Antiretroviral Regimen Durability and Success in Treatment-Naive and Treatment-Experienced Patients by Year of Treatment Initiation, United States, 1996–2011

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Background: Although modern combination antiretroviral therapy (cART) regimens are better tolerated and less complex than earlier treatments, regimen modification or discontinuation remains a concern.

Methods: We studied HIV Outpatient Study (HOPS) participants who initiated the first or second cART regimens during: 1996–1999, 2000–2003, 2004–2007, and 2008–2011. We analyzed regimen durability (time to regimen modification) and success (achieving undetectable plasma HIV RNA) for the first and second cART regimens using Kaplan–Meier curves and log-rank tests, and examined factors associated with durability and success of the first cART regimen using proportional hazards models.

Results: Durability of cART was progressively longer for cART regimens initiated in more recent periods: median first cART regimen durations were 1.0, 1.1, 2.1, and 4.6 years in 1996–1999, 2000–2003, 2004–2007, and 2008–2011, and the median second cART durations were 0.9, 1.2, 2.8, and 3.9 years, respectively (both $P < 0.001$). Comparing 1996–1999 and 2008–2011, the percentage of patients who achieved an undetectable HIV RNA within 6 months of first cART initiation increased from 65% to 81% and from 63% to 80% on second cART (both $P < 0.001$). Among patients initiating first cART during 2008–2011, black non-Hispanic/Latino race/ethnicity and ≥twice-daily dosing were significantly associated with higher rates of regimen modification ($P < 0.05$), and higher baseline HIV RNA levels were associated with failure to achieve an undetectable HIV RNA ($P < 0.001$).

Conclusions: Among HIV-infected U.S. adults in routine HIV care, durability of the first and second cART regimens and the likelihood of prompt virological suppression increased during 1996–2011, coincident with the availability of more tolerable, less complex cART options.

Key Words: antiretroviral therapy, durability, cohort study

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INTRODUCTION

Combination antiretroviral therapy (cART) has resulted in marked and sustained reductions in morbidity and mortality among HIV-infected persons.[1] Although newer drug combinations allow for reduced pill burden and improved toxicity profiles, remaining concerns that may account for regimen discontinuation or modification include drug resistance, tolerability, regimen complexity, financial cost, and concerns over potential medication interactions. The risk of cART treatment failure decreases with increased duration of HIV RNA suppression and increases with successive cART regimens.[2,3] Maximizing the durability of the first and subsequent effective cART regimens remains crucial for optimizing long-term management for HIV-infected patients.

Reports from U.S. studies early in the cART era indicated that initial cART regimen duration ranged from a median of 11.8 months to 2.8 years, depending on year of treatment initiation.[2,4–7] Previously, we reported that patients in the HIV Outpatient Study (HOPS) seen in 1994–2002 received a mean of 1.8 cART regimens per person over a 39-month follow-up period and spent progressively less time on subsequent regimens.[2] Factors associated with shorter duration of initial regimens included not receiving a protease inhibitor (PI)-containing regimen and higher baseline HIV RNA levels (>100,000 copies/mL). A single-center study of HIV-infected patients initiating cART in 2000–2007 indicated that the median duration of the first cART regimen lengthened from more than 2.1 to 2.9 years after the introduction of once-daily, fixed-dose combination regimens in 2004,[5] suggesting

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improved regimen durability as a result of regimen simplification. A recent analysis of data from the Multicenter AIDS Cohort Study found that median duration of first cART regimens for antiretroviral-naive men initiating cART in 2006–2009 was more than 3 years, a substantial improvement since earlier years.[7]

We examined how cART regimen use, duration, and factors associated with regimen modification have evolved in the HOPS during 1996–2011. Given changing trends in antiretroviral toxicities, regimen complexity, and resultant challenges in medication adherence,[8–10] we sought to determine whether regimen duration and rates of virological suppression have increased over this 15-year period among patients who initiated the first and/or second cART regimens.

