


Time to Drug-Resistant Tuberculosis Treatment in a Prospective South African Cohort

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Abstract

This study examined time to treatment initiation by age among a prospective cohort with drug-resistant tuberculosis (DR-TB). Participants aged 13 years or older nested within a cluster-randomized trial in 2 South African provinces were evaluated. Outcomes were treatment initiation within 5 days of DR-TB diagnosis (National Tuberculosis Program guidelines) and days from diagnosis to treatment. A total of 521 participants met inclusion criteria. Eighty-two patients (16%) met national guidelines; median time to treatment was 11 days (range = 0–180). No patient (age, sex, prior TB history, HIV status) or health system characteristics (geographic urban/rural location, province) were associated with treatment initiation per guidelines except geographic location ($t = 3.64$, degrees of freedom = 1, $P = .0003$). One in 6 individuals with DR-TB received treatment per guidelines, and average time to treatment was 11 days. Strategies are needed to decrease treatment delays and meet the recommended guidelines for treatment for patients of all ages.

Keywords

tuberculosis, drug-resistance, adolescent medicine, infectious diseases, treatment

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Introduction

Mycobacterium tuberculosis is the leading cause of infectious disease deaths worldwide. More than 95% of tuberculosis (TB) deaths occur in low- and middle-income countries.¹ Although 83% of patients with drug-susceptible TB are successfully treated or cured, only 28% to 52% of patients who initiate drug-resistant TB (DR-TB) treatment are successfully treated or cured.¹ Early diagnosis and prompt, accurate treatment is critical to cure, prevention of transmission, and the prevention of further drug resistance.¹

In sub-Saharan Africa, HIV is a driving force of the resurgence and spread of DR-TB.² South Africa has the world's third highest DR-TB burden and carries the largest burden of HIV infection globally.³ An estimated 1.8% (279 851) of new TB cases have drug resistance and an estimated 6.7% (80 580) of TB retreatment cases have drug resistance in South Africa.² Only 62% of individuals with DR-TB in South Africa initiate treatment in the year of diagnosis.² To improve patient outcomes and

prevent transmission of DR-TB, South Africa recommends starting treatment within 5 days of diagnosis.⁴

The burden of DR-TB in children and youth is not fully understood.^{1,5,6} Some youth with HIV delay anti-retroviral therapy; yet, this is less known for youth with TB or DR-TB.^{7,8} There is also inadequate information on individual- and system-level factors associated with treatment initiation for DR-TB in South Africa particularly for youth.^{9,10}

Thus, the purpose of this study was to describe the time from DR-TB diagnosis to treatment initiation for people in South Africa and to evaluate the influence of

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age on the timing of treatment initiation after controlling for patient and health system characteristics. It was hypothesized that younger patients would have a greater number of days from DR-TB diagnosis to treatment initiation.

Methods

Design

This secondary analysis was designed to (1) determine whether DR-TB treatment was initiated in 5 or less days from DR-TB diagnosis per South African guideline and (2) describe the number of days from DR-TB diagnosis to DR-TB treatment initiation. Data were collected as part of an ongoing, 5-year cluster-randomized trial investigating the effects of nurse-led case management to improve treatment outcomes in individuals 13 years of age and older with DR-TB residing in 2 South African provinces. Institutional review board approval was granted by Duke University (Pro00067846) and Johns Hopkins University (NA_00078899/CIR00009135).

Parent Study

The parent trial began in November 2014 at 10 sites randomized to either a nurse case management (NCM) intervention or control arm with the primary outcome being successful treatment. The NCM intervention consists of a nurse coordinating DR-TB treatment with weekly phone calls and/or visits during the intensive first 6 months of treatment to monitor patient progress, and conduct monthly visits during the continuation phase. Patients at control sites receive physician-led standard of care with no optimized nursing support. The parent study protocol is described elsewhere (NCT02129244). Treatment initiation began prior to the NCM intervention.

