9)	0.163
Laboratory values			
Albumin, g·dL ^{−1}			
≥3.5	4070.5 (34.0)	3839.1 (29.8)	−0.042
3–3.49	3935.0 (32.9)	4550.6 (35.3)	0.024
<3	3361.2 (28.1)	3986.4 (30.9)	0.028
Missing	596.9 (5.0)	510.9 (4.0)	−0.010
Alanine aminotransferase, IU·L ^{−1}			
<20	3461.5 (28.9)	3151.6 (24.5)	−0.045
20–39	4786.1 (40.0)	5418.4 (42.0)	0.020
≥40	3195.2 (26.7)	3995.4 (31.0)	0.043
Missing	520.8 (4.4)	321.6 (2.5)	−0.019
Aspartate aminotransferase, IU·L ^{−1}			
<20	2285.0 (19.1)	1586.6 (12.3)	−0.068
20–39	5309.3 (44.4)	5767.2 (44.8)	0.004
≥40	4369.3 (36.5)	5533.2 (42.9)	0.064
Creatinine, mg·dL ^{−1}			
<1.2	5238.4 (43.8)	5616.3 (43.6)	−0.002
1.2–1.99	4423.3 (37.0)	4862.7 (37.7)	0.008
≥2	2196.7 (18.4)	2367.4 (18.4)	0.000
Missing	105.2 (0.9)	40.6 (0.3)	−0.006
Fibrosis-4 index			
<1.45	2289.3 (19.1)	2087.1 (16.2)	−0.029
1.45–3.25	4791.3 (40.0)	5341.2 (41.4)	0.014
>3.25	4308.2 (36.0)	5107.3 (39.6)	0.036
Missing	574.8 (4.8)	351.5 (2.7)	−0.021
Lactate, mmol·L ^{−1}			
<1.2	1764.8 (14.8)	2009.6 (15.6)	0.008
1.2–<2.0	3020.2 (25.2)	3732.9 (29.0)	0.037
≥2.0	1626.1 (13.6)	2027.5 (15.7)	0.021
Missing	5552.5 (46.4)	5117.0 (39.7)	−0.067
Platelet count, μL ^{−1}			
≥150	7892.8 (66.0)	8381.1 (65.0)	−0.009
<150	3988.7 (33.3)	4482.4 (34.8)	0.014
Missing	82.1 (0.7)	23.6 (0.2)	−0.005
Total bilirubin, mg·dL ^{−1}			
<1	8779.4 (73.4)	9524.9 (73.9)	0.005
1–1.2	1004.1 (8.4)	1187.0 (9.2)	0.008
>1.2	1664.4 (13.9)	1857.2 (14.4)	0.005
Missing	515.7 (4.3)	318.0 (2.5)	−0.018

Continued

TABLE 2 Continued

	Dexamethasone		SMD
	No	Yes	
White blood cell count, μL^{-1}			
4–10	6641.3 (55.5)	6266.6 (48.6)	–0.069
<4	3139.3 (26.2)	3812.3 (29.6)	0.033
>10	2183.1 (18.2)	2808.2 (21.8)	0.035
C-reactive protein measured	6674.9 (55.8)	7810.0 (60.6)	0.048
D-dimer measured	8791.6 (73.5)	10 350.8 (80.3)	0.068
Vital signs			
Highest temperature, °F (°C)			
<99 (<37.2)	4466.1 (37.3)	4443.3 (34.5)	–0.029
99–100 (37.2–37.8)	2919.2 (24.4)	3106.8 (24.1)	–0.003
100–102 (38.3–38.9)	3077.0 (25.7)	3567.9 (27.7)	0.020
>102 (>38.9)	1459.9 (12.2)	1719.3 (13.3)	0.011
Missing	41.4 (0.3)	49.7 (0.4)	0.000
Mean arterial pressure, mmHg			
<60	320.4 (2.7)	282.2 (2.2)	–0.005
60–69	1627.5 (13.6)	1682.2 (13.1)	–0.006
70–89	7805.2 (65.2)	8623.3 (66.9)	0.017
≥ 90	2183.3 (18.2)	2266.1 (17.6)	–0.007
Missing	27.2 (0.2)	33.3 (0.3)	0.000
Lowest oxygen saturation, %			
<88	643.0 (5.4)	1099.6 (8.5)	0.032
88–92	4961.0 (41.5)	6515.0 (50.6)	0.091
93–95	4459.7 (37.3)	3888.3 (30.2)	–0.071
≥ 96	1651.6 (13.8)	1106.9 (8.6)	–0.052
Missing	248.3 (2.1)	277.2 (2.2)	0.001

