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Yoshan Moodley & Andrew Tomita

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Relationship between HIV serostatus, CD4 count and rehospitalisation: Potential implications for health systems strengthening in South Africa

Yoshan Moodley[a],* and Andrew Tomita[b]

[a]*Discipline of Anaesthesiology and Critical Care Medicine, University of KwaZulu-Natal, Durban, South Africa*
[b]*Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Durban, South Africa*
*Corresponding author, email: moodleyyo@ukzn.ac.za

Background: Despite three decades of scientific response to HIV/AIDS, the generalised HIV epidemic continues to persist in South Africa. There is growing acknowledgement that health system strengthening will be critical in tackling HIV/AIDS. Patient rehospitalisation is an important quality benchmark of health service delivery, but there is currently limited data on rehospitalisation of patients with HIV/AIDS in South Africa, a setting with a high burden of HIV disease.
Objectives: To determine the relationship between combined HIV serostatus and CD4 count, and rehospitalisation in South Africa.
Methods: This study was a retrospective analysis of data from 11,362 non-surgical adult patients who attended the Hlabisa Hospital in South Africa. Data related to patient age, gender, HIV serostatus, CD4 count (for HIV-positive patients) and comorbidity were analysed through univariate (Fisher's Exact or χ^2 tests) and multivariate (Cox regression) statistical methods to determine associations with rehospitalisation within 1 month (acute rehospitalisation) or 12 months (long term rehospitalisation).
Results: An HIV-positive serostatus with CD4 count < 350 cells/mm³ or an HIV-positive serostatus with an unknown CD4 count were independently associated with a higher risk of acute ($p = 0.010$ and $p = 0.003$) and long term rehospitalisation ($p < 0.001$ for both categories) when compared with an HIV-negative serostatus group.
Conclusions: HIV-positive individuals with immune deficiency, or lacking a CD4 count measurement are at risk of rehospitalisation. Strengthening primary healthcare service delivery of these key affected inpatient populations should be a priority.

Keywords: CD4 count, HIV, patient re-admission, rehospitalisation, serostatus

Introduction

Southern Africa is considered the epicenter of the global HIV epidemic with 6.4 million people living with the disease in South Africa alone.[1] The generalised HIV epidemic persists despite three decades of scientific response to HIV/AIDS. There is growing acknowledgement that health system performance will be critical, particularly in public hospital settings where the disease burden related to HIV infection is often high.[2] In the KwaZulu-Natal province of South Africa, HIV has placed significant strain on health service resources.[3] There is an urgent need to identify ways in which public hospitals can provide optimal quality care for HIV/AIDS patients. Reducing patient rehospitalisation is not only a financial imperative, but also a potentially important benchmark for quality of care performance within healthcare facilities. Indeed, rehospitalisation has been included as an adverse outcome in the World Health Organisation's "Performance Assessment tool for Quality Improvement in Hospitals",[4] signifying its importance related to measuring healthcare quality at a global level. Stanley *et al.*, also note that rehospitalisation is a potential marker of inefficiencies in the overall health system in South Africa where the high burden of HIV-related disease exacerbates bed shortages within public healthcare facilities.[5] Instituting such a benchmark is understood to encourage an improvement in care transition and mitigation of potential risks, thereby reducing the number of patients requiring rehospitalisation. While rehospitalisation has not been used as benchmark for quality of care in South African HIV-infected patients, it has been used in American studies of HIV-infected populations.[6, 7]

Determining HIV serostatus and CD4 count measurements are critical for long term patient care/management.[8] In addition, HIV serostatus and CD4 count are also independent predictors of rehospitalisation.[6, 9] However, little is known about the relationship between HIV serostatus, CD4 count, and rehospitalisation in South Africa. Considering the high burden of HIV infection in South Africa and the widely practiced "opt-in" approach to HIV counselling and testing (HCT),[10] it is likely that an HIV-positive serostatus (and possible low CD4 counts) might be missed in a number of patients who do not consent to HCT. Undiagnosed HIV infection and possible immunodeficiency in patients who are actually HIV-positive hinders linkages to appropriate treatment, representing a missed opportunity to prevent future HIV transmission. This study sought to determine the relationship between combined HIV serostatus and CD4 count, and its relationship to rehospitalisation in a South African setting.