METHODS

The HIV Outpatient Study

The HOPS is an ongoing, prospective observational cohort study that has continuously recruited and followed HIV-infected patients since 1993. In the time frame of this analysis, study sites included 12 clinics (6 university, 4 public, and 2 private) in 8 U.S. cities, with a total enrollment of more than 10,000 patients (approximately 2500 actively seen in any given year). We analyzed data from HOPS participants seen at clinic sites located in Tampa, FL (2 sites); Washington, DC; Denver, CO (2 sites); Chicago, IL (2 sites); Portland, OR; Walnut Creek, CA; Oakland, CA; Stony Brook, NY; and Philadelphia, PA. HOPS clinicians have extensive experience treating HIV-infected patients. The study protocol is approved and renewed annually by each participating institution's ethical review board. All study participants provide written informed consent.

Trained staff at each site abstract outpatient medical record information and electronically enter these data and submit them to the data management center to be compiled centrally, reviewed, and edited before analysis. Abstracted information includes demographic characteristics and risk factors for HIV infection; diagnoses; prescribed medications, including dose and duration; laboratory values, including $CD4^+$ cell counts and plasma HIV RNA levels (viral loads); causes of mortality and hospitalizations; and primary medical care payment source.

Study Population

We limited analysis to patients who were ART-naive before starting their first cART regimen, had complete documentation of ART history, and initiated either the first or second cART regimen during one of 4 calendar periods: 1996–1999, 2000–2003, 2004–2007, or 2008–2011 while under the observation in the HOPS. We used the HOPS data set updated as of December 31, 2013; data from patients receiving ongoing cART regimens were censored for analysis on June 30, 2013 to allow for lag in data entry. In this way, we ensured that patients who initiated cART through the end of 2011 had an opportunity to be observed while receiving cART for at least 1 year.

Definitions of Predictor and Outcome Variables

For this analysis, we defined cART as 3 or more antiretroviral drugs. "Baseline" was defined as the date of the first or second cART regimen initiation, as appropriate. Baseline viral load and $CD4^+$ cell counts were the measurements obtained closest to cART regimen start, and within 183 days before and up to 7 days after regimen start. We analyzed 2 outcomes: cART regimen modification and virological suppression after baseline. Regimen modification was defined as a change in at least 1 antiretroviral drug in the regimen not including dose changes, switches to a fixed-dose combination of the same drugs, or switches between lamivudine and emtricitabine, and could include regimen discontinuation (temporary or permanent) defined as discontinuation of all drugs in the regimen for at least 14 days. Since discontinuations accounted for a minority of such events, we henceforth refer to regimen modification as encompassing modification/discontinuation. We characterized the first cART regimens by whether they contained nonnucleoside reverse transcriptase inhibitors (NNRTIs), low-dose ritonavir (RTV)-boosted or nonboosted PIs, or integrase or entry inhibitors, creating exclusive categories in the following order: NNRTI, integrase or entry inhibitor, RTV-boosted PI, and nonboosted PI. Virological suppression was defined as achieving an undetectable plasma HIV viral load (per manufacturer's assay-specific lower limit of detection cutoff) and calculated for HIV viral load tests with lower limit of detection <400 copies per milliliter ($n = 1652$ or 15% of viral load measurements using assays with a lower limit of detection of 400 copies/mL or higher in earlier calendar years were excluded from analysis).

Statistical Analyses

To compare distinct subgroups of patients across the 4 calendar periods, we used a likelihood ratio χ^2 or a Jonckheere–Terpstra trend test. For treatment-naive persons who initiated the first cART regimen during one of the calendar periods (1996–1999, 2000–2003, 2004–2007, and 2008–2011), we used Kaplan–Meier survival curves that incorporate the censoring to estimate time to regimen modification and time to virological suppression and log-rank tests to compare curves among calendar periods. We similarly analyzed cART treatment-experienced persons who initiated second cART regimens during these periods. Because some patients were included in both the first and second cART regimen analyses (see Results for details), outcomes for the first and second regimen durations for these patients are correlated; thus, the first vs. the second regimen durations for the same calendar period were not directly compared statistically in our analysis. Furthermore, for treatment-naive patients who initiated the first cART regimens, we used multivariable proportional hazards regression models to identify factors independently associated with regimen modification and with virological suppression for regimens initiated in each calendar period. We adjusted for sociodemographic variables (eg, sex, race/ethnicity, and insurance) and HIV-related measures (eg, baseline $CD4^+$ cell count