Data are presented as n or n (%) for the pseudo-populations. SMD: standardised mean difference; AUDIT-C: Alcohol Use Disorders Identification Test-Concise; CHF: congestive heart failure; CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease.

within 24 or 48 h of the index date. In addition, we considered exposure to any systemic corticosteroids within the first 48 h. We also evaluated the average treatment effect among the treated (ATT) population that received dexamethasone in weighted Cox proportional hazards models, and constructed unweighted, but multivariable adjusted models for all primary and subgroup analyses (supplementary tables E2 and E3).

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $p < 0.05$.

Study findings are reported as per the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (supplementary table E4).

Results

Patient characteristics, dexamethasone exposure and respiratory support

Patients hospitalised during the seven phases ($n=19973$) were mostly male (95%). Median (interquartile range) age was 71 (62–77) years; 55% were non-Hispanic White, 27% non-Hispanic Black and 9% Hispanic (table 1). Most patients (83%) were admitted within 1 day after a positive SARS-CoV-2 test. More than half overall (60%) received corticosteroids within 48 h, of whom 95% received dexamethasone. Concurrent remdesivir and prophylactic anticoagulants initiated within 48 h of admission were more common in those who received dexamethasone than in those who did not (remdesivir 43% versus 13% and anticoagulants 46% versus 10%, respectively).

When stratified by highest level of respiratory support in the first 48 h of admission, 77% of patients were on either no oxygen (47%) or NC only (30%) (table 1). Dexamethasone was administered to 34% without oxygen, 75% on NC only, 69% on other supplemental oxygen/NIV, 91% on HFNC and 90% on IMV.