Methods

Study design, setting, data source, and outcome definitions

This study was a retrospective analysis of data collected by the Africa Centre Demographic Information System (ACDIS),[11] and involved 11,362 unique adult patients who were admitted to the Hlabisa Hospital in South Africa for medical (non-surgical) reasons between October 2009 and February 2014. The Hlabisa hospital provides services at the primary healthcare level to residents of Hlabisa, Mtubatuba and parts of the "big five" municipalities in northern KwaZulu-Natal province, South Africa. The general population of the Hlabisa district has been described in detail elsewhere.[11] The overall incidence of HIV in the Hlabisa district has been estimated at 3.2/100 person years.[11] Briefly, data related to age, gender, and HIV serostatus (HIV-positive, HIV-negative, or HIV-unknown) were extracted from the ACDIS dataset for each patient at the index hospital admission, and

defined as the first recorded hospital admission for the patient that was within the data collection timeframe for this study. For patients with a recorded HIV-positive serostatus, data related to CD4 count measurements (categorised as "<350 cells/mm³", "≥ 350 cells/mm³", or "CD4 count unknown"), and antiretroviral therapy (ART) prescription (categorised as "yes", "no", or "unknown") was also collected. A set of ICD-10 codes were used to identify the presence of comorbidities potentially associated with rehospitalisation for each patient.[12] The relationship between these comorbid conditions and a higher risk of rehospitalisation has been described elsewhere.[13] In lieu of current estimates for the burden of tuberculosis (TB) infection in Africa, we also decided to investigate the potential impact of TB infection on rehospitalisation.[14] A patient was considered rehospitalised within 1 month (acute rehospitalisation) or 12 months (long term rehospitalisation) if a second hospital admission was recorded for the patient within the aforementioned time periods following their index hospital admission. Rehospitalisation events which fell outside of the 1 or 12 month time period were censored for each time period analysis. Data related to second rehospitalisations were not analysed in this study. Furthermore, reasons for rehospitalisation were also not analysed in this study. This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa (Protocol EXM277/15).

Statistical analysis

Separate statistical analyses were performed for each outcome investigated in this study (acute and long term rehospitalisation). Age data was analysed via a Mann-Whitney U test. Gender, CD4 count categories, and comorbidity data were analysed using Fisher's Exact or χ^2 tests, where appropriate. Variables attaining a p-value < 0.2 from the aforementioned univariate analyses were purposefully selected for inclusion in a Cox regression model. Results for the Cox regression analyses are presented as hazard ratio's (HR) with 95% confidence intervals (95% CI). A p- value < 0.05 was considered statistically significant. All data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) Version 23 (IBM Corporation, USA).

Results

Sample demographic and clinical characteristics (Entire cohort)

Demographic and clinical characteristics for the entire study cohort are shown in Table 1. The median age of the entire cohort was 34.0 (interquartile range: 26.0–50.0) years. Males comprised 38.9% of the entire cohort. The percentage of patients in the entire cohort which fell within each HIV serostatus and CD4 count category were as follows: HIV-positive serostatus with CD4 count < 350 cells/mm³ = 5.1%; HIV-positive serostatus with CD4 count ≥ 350 cells/mm³ = 1.8%; HIV-positive serostatus with unknown CD4 count = 29.5%; HIV-negative serostatus = 9.7%; and, HIV serostatus unknown = 53.9%. The percentage of patients in the entire cohort which fell within each HIV serostatus-ART category were as follows: HIV-positive serostatus, no ART = 19.8%; HIV-positive serostatus with ART = 16.4%; HIV-positive serostatus, ART unknown = 0.2%; HIV-negative serostatus, no ART = 9.7%; and, HIV serostatus unknown, no ART = 53.9%. Tuberculosis, uncomplicated diabetes, and renal disease were the three most prevalent comorbidities observed at the index hospital admission (Table 1). The percentage of patients in the entire cohort rehospitalised within 1 month or 12 months from an index hospital admission was 3.8% and 12.5%, respectively.