and class of cART regimen) that we considered as potentially associated with achieving a more durable response and virological suppression while on cART. All variables were included in each of the models regardless of significance, with the exception of variables that were not relevant in the period of interest, ie, integrase inhibitor use before 2008. In the analysis of time to virological suppression, for patients with missing baseline viral load values, we used the Markov chain Monte Carlo method for multiple imputations[11,12] to estimate baseline viral loads using demographic and baseline $CD4^+$ cell count data. This process involves using information from patients with known baseline viral loads to estimate baseline viral loads for patients with unknown information. Assuming that patients with similar baseline $CD4^+$ cell counts and demographic characteristics are also likely to have similar baseline viral loads, we created new data sets that included baseline viral load information statistically "imputed" for patients previously missing these data. Five imputations, the default quantity, were created by the statistical software. The results of the 5 analyses were then combined to obtain a measure of the error produced by this imputation process. Statistical analyses were performed using SAS v9.3 (Cary, NC).

RESULTS

Demographic and Clinical Characteristics

Among 8910 HOPS patients with ≥2 visits during 1996–2011, we identified 1734 patients who met inclusion criteria for the first cART regimen analyses; we excluded 6827 patients who were ART-experienced at the start of HOPS observation or before 1996, 204 patients with an incomplete ART history recorded, and 145 patients who initiated cART after 2011 (ie, outside the time frame for this analysis).

In a separate selection process, among 3068 HOPS patients with ≥2 visits during 1996–2011, complete ART histories, and whose only antiretroviral experience was a single cART regimen (initiated before or after start of HOPS observation), we identified 897 patients meeting inclusion criteria for the second cART regimen analyses; we excluded 2104 patients who did not start the second cART regimen during HOPS observation, and 67 who started the second cART after 2011 (ie, outside the time frame for this analysis).

Thus, we analyzed 1734 persons who initiated the first cART regimens (494 in 1996–1999, 422 in 2000–2003, 410 in 2004–2007, and 408 in 2008–2011) and 897 who initiated the second cART regimens (181 in 1996–1999, 268 in 2000–2003, 246 in 2004–2007, and 202 during 2008–2011) during the study period. Of the 897 patients included in the analysis of the second cART, 579 were included in the analyses of the first cART (122 in 1996–1999, 149 in 2000–2003, 172 in 2004–2007, and 136 in 2008–2011). Demographic and clinical characteristics of patients starting the first and second cART regimens are shown in Table 1. Of the 1734 and 897 who initiated the first and second cART regimens, there were 212 (12.2%) and 30 (3.3%), respectively, with no pre-cART viral load recorded whose values were therefore imputed.

Among first cART initiators, median age was 38 years [interquartile range (IQR) 31–45], and the most were male (77%), many were white non-Hispanic/Latino (44%), in the risk group of men who have sex with men (53%), and had private insurance (53%). Among patients who initiated second cART, median age was 40 years (IQR 34–47), and most were male (82%), white non-Hispanic/Latino (50%), men who have sex with men (59%), and had private insurance (66%). Most demographic characteristics did significantly change over time among patients who initiated first cART: median age increased slightly, the percentage of black non-Hispanic/Latinos and Hispanic/Latinos increased, and the percentage who reported a history of injection drug use (IDU) or who received cART regimens dosed more often than once daily decreased across the calendar periods; for second cART, median age increased, and the proportion who reported a history of IDU or who received cART regimens dosed more often than once daily decreased across the calendar periods (Table 1). These demographic trends were comparable with those observed across these calendar periods in the overall HOPS cohort (data not shown).[13,14]

Among the first cART initiators, median baseline plasma viral load was 4.8 $\log_{10}$ copies per milliliter (IQR 4.2–5.3) and median baseline $CD4^+$ cell count was 260 cells per cubic millimeter (IQR 102–407); median baseline viral load decreased among patients initiating cART over the 4 calendar periods, ranging from 4.7 to 4.5 $\log_{10}$ copies per milliliter ($P = 0.002$ for trend), and median $CD4^+$ cell count increased over time from 262 to 318 cells per cubic millimeter ($P = 0.001$ for trend). For the second cART initiators, median baseline plasma viral load was 2.0 $\log_{10}$ copies per milliliter (IQR 1.4–3.5) and median baseline $CD4^+$ cell count was 397 cells per cubic millimeter (IQR 219–639); median baseline viral load was progressively lower over the 4 calendar periods, ranging from 3.0 to 1.7 $\log_{10}$ copies per milliliter, and median $CD4^+$ cell count increased over time from 294 to 480 cells per cubic millimeter (both $P < 0.001$).