Setting and Sample

All treatment sites were public facilities in KwaZulu Natal and the Eastern Cape provinces, 2 provinces with high DR-TB incidence.⁴ Sites did not collect racial statistics; however, most individuals receiving care were Black South Africans. All racial groups were screened for eligibility and had equal access to recruitment. Any patient enrolled in another clinical trial was not eligible. Participants were eligible if they had initial DR-TB diagnosis and were consented within 7 days of treatment.

As of November 2016, baseline and medication data were available for 542 individuals 13 years or older with

DR-TB initiated on treatment between November 2014 and August 2016. One participant did not have an initial diagnosis of DR-TB, and complete data were unavailable for 20 participants (Figure 1).

Data Sources and Procedures

Trained study personnel obtained information by patient interview and medical chart review. Treatment initiation and HIV status were confirmed in medical charts, and sputum sample dates for DR-TB diagnosis were obtained from the National Health Laboratory System. Data captured concurrent with care were written on paper case report forms. After comparing medical records with paper case report forms, the latter were scanned for secure storage. All data were manually entered in REDCap, a web-based application. REDCap data were downloaded into an analytic data set archived on a password-protected server. Data were cleaned and missing values entered by verification on original case report forms. Data analysis was conducted using SAS (version 9.3, Cary, NC).

Measures

Definition of Outcomes. The time to treatment initiation outcomes were (1) DR-TB treatment initiated in 5 or less days from the DR-TB diagnosis, as defined per South African guideline (primary outcome); and (2) days from DR-TB diagnosis to DR-TB treatment initiation. Time to treatment initiation was determined as the time from sputum sample collection from which at least rifampicin resistance was determined to the date second-line anti-TB treatment was initiated.

Patient and System Characteristics. Patient-level characteristics included age, sex, history of TB disease, and HIV coinfection. Antiretroviral treatment status, prior exposure to TB, education level (none, some education, some/complete university), marital status (married/living with partner, single), and employment status (unemployed, employed, student) were obtained and presented as additional descriptive data. Two system-level characteristics were examined. Urban-rural classification where treatment was provided was designated by the parent study and categorized as urban/peri-urban or rural. Geographic location was defined by treatment site province (Eastern Cape or KwaZulu-Natal).

Data Analysis

Descriptive statistics summarize (1) demographic and clinical characteristics of the patients, (2) site characteristics of the health care system, and (3) time to treatment