Sample demographic and clinical characteristics (Stratified by rehospitalisation status)

Demographic and clinical characteristics for the entire cohort stratified by rehospitalisation status are also shown in Table 1. The median age of patients with long term rehospitalisation was significantly older than that for patients without long term rehospitalisation (p < 0.001). A statistical trend toward rehospitalisation in older patients was also observed for acute rehospitalisation (p = 0.058). Male gender was statistically associated with long term rehospitalisation (p < 0.001), but not acute rehospitalisation (p = 0.182). Overall, HIV serostatus-CD4 count appeared to be associated with acute and long term rehospitalisation (p = 0.003 and p < 0.001, respectively). Similarly, HIV-serostatus-ART status also appeared to be associated with acute and long term rehospitalisation (p = 0.006 and p < 0.001, respectively). Not all of the established comorbidities associations with acute or long term rehospitalisation were univariate in this study (Table 1).

Cox regression analyses

The results of the Cox regression analyses are shown in Table 2. When compared with the HIV-negative serostatus group, an HIV-positive serostatus with a CD4 count < 350 cells/mm³ or an HIV-positive serostatus with an unknown CD4 count were independent predictors of acute (p = 0.010 and p = 0.003, respectively) and long term (p < 0.001 for both CD4 categories) rehospitalisation. Non-statistically significant increases in risk were noted for patients with an HIV-positive serostatus with a CD4 count ≥ 350 cells/mm³ or an HIV-unknown serostatus (Table 2). Similarly, when compared with the HIV-negative, no ART group, HIV-positivity with ART or HIV-positivity without ART were independent predictors of acute (p = 0.004 and p = 0.006, respectively) and long term (p < 0.001 for both ART categories) rehospitalisation. Of the remaining ART categories, only HIV-unknown with no ART was independently associated with rehospitalisation (long term only, p = 0.031). Male gender and age were found to be independent predictors of long term rehospitalisation (p = 0.015 and p < 0.001, respectively). Non-metastatic malignancy and uncomplicated diabetes were the only two comorbid conditions which were independently associated with acute rehospitalisation, while the importance of comorbidities such as congestive heart failure and mild liver disease was noted for the long term rehospitalisation (Table 2). Tuberculosis with either an HIV-positive or HIV-negative serostatus was independently associated with a higher risk of long term rehospitalisation only (p = 0.001 and p = 0.043, respectively). A non-statistically significant trend toward a higher risk of long term rehospitalisation in tuberculosis patients with unknown HIV-serostatus was also noted (Table 2).

Discussion

Impact of HIV serostatus and CD4 count on rehospitalisation

While the uptake of HIV testing in this study might appear low (only 46.1% of the study population had a known HIV status despite the high burden of HIV infection in Hlabisa), the uptake levels of HIV testing observed in this research lie within the estimates of 38% and 58%, which have previously been reported for the general population of Hlabisa.[11] We found a two-fold increase in risk for acute rehospitalisation in patients who had an HIV-positive serostatus with a CD4 count < 350 cells/mm³ or an HIV-positive serostatus with an unknown CD4 count. Significantly higher risk in the aforementioned HIV serostatus or CD4 count categories was also noted for long term rehospitalisation. A non-statistically

Table 1: Characteristics of the study population (stratified by rehospitalisation status) expressed as a frequency (%)