The most commonly prescribed the first cART regimens included a nonboosted PI in calendar period 1996–1999, an NNRTI in 2000–2003 and 2008–2011, and a RTV-boosted PI in 2004–2007 (Table 1). The second cART regimens were most likely to include a nonboosted PI in 1996–1999, an NNRTI in 2000–2003 and 2004–2007, and an integrase or entry inhibitor in 2008–2011. Over time, the daily dosing frequency of the first and second cART regimens diminished; for example, 50% of the first cART regimens were dosed 3 times daily in 1996–1999 compared with less than 1% in 2008–2011. The first and second cART regimens were more likely to involve once-daily dosing in more recent periods ($P < 0.001$). Among regimens prescribed during 2008–2011, 72% of the first and 63% of the second cART regimens were once-daily.

cART Regimen Duration and Success

Combination ART regimens were modified for 1231 (71%) of 1734 patients initiating the first cART regimen and 641 (72%) of 897 patients initiating the second cART regimen; observation time was censored for the remaining patients who continued cART regimens past the end of the

TABLE 1. Baseline Demographic and Clinical Characteristics of Patients Initiating First and Second cART, the HOPS, 1996–2011

Baseline Characteristics Number (%) or Median (IQR)	Initiating the First cART Regimen					
	Overall (n = 1734)	1996–1999 (n = 494)	2000–2003 (n = 422)	2004–2007 (n = 410)	2008–2011 (n = 408)	*P**
Age, yrs	38 (31–45)	36 (32–43)	38 (32–44)	38 (31–46)	40 (90–47)	0.004
Male sex	1330 (76.7)	393 (79.6)	297 (70.4)	320 (78.1)	320 (78.4)	0.006
Race/ethnicity						0.001
White, non-Hispanic/Latino	767 (44.2)	258 (52.2)	165 (39.1)	185 (45.1)	159 (39.0)	
Black, non-Hispanic/Latino	672 (38.8)	162 (32.8)	181 (42.9)	151 (36.8)	178 (43.6)	
Hispanic/Latino	223 (12.9)	54 (10.9)	58 (13.7)	52 (12.7)	59 (14.5)	
Other race/ethnicity	72 (4.2)	20 (4.1)	18 (4.3)	22 (5.4)	12 (2.9)	
HIV transmission risk category						<0.001
MSM	923 (53.2)	281 (56.9)	184 (43.6)	225 (54.9)	233 (57.1)	
Heterosexual sex	571 (32.9)	146 (29.6)	170 (40.3)	125 (30.5)	130 (31.9)	
Intravenous drug use	123 (7.1)	45 (9.1)	35 (8.3)	28 (6.8)	15 (3.7)	
Other/unknown	117 (6.8)	22 (4.5)	33 (7.8)	32 (7.8)	30 (7.4)	
Insurance						0.011
Private	919 (53.0)	276 (55.9)	206 (48.8)	240 (58.5)	197 (48.3)	
Public	533 (30.7)	135 (27.3)	141 (33.4)	120 (29.3)	137 (33.6)	
Other/unknown	282 (16.3)	83 (16.8)	75 (17.8)	50 (12.2)	74 (18.1)	