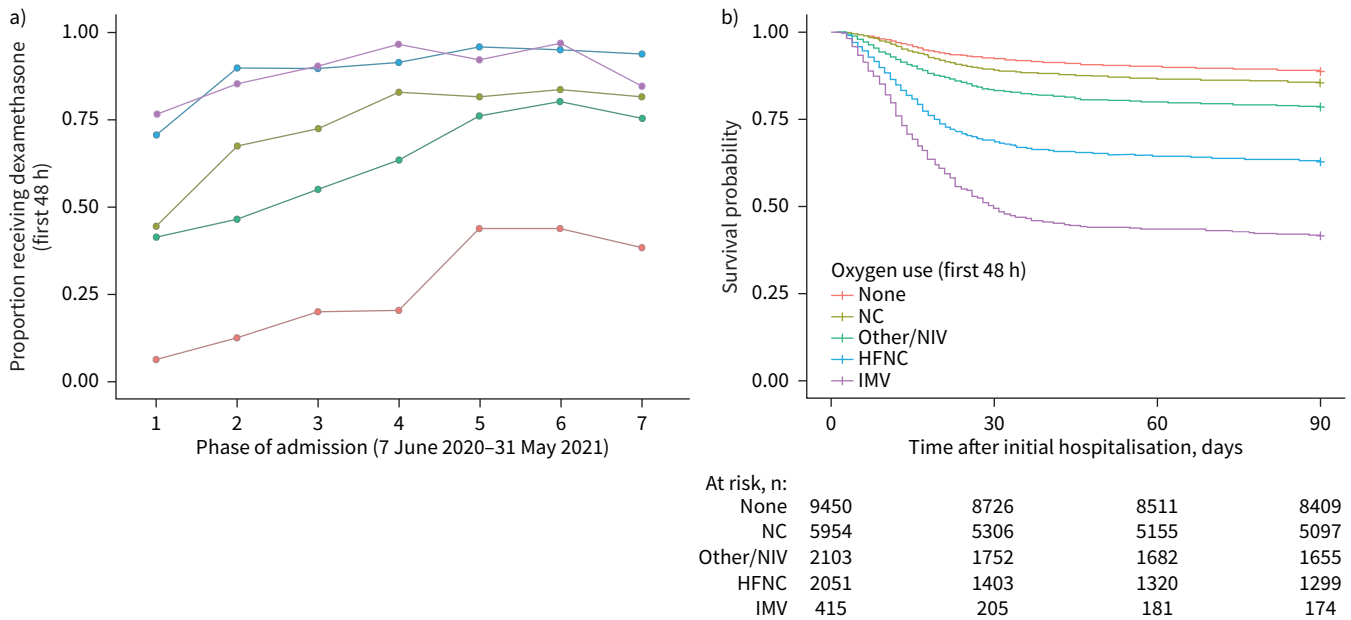


FIGURE 2 a) Proportion of patients hospitalised for COVID-19 exposed to dexamethasone and b) unadjusted Kaplan–Meier survival curves for 90-day mortality according to respiratory support level. Phase 1: 7 June–11 July 2020; phase 2: 12 July–15 Aug 2020; phase 3: 16 Aug–31 Oct 2020; phase 4: 1 Nov–30 Nov 2020; phase 5: 1 Dec–31 Dec 2020; phase 6: 1 Jan–31 Jan 2021; phase 7: 1 Feb–31 May 2021. Note that the RECOVERY trial was halted on 8 June 2020, with a press release of results on 16 June 2020 (www.recoverytrial.net) [1]. NC: nasal cannula; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation.

Use of dexamethasone generally increased over time (figure 2a). Overall, unadjusted 90-day mortality was 17% and varied by respiratory support (figure 2b).

Dexamethasone and mortality in patients without IRS

Among patients without IRS, the median (IQR) duration of inpatient dexamethasone administration was 5 (3–8) days in patients without oxygen and 6 (4–9) days in patients on NC only. These were similar to hospital length of stay (table 1). Only 341 (3.6%) and 115 (1.9%) patients, respectively, received only 1 day of inpatient dexamethasone.

After propensity score weighting, our samples (pseudo-populations) were well balanced (table 2 and supplementary table E1). Among patients without oxygen, weighted Kaplan–Meier curves (figure 3a) show that those who received dexamethasone had higher mortality over 90 days than those who did not,

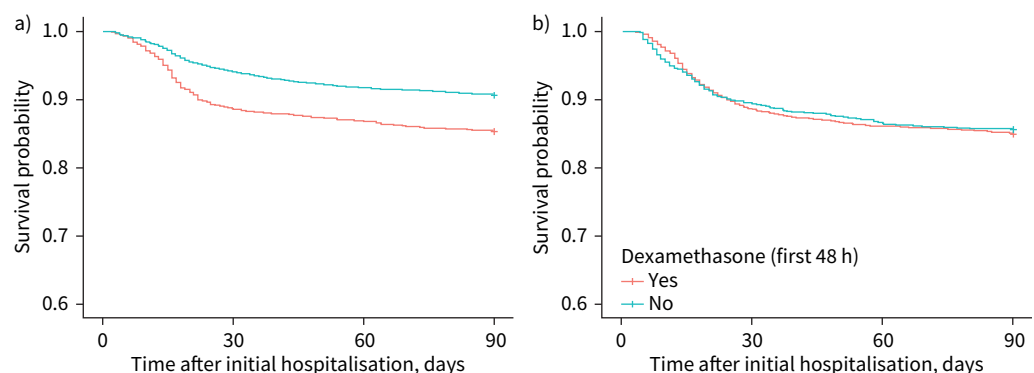


FIGURE 3 Inverse probability of treatment weighting Kaplan–Meier survival curves for 90-day mortality by dexamethasone use among patients hospitalised for COVID-19 on a) no oxygen or b) nasal cannula only in average treatment effect models.