Characteristic	Major Category	Sub-Category	Entire Cohort (*n* = 11362)	Acute rehospitalisation			Long term rehospitalisation		
				Patients with Rehospitalisation (*n* = 431)	Patients without Rehospitalisation (*n* = 10931)	*p*-value	Patients with Rehospitalisation (*n* = 1420)	Patients without Rehospitalisation (*n* = 9942)	*p*-value
Median Age in years (IQR)	-	-	34.0 (26.0–50.0)	36.0 (28.0–49.0)	34.0 (26.0–50.0)	0.058	39.0 (29.0–56.0)	34.0 (25.0–49.0)	<0.001
Male Gender	-	-	4422 (38.9)	181 (42.0)	4241 (38.8)	0.182	612 (43.1)	3810 (38.3)	0.001
HIV serostatus						0.003			<0.001
	Negative	-	1102 (9.7)	27 (6.3)	1075 (9.8)		92 (6.5)	1010 (10.2)	
	Positive	CD4 count <350 cells/mm³	579 (5.1)	28 (6.5)	551 (5.0)		90 (6.3)	489 (4.9)	
		CD4 count ≥350 cells/mm³	209 (1.8)	5 (1.2)	204 (1.9)		25 (1.8)	184 (1.9)	
		CD4 count unknown	3349 (29.5)	155 (36.0)	3194 (29.2)		508 (35.8)	2841 (28.6)	
	Unknown	-	6123 (53.9)	216 (50.1)	5907 (52.0)		705 (49.6)	5418 (54.5)	
Antiretroviral Therapy (ART)						0.006			<0.001
	HIV-negative (No ART)	-	1102 (9.7)	27 (6.3)	1075 (9.8)		92 (6.5)	1010 (10.2)	
	HIV-positive	No	2254 (19.8)	99 (23.0)	2155 (19.7)		314 (22.1)	1940 (19.5)	
		Unknown	20 (0.2)	1 (0.2)	19 (0.2)		1 (0.1)	19 (0.2)	
		Yes	1863 (16.4)	88 (20.4)	1775 (16.2)		308 (21.7)	1555 (15.6)	
	HIV-unknown (No ART)	-	6123 (53.9)	216 (50.1)	5907 (54.0)		705 (49.6)	5418 (54.5)	
Congestive heart failure	-	-	350 (3.1)	19 (4.4)	331 (3.0)	0.104	83 (5.8)	267 (2.7)	<0.001
Connective tissue disease	-	-	4 (<0.1)	0 (0.0)	4 (<0.1)	0.999	1 (0.1)	3 (<0.1)	0.414
Chronic obstructive pulmonary disease	-	-	87 (0.8)	5 (1.2)	82 (0.8)	0.387	16 (1.1)	71 (0.7)	0.095
Cerebrovascular disease	-	-	12 (0.1)	0 (0.0)	12 (0.1)	0.999	1 (0.1)	11 (0.1)	0.999
Dementia	-	-	27 (0.2)	0 (0.0)	27 (0.2)	0.625	7 (0.5)	20 (0.2)	0.071
Complicated diabetes	-	-	62 (0.5)	3 (0.7)	59 (0.5)	0.510	14 (1.0)	48 (0.5)	0.016
Uncomplicated diabetes	-	-	598 (5.3)	31 (7.2)	567 (5.2)	0.067	110 (7.7)	488 (4.9)	<0.001
Hemiplegia or paraplegia	-	-	72 (0.6)	5 (1.2)	67 (0.6)	0.199	13 (0.9)	59 (0.6)	0.153
Metastatic malignancy	-	-	1 (<0.1)	0 (0.0)	1 (<0.1)	0.999	0 (0.0)	1 (<0.1)	0.999
Myocardial infarction	-	-	0 (0.0)	0 (0.0)	0 (0.0)	*	0 (0.0)	0 (0.0)	*
Mild liver disease	-	-	31 (0.3)	2 (0.5)	29 (0.3)	0.330	9 (0.6)	22 (0.2)	0.011

(Continued)

Table 1: (Continued)

Characteristic	Major Category	Sub-Category	Entire Cohort (*n* = 11362)	Acute rehospitalisation			Long term rehospitalisation		
				Patients with Rehospitalisation (*n* = 431)	Patients without Rehospitalisation (*n* = 10931)	*p*-value	Patients with Rehospitalisation (*n* = 1420)	Patients without Rehospitalisation (*n* = 9942)	*p*-value
Moderate or severe liver disease	-	-	12 (0.1)	0 (0.0)	12 (0.1)	0.999	1 (0.1)	11 (0.1)	0.999
Non-metastatic malignancy	-	-	196 (1.7)	23 (5.3)	173 (1.6)	<0.001	67 (4.7)	129 (1.3)	<0.001
Peptic ulcer	-	-	67 (0.6)	2 (0.5)	65 (0.6)	0.999	13 (0.9)	54 (0.5)	0.086
Peripheral vascular disease	-	-	5 (<0.1)	0 (0.0)	5 (<0.1)	0.999	1 (0.1)	4 (<0.1)	0.487
Renal disease	-	-	268 (2.4)	14 (3.2)	254 (2.3)	0.215	42 (3.0)	226 (2.3)	0.112
Tuberculosis						0.807			<0.001
	No	-	9172 (80.7)	342 (79.4)	8830 (80.8)		1070 (75.4)	8102 (81.5)	
	Yes	HIV-negative	138 (1.2)	7 (1.6)	131 (1.2)		24 (1.7)	114 (1.1)	
		HIV-positive	1613 (14.2)	65 (15.1)	1548 (14.2)		265 (18.7)	1348 (13.6)	
		HIV-unknown	439 (3.9)	17 (3.9)	422 (3.9)		61 (4.3)	378 (3.8)	