HIV viral load, $\log_{10}$ c/mL	4.8 (4.2–5.3)	4.7 (4.2–5.3)	4.8 (4.3–5.4)	5.0 (4.5–5.4)	4.5 (4.0–5.0)	0.002
$CD4^+$ count, cells/mm^3	260 (102–407)	262 (98–458)	220 (53–379)	246 (103–349)	318 (186–440)	0.010
Regimen dosing						<0.001
Once daily	607 (35.0)	0 (0.0)	56 (13.3)	256 (62.4)	295 (72.3)	
Twice daily	867 (50.0)	249 (50.4)	353 (83.7)	153 (37.3)	112 (27.5)	
Thrice daily	260 (15.0)	245 (49.6)	13 (3.1)	1 (0.2)	1 (0.3)	
cART regimen components						<0.001
NNRTI	676 (39.0)	120 (24.3)	206 (48.8)	175 (42.7)	175 (42.9)	
NRTI's only	55 (3.2)	11 (2.2)	40 (9.5)	4 (1.0)	0 (0.0)	
PI and NNRTI	51 (5.9)	26 (5.3)	15 (3.6)	8 (2.0)	2 (0.5)	
Boosted PI	401 (23.1)	12 (2.4)	73 (17.3)	198 (48.3)	118 (28.9)	
Nonboosted PI	452 (26.1)	325 (65.8)	88 (20.9)	24 (5.9)	15 (3.7)	
Integrase or entry inhibitor	99 (5.7)	0 (0.0)	0 (0.0)	1 (0.2)	98 (24.0)	
ZDV or d4T-containing cART	892 (51.4)	478 (96.8)	328 (77.7)	76 (18.5)	10 (2.5)	<0.001
ABC or TDF-containing cART	908 (52.4)	20 (4.1)	161 (38.2)	334 (81.5)	393 (96.3)	<0.001
Baseline Characteristics Number (%) or Median (IQR)	**Initiating the Second cART Regimen**					
	Overall (n = 897)	**1996–1999 (n = 181)**	**2000–2003 (n = 268)**	**2004–2007 (n = 246)**	**2008–2011 (n = 202)**	***P****
Age, yrs	40 (34–47)	38 (34–45)	40 (34–45)	40 (34–47)	44 (36–51)	<0.001
Male sex	735 (81.9)	157 (86.7)	218 (81.3)	208 (84.6)	152 (75.3)	0.019
Race/ethnicity						0.33
White, non-Hispanic/Latino	452 (50.4)	89 (49.2)	136 (50.8)	133 (54.1)	94 (46.5)	
Black, non-Hispanic/Latino	309 (34.5)	70 (38.7)	93 (34.7)	74 (30.1)	72 (35.6)	
Hispanic/Latino	110 (12.3)	19 (10.5)	34 (12.7)	32 (13.0)	25 (12.4)	
Other race/ethnicity	26 (2.9)	3 (1.7)	5 (1.9)	7 (2.9)	11 (5.5)	
HIV transmission risk category						0.54
MSM	531 (59.2)	104 (57.5)	161 (60.1)	157 (63.8)	109 (54.0)	
Heterosexual sex	258 (28.8)	52 (28.7)	77 (28.7)	64 (26.0)	65 (32.2)	
Intravenous drug use	56 (6.2)	16 (8.8)	16 (6.0)	12 (4.9)	12 (5.9)	
Other/unknown	52 (5.8)	9 (5.0)	14 (5.2)	13 (5.3)	16 (7.9)	
Insurance						0.07
Private	590 (65.8)	122 (67.4)	173 (64.6)	177 (72.0)	118 (58.4)	
Public	223 (24.9)	44 (24.3)	68 (25.4)	46 (18.7)	65 (32.2)	
Other/unknown	84 (9.4)	15 (8.3)	27 (10.1)	23 (9.4)	19 (9.4)	
HIV viral load, $\log_{10}$ c/mL	2.0 (1.4–3.5)	3.0 (1.9–4.4)	2.3 (1.4–3.6)	1.6 (1.4–3.0)	1.7 (1.4–2.6)	<0.001

TABLE 1. (*Continued*) Baseline Demographic and Clinical Characteristics of Patients Initiating First and Second cART, the HOPS, 1996–2011