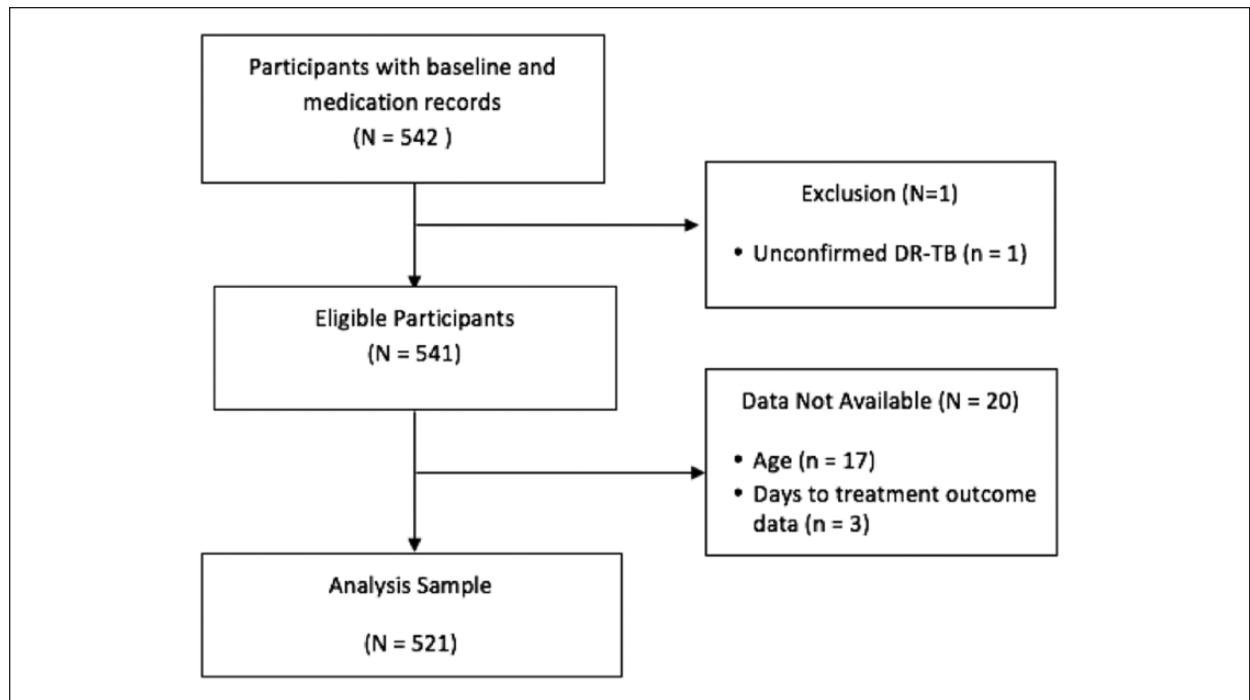


Figure 1. Participant flow diagram.

Abbreviation: DR-TB, drug-resistant tuberculosis.

outcome variables. Nondirectional statistical tests were performed with significance set at .05. Effect sizes were used to address clinical significance.

Sample Characteristics. Descriptive statistics were used to describe sociodemographic and clinical characteristics for the total sample, adults, and youth. Youth included individuals aged 13 to 24 years. Chi-square tests or Fisher's exact tests were used to test for group differences in proportions for categorical measures, and general linear models (GLMs, adjusting for sample size differences) were used to test for differences in means for continuous measure. Descriptive statistics were also used to detail site characteristics and time to treatment initiation outcomes.

DR-TB Treatment Initiation in 5 or Less Days, per South African Guideline. Treatment initiation occurring in 5 or less days from DR-TB diagnosis was coded as 0 (no) and 1 (yes). As a preliminary step, a $4 \times 2 \chi^2$ test was conducted to compare differences in the proportion of patients in which the treatment was initiated within 5 days in 4 age subgroups (1) youth, aged 13 to 24 years; (2) adults, aged 25 to 35 years; (3) adults, aged 36 to 50 years; and (4) adults, aged 50 years or older.^{11,12}

For the primary analysis, logistic regression for binary outcomes was used to examine the influence of

age on the guideline outcome and each covariate. Age was included as a continuous variable. Covariates were clinical characteristics of patients (sex, history of TB disease, HIV coinfection) and characteristics of the health care system (urban/rural, province). Table 3 includes the set of bivariate models. To address clinical significance, the odds ratio and 95% confidence interval for each explanatory variable was calculated.

Days to DR-TB Treatment Initiation. Descriptive statistics for the days to treatment initiation indicated that the data distribution was severely right skewed (skewness = 3.5). A natural log transformation was employed to normalize the data for this continuous outcome. The variable log (days to treatment + 1) was derived for each patient by adding +1 to the days to treatment initial value and calculating the natural log of that value. Adding the constant 1 was necessary because days to treatment value was 0 for some patients (initiation same day as diagnosis, N = 2). This "log of days to treatment" variable was used in all subsequent analysis.

The analytic approach applied for days to treatment initiation was the same as the "in 5 or less days" outcome, except that the analytic tools designed for continuous measures were applied. For the preliminary analysis, days to treatment in the 4 age groups were compared using a nonparametric Kruskal-Wallis test

Table 1. Sample Characteristics^a.