Note: ART: Antiretroviral therapy.
*Unable to compute.

significant increase in risk for the CD4 count ≥ 350 cells/mm³ group was noted for acute and long term rehospitalisation (HR > 1.0, but did not reach statistical significance). The findings for the aforementioned HIV serostatus or CD4 count categories is similar to the findings of Berry et al., who found that any positive HIV serostatus (irrespective of CD4 count) is potentially associated with a higher risk of rehospitalisation.[6] This study did not establish an independent association between an unknown HIV serostatus and a higher risk of acute or long term rehospitalisation. However, the risk estimates obtained from the Cox regression analyses suggest a trend toward a harmful association between an unknown HIV serostatus and a higher risk of rehospitalisation (36.3% higher risk for acute rehospitalisation, and 17.5% higher risk for long term rehospitalisation). Considering our findings for the HIV-positive serostatus with CD4 count < 350 cells/mm³ and the HIV-positive serostatus with unknown CD4 count groups, it is likely that a large proportion of patients with an unknown HIV serostatus in this study were actually HIV-positive. It remains important that in settings with a high burden of HIV infection, every effort should be made to determine HIV serostatus (and also CD4 count) in patients where there is none recorded.

Impact of other clinical factors on rehospitalisation

Both HIV-infected patients on ART, and HIV-infected patients not on ART experienced an almost 2-fold higher risk of acute and long term rehospitalisation. This finding is in disagreement with the findings of a matched cohort study conducted by Nosyk et al.,[15] which reported a 28% lower readmission rate in HIV-infected patients receiving ART when compared with HIV-infected patients who were not receiving ART. Important to note, however, the study of Nosyk and colleagues[15] was conducted in a low-burden tuberculosis setting (Canada), when compared with our study setting. It is possible that a higher burden of latent tuberculosis and subsequent immune reconstitution inflammatory syndrome in patients on ART in our setting may account for the high rate of rehospitalisation in this group. This is supported by the findings of our research which show a higher

risk of rehospitalisation (long term) in tuberculosis patients with HIV versus tuberculosis patients without HIV.

We also found age and gender to be independently associated with rehospitalisation. The findings for age in keeping with the majority of published studies which had sought to develop models to predict rehospitalisation.[16] We found that the male gender was associated with a higher risk of rehospitalisation, which is in agreement with a British study by Woz and colleagues.[17] In that study, hospital utilisation in the 6 months prior to the index hospitalisation, being unmarried, having a positive depression screen and no primary care physician visit within 30 days, were identified as major risk factors for rehospitalisation in males (versus females).[17] There is a lack of gender-specific data related to risk factors for all-cause rehospitalisation in a South African setting, and it is therefore unknown whether the risk factors identified in the study of Woz et al.,[17] would still be applicable in this setting. Further research investigating risk factors for higher rehospitalisation in males versus females in this setting is required.

A number of the comorbid diseases associated with a higher risk of rehospitalisation elsewhere[13] were not identified as risk factors for rehospitalisation in this study. This finding might be related to the current epidemiological transition being experienced in South Africa,[18] as opposed to the burden of non-communicable disease versus communicable disease in countries from which the established risk factors are reported. This difference is further highlighted by our findings for TB infection.