Baseline Characteristics Number (%) or Median (IQR)	Initiating the Second cART Regimen					
	Overall (n = 897)	1996–1999 (n = 181)	2000–2003 (n = 268)	2004–2007 (n = 246)	2008–2011 (n = 202)	*P**
$CD4^+$ count, cells/mm^3	397 (219–639)	294 (150–552)	409 (232–668)	380 (237–596)	480 (284–728)	<0.001
Regimen dosing						<0.001
Once daily	412 (45.9)	20 (11.1)	77 (28.7)	187 (76.0)	128 (63.4)	
Twice daily	436 (48.6)	117 (64.6)	187 (69.8)	59 (24.0)	73 (36.1)	
Thrice daily	49 (5.5)	44 (24.3)	4 (1.5)	0 (0.0)	1 (0.5)	
cART regimen components						<0.001
NNRTI	335 (37.4)	55 (30.4)	124 (46.3)	110 (44.7)	46 (22.8)	
NRTI's only	27 (3.0)	2 (1.1)	23 (8.6)	1 (0.4)	1 (0.5)	
PI and NNRTI	52 (5.8)	21 (11.6)	18 (6.7)	7 (2.9)	6 (3.0)	
Boosted PI	212 (23.6)	4 (2.2)	56 (20.9)	95 (38.6)	57 (28.2)	
Nonboosted PI	190 (21.2)	99 (54.7)	47 (17.5)	31 (12.6)	13 (6.4)	
Integrase or entry inhibitor	81 (9.0)	0 (0.0)	0 (0.0)	2 (0.8)	79 (39.1)	
ZDV or d4T-containing cART	421 (46.9)	167 (92.3)	193 (72.0)	47 (19.1)	14 (6.9)	<0.001
ABC or TDF-containing cART	559 (62.3)	20 (11.1)	122 (45.5)	224 (91.1)	193 (95.5)	<0.001

*Jonckheere–Terpstra test of trend from earlier to later periods or likelihood ratio χ^2 test.
ABC, abacavir; c/mL, copies per milliliter; d4T, stavudine; MSM, men who have sex with men; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

follow-up period (Table 2). These regimen modifications included 318 regimen discontinuations (of at least 2 weeks) for the first cART regimens and 109 regimen discontinuations for the second cART regimens. Estimated median durations of the first and second cART regimens were 1.6 [95% confidence interval (CI): 1.4 to 1.7] and 1.6 (95% CI: 1.4 to 1.8) years, respectively, and each increased significantly across calendar periods (Figs. 1A, B, $P < 0.001$). The median first cART regimen durations increased over calendar time; they were 1.0 (95% CI: 0.8 to 1.1), 1.1 (95% CI: 1.0 to 1.5), 2.1 (95% CI: 1.6 to 2.6), and 4.6 (3.8 to indeterminate upper confidence limit) years for regimens initiated in 1996–1999, 2000–2003, 2004–2007, and 2008–2011, respectively. The percentage of patients remaining on the first cART regimens at 24 months after initiation was 45% overall; this percentage was 33%, 38%, 51%, and 63%, respectively, for patients starting the first cART during each of the 4 calendar periods (Table 2). The median second cART regimen durations also increased over calendar time; they were 0.9 (95% CI: 0.7 to 1.1), 1.2 (95% CI: 0.9 to 1.3), 2.8 (95% CI: 2.1 to 4.7), and 3.9 (95% CI: 2.3 to indeterminate upper confidence limit) years, respectively. The percentage of patients remaining on the second cART regimens at 24 months after initiation was 43% overall, and 25%, 31%, 57%, and 58%, respectively, for the 4 calendar periods (Table 2).

The percentage of patients who achieved virological suppression within 6 months of cART initiation significantly increased over the 4 calendar periods, from 65% to 81% for the first cART regimen, and from 63% to 80% for the second cART regimen (Figs. 1C, D, $P < 0.001$ for each). Among patients with baseline HIV viral loads >1000 copies per milliliter, the percentage who achieved virological suppression within 6 months of regimen initiation also increased over time, from 41% to 64% on the first cART regimen ($P < 0.001$) and from 33% to 67% on the second cART regimen ($P < 0.001$).