TABLE 3 Inverse probability of treatment weighting Cox proportional hazards models for 90-day mortality associated with early dexamethasone exposure in patients hospitalised for COVID-19 without intensive respiratory support

	No oxygen supplementation	Nasal cannula only	Combined group (no oxygen or nasal cannula only)
Primary analysis	1.76 (1.47–2.12)	1.08 (0.86–1.36)	1.59 (1.39–1.81)
Sensitivity and subgroup analyses			
Restricted to positive SARS-CoV-2 test within 24 h	1.94 (1.50–2.53)	1.23 (0.93–1.64)	1.54 (1.26–1.87)
Restricted to positive SARS-CoV-2 test within 48 h	2.01 (1.55–2.60)	1.27 (0.96–1.68)	1.58 (1.30–1.92)
Any systemic corticosteroid	1.77 (1.49–2.11)	1.15 (0.92–1.43)	1.61 (1.41–1.84)
Excluding patients admitted to the ICU within 48 h	1.80 (1.36–1.74)	1.18 (0.89–1.58)	1.45 (1.19–1.67)
Restricted to patients aged ≥ 70 years	1.76 (1.36–2.28)	1.30 (0.99–1.72)	1.53 (1.27–1.84)

Data are presented as hazard ratio (95% CI). Models present the average treatment effect in the entire population (ATE models). SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ICU: intensive care unit.

with differences beginning to appear 10 days after the index date. In ATE estimates (table 3), patients without oxygen who received dexamethasone had a 76% increased hazard of 90-day mortality (HR 1.76, 95% CI 1.47–2.12).

In patients on NC only, 90-day mortality was similar in those who did and did not receive dexamethasone, as shown in weighted Kaplan–Meier curves (figure 3b). ATE estimates demonstrated a nonsignificant 8% increased mortality risk (HR 1.08, 95% CI 0.86–1.37) in patients on NC only who received dexamethasone. When combining patients on no oxygen or NC only, dexamethasone was associated with ~60% or more increased mortality risk.

Subgroup and sensitivity analyses

Results were similar in subgroup analyses excluding patients admitted to the ICU within the first 48 h and limiting the sample to patients aged ≥ 70 years (table 3). Findings were also consistent considering SARS-CoV-2 testing within 24 or 48 h of the index date, exposure to all corticosteroids and when using ATT or multivariable Cox models (supplementary tables E2 and E3). Among patients on NC only, hazard ratios were similar using ATT estimates, but dexamethasone was associated with a statistically significant increase in mortality in multivariable Cox models (HR 1.31, 95% CI 1.08–1.60) (supplementary table E3).

Discussion

In this US national cohort of hospitalised patients with COVID-19, dexamethasone use was common and increased over time. Among patients on IRS, 90% received dexamethasone within 48 h of admission. Focusing on patients without IRS, where there is less evidence supporting corticosteroid use, we found that among patients without oxygen in the first 48 h, dexamethasone was administered in 34% and was associated with 76% increased 90-day mortality. Among those on NC only in the first 48 h, dexamethasone was administered in 75% and was associated with no mortality benefit. This real-world evidence does not support the use of dexamethasone in hospitalised COVID-19 patients without IRS in the first 48 h.

While we cannot rule out residual confounding, our findings were robust, employing several different approaches and in subgroup and sensitivity analyses, including limiting the time window for SARS-CoV-2 test result, exposure to any systemic corticosteroid, restricted to patients aged ≥ 70 years and excluding those who were admitted to the ICU within 48 h. Results were consistent using ATE, reflecting the overall population from which the sample was taken, and using ATT, reflecting the population who received dexamethasone. They were also consistent controlling for potential confounders such as demographics, phase of the pandemic, site prescribing patterns, comorbidities, vital signs, laboratory values and co-administration of medications, including remdesivir [16].