Study limitations

This study had several limitations. Firstly, this is a subanalysis of data collected from a single healthcare facility, and therefore the findings of this study might not be applicable to the greater HIV-infected population. Secondly, we did not present data related to viral load in the HIV-infected population as these data were not available. Finally, we were unable to investigate the potential importance of any inpatient hospital laboratory results (besides

Table 2: Results of the Cox regression analysis

Outcome	Characteristic	HR (95% CI)	*p*-value
Acute rehospitalisation	HIV-positive serostatus with CD4 count <350 cells/mm3*	2.016 (1.186–3.425)	0.010
	HIV-positive serostatus with CD4 count ≥350 cells/mm3*	1.005 (0.387–2.610)	0.992
	HIV-positive serostatus with unknown CD4 count*	1.863 (1.236–2.810)	0.003
	HIV serostatus unknown*	1.363 (0.907–2.049)	0.136
	Age (per year increase)	0.998 (0.992–1.004)	0.559
	Male gender	1.132 (0.932–1.373)	0.211
	Congestive heart failure	1.582 (0.982–2.548)	0.059
	Uncomplicated diabetes	1.634 (1.106–2.414)	0.014
	Hemiplegia or paraplegia	2.036 (0.841–4.932)	0.115
	Non-metastatic malignancy	3.389 (2.216–5.183)	<0.001
	HIV-positive serostatus with no ART**	1.829 (1.186–2.822)	0.006
	HIV-positive serostatus with unknown ART**	2.187 (0.282–16.954)	0.454
	HIV-positive serostatus with ART**	1.910 (1.229–2.969)	0.004
	HIV-unknown serostatus with no ART**	1.366 (0.904–2.065)	0.139
Long term rehospitalisation	HIV-positive serostatus with CD4 count <350 cells/mm3*	1.183 (1.348–2.437)	<0.001
	HIV-positive serostatus with CD4 count ≥350 cells/mm3*	1.443 (0.926–2.248)	0.105
	HIV-positive serostatus with unknown CD4 count*	1.721 (1.373–2.157)	<0.001
	HIV serostatus unknown*	1.175 (0.941–1.467)	0.155
	Age (per year increase)	1.009 (1.006–1.012)	<0.001
	Male gender	1.142 (1.026–1.271)	0.015
	Congestive heart failure	1.826 (1.448–2.302)	<0.001
	Chronic obstructive pulmonary disease	1.448 (0.883–2.376)	0.142
	Dementia	2.015 (0.952–4.265)	0.067
	Complicated diabetes	1.595 (0.921–2.763)	0.096
	Uncomplicated diabetes	1.472 (1.189–1.823)	<0.001
	Hemiplegia or paraplegia	1.495 (0.864–2.585)	0.151
	Mild liver disease	2.620 (1.357–5.061)	0.004
	Non-metastatic malignancy	3.099 (2.417–3.972)	<0.001
	Peptic ulcer	1.447 (0.836–2.505)	0.187
	Renal disease	1.093 (0.802–1.490)	0.573
	HIV-positive serostatus with no ART**	1.973 (1.481–2.627)	<0.001
	HIV-positive serostatus with unknown ART**	0.709 (0.093–5.400)	0.740
	HIV-positive serostatus with ART**	2.248 (1.683–3.002)	<0.001
	HIV-unknown serostatus with no ART**	1.343 (1.028–1.755)	0.031
	Tuberculosis, HIV-positive serostatus***	2.341 (1.401–3.912)	0.001
	Tuberculosis, HIV-negative serostatus***	1.198 (1.006–1.428)	0.043
	Tuberculosis, unknown HIV serostatus***	1.293 (0.971–1.724)	0.079

Notes: ART: Antiretroviral therapy; HR: Hazard ratio.
*When compared with reference group: HIV-negative serostatus.
**When compared with reference group: HIV-negative (No ART).
***When compared with reference group: No Tuberculosis.

CD4 count) in this study as these data was not collected as part of the ACDIS. Although this study does have limitations, it nevertheless presents important data related to HIV status and acute or long term rehospitalisation events from a setting with a high burden of HIV infection.

Conclusion

In summary, we found independent associations between some combined HIV serostatus or CD4 count categories (HIV-positive serostatus with a CD4 count < 350 cells/mm^3 or an HIV-positive serostatus with an unknown CD4 count) and a higher risk of acute and long term rehospitalisation. There were non-statistically significant trends toward a higher risk of acute and long term rehospitalisation observed for some categories (HIV-positive serostatus group with CD4 count ≥ 350 cells/mm^3 or unknown HIV serostatus group). Although further research is required to confirm the findings of our study, it highlights the potential importance of strengthening primary healthcare service delivery for HIV-infected patients with low CD4 counts, or patients with missing HIV serostatus and CD4 counts.

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