Factors Associated With the First cART Regimen Duration and Success

For the first cART regimens initiated during the first calendar period (1996–1999), factors independently associated with higher rates of regimen modification were being of black non-Hispanic/Latino race/ethnicity, having public or no insurance, having a baseline $CD4^+$ cell count <200 cells per cubic millimeter, and receiving nonboosted PI-containing regimens [adjusted hazard ratios (aHRs) 1.30, 1.32, 1.25, and 1.27, respectively, Table 3]. For the first cART regimens initiated during 2000–2003, twice-or-more daily dosing was associated with higher rates of first cART modification (aHR 1.50). For the first cART regimens initiated during 2004–2007, age <40 years, IDU HIV transmission risk, twice-or-more daily dosing, and receiving a regimen containing RTV-boosted PI was associated with higher rates of first cART modification (aHRs 1.35, 1.59, 1.58, and 1.57, respectively). For the first cART regimens initiated during 2008–2011, black non-Hispanic/Latino race/ethnicity (aHR 1.64) and twice-or-more daily dosing (aHR 1.72) were associated with higher rates of first cART modification.

For the first cART regimens initiated during 1996–1999, factors independently associated with lower rates of achieving virological suppression included IDU HIV transmission risk (aHR 0.32) and having public or no insurance (aHR 0.66, Table 4). For the first cART regimens initiated during 2000–2003, black non-Hispanic/Latino race/ethnicity was associated with not achieving virological suppression (aHR 0.57). For the first cART regimens initiated during 2004–2007, black non-Hispanic/Latino race/ethnicity, higher baseline viral load (per $\log_{10}$ copies/mL increase), twice-or-more daily dosing, and receiving nonboosted PI-containing regimens were associated with not achieving virological suppression (aHR 0.69, 0.75 per 1 $\log_{10}$ copies/mL, 0.71, and 0.46, respectively). For the first cART regimens initiated during 2008–2011, higher baseline

TABLE 2. The First and Second cART Regimen Modifications and Discontinuations by Calendar Period of Regimen Initiation, the HOPS, 1996–2011