Importantly, patients without IRS in the initial 48 h represent the majority (77%) of COVID-19 admissions in the cohort; thus, our findings have important clinical implications on the potential unintended consequences of widespread dexamethasone adoption for COVID-19 among patients who are without IRS. We found that uptake of dexamethasone for COVID-19 patients hospitalised in the VA was rapid after release of the RECOVERY trial results in early June 2020 (www.recoverytrial.net) [1]. By mid-July 2020, most facilities had increased the proportion of patients administered dexamethasone to 90% of patients on

HFNC or IMV within 48 h of admission, exceeding national estimates from other health systems [6]. However, sites also increased use of dexamethasone for patients with less severe COVID-19, including those not on oxygen or on NC only (figure 2), suggesting indication creep.

Our results provide real-world evidence of practice patterns and extend the findings from RECOVERY [1]. We provide clinically actionable evidence demonstrating significantly and substantially increased mortality in hospitalised COVID-19 patients not on oxygen who received early dexamethasone. Moreover, our results inform an area of significant clinical uncertainty, namely the use of dexamethasone in COVID-19 patients with less severe respiratory failure. Clinical guidelines issued by the US National Institutes of Health provide a moderate recommendation for corticosteroids in hospitalised COVID-19 patients “on supplemental oxygen” [22]. While dexamethasone was associated with improved outcomes in patients on oxygen support in RECOVERY, this category included all forms of oxygen, except for IMV, but inclusive of NIV. We further stratified patients by level of oxygen support during the initial 48 h of hospitalisation, addressing a significant knowledge gap [12]. We found a lack of benefit associated with dexamethasone in patients on only low-flow NC within 48 h of admission, suggesting that use of corticosteroids in this population should be re-considered and requires further prospective study.

Even before COVID-19, the impact of corticosteroids has been inconsistent in other causes of pneumonia, including influenza, community-acquired pneumonia and the original SARS [8, 23–26]. The impact of corticosteroids likely depends on multiple factors, including patient age and other characteristics, heterogeneity in host response to infection, aetiology of pneumonia, time since onset of infection, and presence and severity of acute respiratory distress syndrome [8, 10, 27–31]. While corticosteroids may decrease host inflammatory response, potentially modulating lung injury, they may also have harmful side-effects or unintended consequences on adaptive immune responses that may be important to resolution of infection and increase the risk of secondary infection.

There remain unanswered questions regarding the use of dexamethasone for patients hospitalised with COVID-19, particularly those without IRS. For some patients, initiation within 48 h of hospitalisation may be too early and could impair viral clearance [32]. While most patients in our cohort had positive SARS-CoV-2 testing within 1 day of hospitalisation, we do not know how long symptoms preceded seeking medical attention and testing. Corticosteroids may also have a differential effect depending on the degree of inflammation [33], but often extensive missing data and selection bias in obtaining tests such as C-reactive protein and interleukin-6 make this difficult to explore in real-world data. Furthermore, it is unclear whether the dexamethasone regimen used in RECOVERY is optimal or whether the formulation, dose and duration of corticosteroids should vary by factors such as patient age or severity of COVID-19 [2–4, 32]. While most corticosteroid use in our cohort was dexamethasone, we found consistent results when including all systemic corticosteroids and also when restricting to individuals aged ≥ 70 years, although other reports have found a potential for increased harm in older persons [31]. It is also unknown whether corticosteroids have a differential effect in breakthrough COVID-19 after vaccination or different variants of SARS-CoV-2.

There are several limitations to our study. First, the study was observational. While we used detailed clinical data that included measures reflecting illness severity and administration of co-medications in a large population well balanced by propensity for treatment, residual confounding for severity of illness could have contributed to greater mortality in those exposed to dexamethasone. Some laboratory results could have occurred after dexamethasone exposure, as both were ascertained within 48 h. However, the impact of dexamethasone on acute laboratory results is likely limited and this approach allowed an equal time window to detect the worst results in patients exposed and unexposed to dexamethasone. Although respiratory support algorithms were manually reviewed and validated, some misclassification may have occurred; however, substantial separation in Kaplan–Meier curves showing increasing mortality with greater respiratory support provides face validity. We also cannot rule out alternative indications for dexamethasone beyond COVID-19 in patients not on oxygen or on NC only. However, we excluded those on corticosteroids prior to admission and patients on vasopressors within the initial 48 h. Furthermore, we did not calculate dose and only assessed days of inpatient dexamethasone exposure. However, most patients had length of inpatient dexamethasone treatment equal to their hospital length of stay and very few received only one dose of dexamethasone (<4%). Finally, our cohort consisted predominantly of male Veterans, but had excellent racial and geographic variability.