Baseline Characteristic	N	Total (N = 521)	Adult (n = 434)	Youth (n = 87)	P
Age, years	521	35.6 ± 10.9	38.4 ± 9.7	21.7 ± 2.6	<.000
Male	521	286 (54.9%)	250 (57.6%)	36 (41.4%)	.006
Education level ^b	516				.030
None		24 (4.7%)	24 (5.6%)	0 (0.0%)	
Some education		461 (9.0%)	381 (88.8%)	80 (92.0%)	
Some/complete university		31 (6.0%)	24 (5.6%)	7 (8.1%)	
Employment status ^c	512				<.000
Unemployed		273 (53.3%)	231 (54.4%)	42 (48.3%)	
Employed		199 (38.9%)	187 (44.0%)	12 (13.8%)	
Student		40 (7.8%)	7 (1.7%)	33 (37.9%)	
Living with partner ^d	520	103 (19.8%)	100 (23.1%)	3 (3.5%)	<.000
HIV coinfection	510	384 (75.3%)	343 (80.9%)	41 (47.7%)	<.000
HIV patients on ART	244	202 (82.8%)	186 (83.0%)	16 (80.0%)	.730
History of TB disease	514	271 (52.7%)	245 (57.4%)	26 (29.9%)	<.000
Prior TB exposure	485	150 (30.9%)	119 (29.5%)	31 (38.3%)	.117
Exposure drug resistant TB	127	58 (45.7%)	41 (41.4%)	17 (60.7%)	.070
Eastern Cape province	521	234 (44.9%)	199 (45.9%)	35 (40.2%)	.336
Urban site	521	242 (46.4%)	199 (45.9%)	43 (49.4%)	.542
Hospital admission	517	266 (51.5%)	225 (52.2%)	41 (47.7%)	.443

Abbreviations: ART, antiretroviral treatment; TB, tuberculosis.

^aYouth = aged 13 to 24 years; n (%) for categorical variables; mean ± standard deviation for continuous measures; χ^2 /Fisher's exact test for categorical characteristics; general linear model (GLM) for continuous characteristics.

^bEmployed includes full-time, part-time, homemaker, and retired.

^cSome education includes some primary, secondary, or technical school complete.

^dLiving with partner includes married, living with boyfriend/girlfriend.

due to skewness, and the means of the log of days to treatment were compared using a GLM to conduct the 1-way ANOVA.

For the primary analysis, linear regression models were conducted on the log of days to treatment to evaluate the influence of age and each covariate. Age was included as a continuous variable. The final model included the effects of age and covariates significant at the $P < .10$ level on the log of days to treatment outcome.

Results

Sample

The sample included 542 individuals. Twenty-one individuals were excluded (Figure 1). Table 1 summarizes sample characteristics for the total sample (N = 521), adults (n = 434), and youth (n = 87).

Sample Characteristics

The mean age was 35.6 years, ranging from 14.0 to 74.9 years. The sample composition was 55% male, 5% with no formal education, 53% unemployed, 75% coinfecting with HIV, and 53% with a history of TB disease.

Fifty-four percent of patients were treated at rural sites and 45% were treated in the Eastern Cape.

There were 87 youth (17%) in the total sample (Table 1). The comparison of adults and youth indicated that the 2 groups significantly differed. It was more common for youth to have formal education and be students and for adults to be employed and living with a partner. HIV coinfection was 80.9% among adults and 47.7% among youth ($P < .001$). There was no difference in the percentage of adults versus youth with HIV on antiretroviral treatment ($P = .730$). History of TB was also higher among adults (57.4%) versus youth (29.9%; $P < .001$). Supplemental Table 1 (available in the online version of the journal) details patient and site characteristics by treatment site.

Timing of Treatment Initiation

Among the 521 patients enrolled, 82 (16%) received DR-TB treatment in 5 or less days. Table 2 presents the number and percent of patients who received treatment per guideline and median number of days to treatment initiation by age group. Treatment initiation within 5 days did not differ significantly by age subgroups ($\chi^2 = 0.716$, degrees of freedom [df] = 3, $P = .870$). The

Table 2. Days to Tuberculosis Treatment: Descriptive Statistics^a.

Time to Treatment	Total (N = 521)	Age Groups (Years)				P
		13-24 (n = 87)	25-35 (n = 193)	36-50 (n = 184)	50+ (n = 57)	
Per guideline (5 or less days to treatment), n (%)	82 (15.7%)	14 (16.1%)	30 (15.5%)	27 (14.7%)	11 (19.3%)	.8695
Days to treatment						
Mean	17.1	17.2	15.5	19.3	15.3	
Standard deviation	18.4	19.0	14.9	21.7	15.5	
Median	11.0	12.0	10.0	13.5	9.0	.2792
25th, 75th percentiles	7.0, 20.0	8.0, 21.0	7.0, 18.0	7.0, 23.0	7.0, 18.0	
Minimum, maximum	0.0, 180.0	0.0, 142.0	1.0, 87.0	0.0, 180.0	1.0, 77.0	
Log (days to treatment + 1)						
Mean	2.6	2.6	2.5	2.6	2.5	.4435
SD	0.8	0.8	0.7	0.9	0.8	
Median	2.5	2.6	2.4	2.7	2.3	
25th, 75th percentiles	2.1, 3.0	2.2, 3.1	2.1, 2.9	2.1, 3.2	2.1, 2.9	
Minimum, maximum	0.0, 5.2	0.0, 5.0	0.7, 4.5	0.0, 5.2	0.7, 4.4	

^aLog of days to treatment + 1 = natural log of (days to treatment + 1); Per guideline: P value for $4 \times 2 \chi^2$ test; days to treatment: P value for nonparametric Kruskal-Wallis test; Log (days to treatment + 1): P value for a general linear model.

Table 3. DR-TB Treatment per Guidelines (≤ 5 Days): Bivariate Logistic Regression Models^a.

Variables	N	Wald χ^2	df	OR	OR 95% CI	Model R ²	P
Age (years)	521	0.07	1	1.003	0.982-1.025	0.000	.795
Sex	521	0.57	1	0.944	0.587-1.518	0.000	.812
History of TB disease	514	2.31	1	1.455	0.897-2.361	0.005	.128
HIV coinfection	510	1.96	1	1.536	0.842-2.801	0.004	.162
Urban site	521	1.50	1	0.741	0.459-1.197	0.003	.221
EC province site	521	1.56	1	1.351	0.842-2.166	0.003	.212

Abbreviations: DR-TB, disease-resistant tuberculosis; df, degrees of freedom; OR, odds ratio; CI, confidence interval; EC, Eastern Cape.

^aAge included as a continuous variable from older to younger.

median number of days to treatment initiation was 11 (range = 0-180). Time to treatment did not differ by age group in number of days (Kruskal-Wallis: $\chi^2 = 3.841$, $P = .279$) nor log of days to treatment (GLM: $F = 0.89$, $df = 3$, 517, $P = .444$).

Age and Treatment Initiation in 5 Days or Less

Table 3 presents the results from bivariate logistic regression models for treatment initiation per guideline. Treatment initiation per guideline was not associated with age ($P = .795$). No covariates were significant at $P < .10$ level in bivariate analysis.

Age and Days to Treatment Initiation

Table 4 details the results of the set of bivariate and multivariate linear regression models for the log of days to

Table 4. DR-TB Treatment in Total Time to DR-TB Treatment: Bivariate and Multivariate Models^a.

	N	t	df	P
Bivariate models				
Age	521	-0.16	1	.876
Sex	521	0.50	1	.618
History of TB disease	514	-0.44	1	.659
HIV coinfection	510	-1.39	1	.164
Urban site	521	3.58	1	.000
EC Province site	521	-1.68	1	.093
Multivariate model ^b				
Age	521	-.10	1	.924
Urban site	521	3.64	1	.000
EC Province site	521	-1.82	1	.070

Abbreviations: DR-TB, disease-resistant-tuberculosis; EC, Eastern Cape.

^aAge included as a continuous variable from older to younger

^bMultivariate model: age and variables significant at $P < .10$ level.

treatment initiation. Days to treatment was not associated with age ($P = .876$). Urban site ($P = .000$) and Eastern Cape province site ($P = .093$) were retained for the multivariate model in addition to age. Only urban site remained significant ($P = .000$).

Urban Site and Treatment Initiation

Of the covariates examined only location of care was associated with the median days to treatment. Exploratory analysis of the timing of treatment by location found that the median days to treatment initiation for those treated at rural versus urban sites was 10 versus 15 days ($t = 3.64$, $df = 1$, $P = .000$; Supplemental Table 2, available in the online version of the journal). Among rural sites, the timing of treatment for youth was 10 days and adults 10 days. Among urban sites, the timing of treatment for youth was 16 days and adults 14 days.