In summary, we found no evidence of mortality benefit at 90 days associated with early initiation of dexamethasone in patients hospitalised with COVID-19 among those on no oxygen or NC only within the first 48 h of admission and instead found evidence of potential harm. These findings come from a large

population with detailed clinical data providing real-world evidence that was consistent using different analytic approaches to control for confounding and remained robust in a variety of subgroup and sensitivity analyses. Given the frequent and continued administration of dexamethasone to a substantial proportion of patients who are not on oxygen or are on low-flow NC only, the real-world evidence presented here highlights the nonbeneficial and potentially harmful expansion in use of dexamethasone in hospitalised COVID-19 patients without IRS. Future work should also evaluate dexamethasone and associated outcomes among hospitalised patients with COVID-19 breakthrough infections and different SARS-CoV-2 variants.

Author contributions: K. Crothers, J. Tate, M.B. Goetz, B. Jones, V. Marconi, M.E. Ohl, C.T. Rentsch, M.C. Rodriguez-Barradas, A.C. Justice and K.M. Akgün conceived (formulated or helped in the evolution) of the study. J. Tate, R. DeFaccio, P.R. Alba and C.T. Rentsch curated the data. R. DeFaccio and J. Tate performed the formal analysis. K. Crothers, P.R. Alba, A.C. Justice and K.M. Akgün acquired funding. K. Crothers, R. DeFaccio, J. Tate, P.R. Alba, M.E. Ohl, C.T. Rentsch, A.C. Justice and K.M. Akgün designed the methodology. R. DeFaccio, J. Tate and S. Shahrir managed and coordinated the project. K. Crothers, J. Tate, P.R. Alba, B. Jones and K.M. Akgün contributed to validation. K. Crothers, R. DeFaccio, J. Tate and K.M. Akgün wrote the first draft of the manuscript. All authors agree to be accountable for the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. K. Crothers and K.M. Akgün are joint principal investigators. K. Crothers, R. DeFaccio, J. Tate and K.M. Akgün are guarantors.

Data sharing: Owing to US Dept of Veterans Affairs (VA) regulations and our ethics agreements, the analytic datasets used for this study are not permitted to leave the VA firewall without a data use agreement. This limitation is consistent with other studies based on VA data. However, VA data are made freely available to researchers with an approved VA study protocol. For more information, please visit <https://www.virec.research.va.gov> or contact the VA Information Resource Center at VIREC@va.gov.

Conflict of interest: K. Crothers, R. DeFaccio, J. Tate, P.R. Alba, M.B. Goetz, B. Jones, J.T. King, M.E. Ohl, C.T. Rentsch, M.C. Rodriguez-Barradas, S. Shahrir, A.C. Justice and K.M. Akgün have no conflicts of interest to disclose. V. Marconi reports grant funding from Gilead, ViiV, CDC, NIH and VA; honoraria and travel support from Eli Lilly; and participation on a data safety monitoring board.

Support statement: VA/HSR&D, C19-20-406 (K. Crothers/K.M. Akgün) and 13-457 (P.R. Alba); VA/RR&D, 110IRX003666-01 (K. Crothers) and MVP000 (A.C. Justice). The Dept of Veterans Affairs did not have a role in the conduct of the study, in the collection, management, analysis or interpretation of data, or in the preparation of the manuscript. The views expressed in this article are those of the authors and do not necessarily represent the views of the Dept of Veterans Affairs or the US Government. Funding information for this article has been deposited with the Crossref Funder Registry.

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