Discussion

Little is known regarding the time to DR-TB treatment, and to our knowledge, this has never been assessed specifically for youth and adults in South Africa. Treatment was delayed beyond recommendations for 84% of individuals, regardless of age. Only 1 in 6 individuals received DR-TB treatment per South African guidelines with median time to treatment of 11 days. Treatment initiation within 5 days varied from 0% to 38% across locations, with earlier treatment at rural sites. These findings indicate opportunities to improve the timeliness of DR-TB treatment for patients of all ages in South Africa.

The World Health Organization promotes early treatment initiation within 4 weeks of DR-TB diagnosis.¹³ Time to treatment of 11 days in this study is shorter than previously reported studies in South Africa, reporting an average of 2 weeks to more than 2 months.¹⁴⁻¹⁸ Delayed initiation and inappropriate treatment are major barriers to cure for DR-TB in South Africa, leading to widespread community transmission.¹⁹⁻²¹ Of note, none of these prior studies specifically compared youth and adults.

Youth aged 15 to 24 years have been identified as being exceptionally vulnerable to delays in diagnosis, treatment initiation, and appropriate treatment for HIV care.^{7,9,12,22-26} However, age was not a significant predictor of time to treatment initiation in this study. Most youth were in their early 20s and thus the expected delay from previously studied barriers may not have been as prominent. Future studies with a larger proportion of younger youth (13-18 years) may provide more insight into youth outcomes.

Patients at urban sites received treatment in significantly more days than those at rural sites. Some urban centers are overwhelmed with referrals and must place patients on waitlists, potentially contributing to longer delays. Although our study did not examine availability of diagnostic technologies, health care providers, or the provision of centralized care, it is possible that findings were influenced by South African reform initiatives to improve rural DR-TB care.²⁷ Recently, Iruedo et al found that diagnostic modality (GeneXpert, Line Probe Assay, culture) reduced the time for diagnosis of individuals treated in a rural South African setting; however, modality did not affect time from diagnosis to treatment initiation, which was a median of 14 days, similar to results in other studies.^{28,29} Although age was assessed as a factor in these studies, neither compared youth with adults.

Additional research inclusive of youth with DR-TB is necessary to examine modifiable factors that may decrease treatment delays.^{3,30} Guideline implementation is important, and gaining insight into factors related to DR-TB treatment initiation can inform providers and policy makers. Although age did not influence time to treatment in this sample, tailored youth interventions should still be considered and expanded if effective.^{7,30} Inclusiveness of youth and adolescents allows for greater generalizability than many previous reports of adult-only populations.

Limitations

Although there was no evidence that time to treatment was a function of age, this study had an underrepresentation of younger youth. Also, patients were enrolled at time of treatment initiation rather than when sputum was collected. Thus, the sample inherently lacked patients lost to follow-up between providing a sputum and receiving a result. This was a subanalysis of a parent study not specifically designed to evaluate factors affecting treatment timing; however, the NCM intervention did not affect timing because the intervention only began after patients initiated treatment. This study lacked the opportunity to examine additional factors that may have better predicted DR-TB treatment timing, such as attitudes and health beliefs toward treatment initiation or barriers to treatment initiation. Additional characteristics regarding the delivery system differences in each site, such as access to providers and resources, may be informative.

Conclusion

This analysis found that timing of treatment initiation for individuals with DR-TB, with and without HIV

coinfection, in 2 South African provinces did not differ by age yet individuals at rural sites received treatment earlier than at urban sites. Only 16% of individuals met South African guidelines. Early treatment initiation is critical for disease prevention and transmission, and decreasing additional resistance. Future research should aim to include more teens and incorporate data regarding patient and provider attitudes and beliefs toward treatment.

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Author Contributions

BJvdW: Contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JPB: Contributed to conception and design; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SS: Contributed to conception and design; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JH: Contributed to conception and design; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

CKC: Contributed to conception and design; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JEF: Contributed to conception and design; contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Supplemental Material

Supplementary material for this article is available online.

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