	The First cART Regimen					
Characteristic	**Overall (n = 1734)**	**1996–1999 (n = 494)**	**2000–2003 (n = 422)**	**2004–2007 (n = 410)**	**2008–2011 (n = 408)**	***P*‡**
Observed to modify/discontinue cART regimen, n (%)*	1231 (71.0)	453 (91.7)	349 (82.7)	271 (66.1)	158 (38.7)	<0.001
Without recorded viral load	306 (24.9)	105 (23.2)	82 (23.5)	64 (23.6)	55 (34.8)	
With undetectable viral load at last measurement	521 (42.3)	188 (41.5)	142 (40.7)	133 (49.1)	58 (36.7)	
With detectable viral load at last measurement	404 (32.8)	160 (35.3)	125 (35.8)	74 (27.3)	45 (28.5)	0.11
Pre-cART viral load, n (%)						
No pre-cART viral load recorded	212 (12.2)	76 (15.4)	64 (15.2)	39 (9.5)	33 (8.1)	
Pre-cART viral load ≤1000 c/mL	55 (3.2)	8 (1.6)	21 (5.0)	7 (1.7)	19 (4.7)	
Pre-cART viral load >1000 c/mL	1467 (84.6)	410 (83.0)	337 (79.9)	364 (88.8)	356 (87.3)	0.16
Remained on cART regimen at 6m†	72.3 (70.1–74.3)	65.4 (61.0–69.5)	68.8 (64.1–73.0)	75.6 (71.1–79.5)	81.0 (76.8–84.5)	<0.001
Remained on cART regimen at 12m†	59.2 (56.8–61.5)	48.5 (44.0–52.9)	54.0 (49.1–58.7)	62.7 (57.8–67.3)	74.6 (69.9–78.6)	<0.001
Remained on cART regimen at 24m†	44.9 (42.5–47.3)	32.5 (28.3–36.7)	38.0 (33.3–42.8)	50.5 (45.4–55.4)	63.1 (58.0–67.9)	<0.001
Viral load undetectable by 6m of cART initiation†	53.5 (50.6–56.4)	38.8 (33.6–44.5)	51.2 (45.1–57.7)	59.8 (54.2–65.5)	64.6 (59.2–70.1)	<0.001
Viral load undetectable by 12m of cART initiation†	74.6 (71.9–77.2)	60.7 (54.9–66.5)	69.5 (63.4–75.5)	81.9 (77.0–86.3)	85.4 (81.1–89.3)	<0.001
Viral load undetectable by 6m of cART initiation, among those with baseline viral load >1000 c/mL†	55.4 (52.3–58.5)	41.3 (35.6–47.5)	54.9 (48.0–62.0)	61.2 (55.4–67.2)	64.3 (58.6–70.1)	<0.001
Viral load undetectable by 12m of cART initiation, among those with baseline viral load >1000 c/mL†	77.6 (74.8–80.3)	63.3 (57.2–69.5)	74.8 (68.2–81.0)	84.4 (79.4–88.7)	86.5 (81.9–90.4)	<0.001
	The Second cART Regimen					
Characteristic	**Overall (n = 897)**	**1996–1999 (n = 181)**	**2000–2003 (n = 268)**	**2004–2007 (n = 246)**	**2008–2011 (n = 202)**	***P*‡**
Observed to modify/discontinue cART regimen, n (%)*	641 (71.5)	170 (93.9)	232 (86.6)	149 (60.6)	90 (44.6)	<0.001
Without recorded viral load	164 (25.6)	49 (28.8)	50 (21.6)	31 (20.8)	34 (37.8)	
With undetectable viral load at last measurement	286 (44.6)	65 (38.2)	101 (43.5)	78 (52.4)	42 (46.7)	0.002
With detectable viral load at last measurement	191 (29.8)	56 (32.9)	81 (34.9)	40 (26.9)	14 (15.6)	
Pre-cART viral load, n (%)						
No pre-cART viral load recorded	30 (3.3)	8 (4.4)	8 (3.0)	7 (2.9)	7 (3.5)	
Pre-cART viral load ≤1000 c/mL	594 (66.2)	86 (47.5)	176 (65.7)	179 (72.8)	153 (75.7)	<0.001
Pre-cART viral load >1000 c/mL	273 (30.4)	87 (48.1)	84 (31.3)	60 (24.4)	42 (20.8)	
Remained on cART regimen at 6m†	73.6 (70.5–76.4)	63.1 (55.5–69.7)	69.3 (63.3–74.5)	80.8 (75.2–85.3)	80.1 (73.8–85.0)	<0.001
Remained on cART regimen at 12m†	61.3 (58.0–64.4)	47.8 (40.3–54.9)	54.9 (48.6–60.7)	69.0 (62.6–74.5)	72.8 (66.0–78.4)	<0.001
Remained on cART regimen at 24m†	42.8 (39.4–46.1)	25.0 (18.9–31.6)	31.3 (25.6–37.1)	56.7 (50.0–62.9)	58.1 (50.6–64.8)	<0.001
Viral load undetectable by 6m of cART initiation†	63.1 (59.3–67.0)	53.9 (44.6–63.8)	60.1 (52.7–67.6)	66.9 (60.1–73.5)	67.9 (60.5–75.1)	0.002
Viral load undetectable by 12m of cART initiation†	79.7 (76.1–83.0)	61.3 (51.4–71.3)	78.1 (70.7–84.7)	85.4 (79.5–90.3)	83.5 (76.9–89.0)	0.002
Viral load undetectable by 6m of cART initiation, among those with baseline viral load >1000 c/mL†	44.0 (36.2–52.7)	32.6 (20.0–50.2)	35.4 (23.3–51.4)	48.9 (33.8–66.5)	66.9 (49.0–83.8)	<0.001
Viral load undetectable by 12m of cART initiation, among those with baseline viral load >1000 c/mL†	61.7 (52.7–70.8)	42.6 (26.8–62.6)	58.5 (41.9–75.9)	69.8 (53.2–84.9)	79.3 (62.0–92.3)	<0.001

Only viral load tests with lower limit of detection <400 copies per milliliter are included in estimates of time to reach viral load goal.
*Percentage of patients observed to discontinue cART regimen as of December 31, 2013 (the remainder of patients remained on regimen and their observation were censored).
†%, 95% CI, based on the Kaplan–Meier estimate; *P* value represents logrank *P* value.
‡*P* value represents test of trend except where noted.
c/mL, copies per milliliter; m, months.

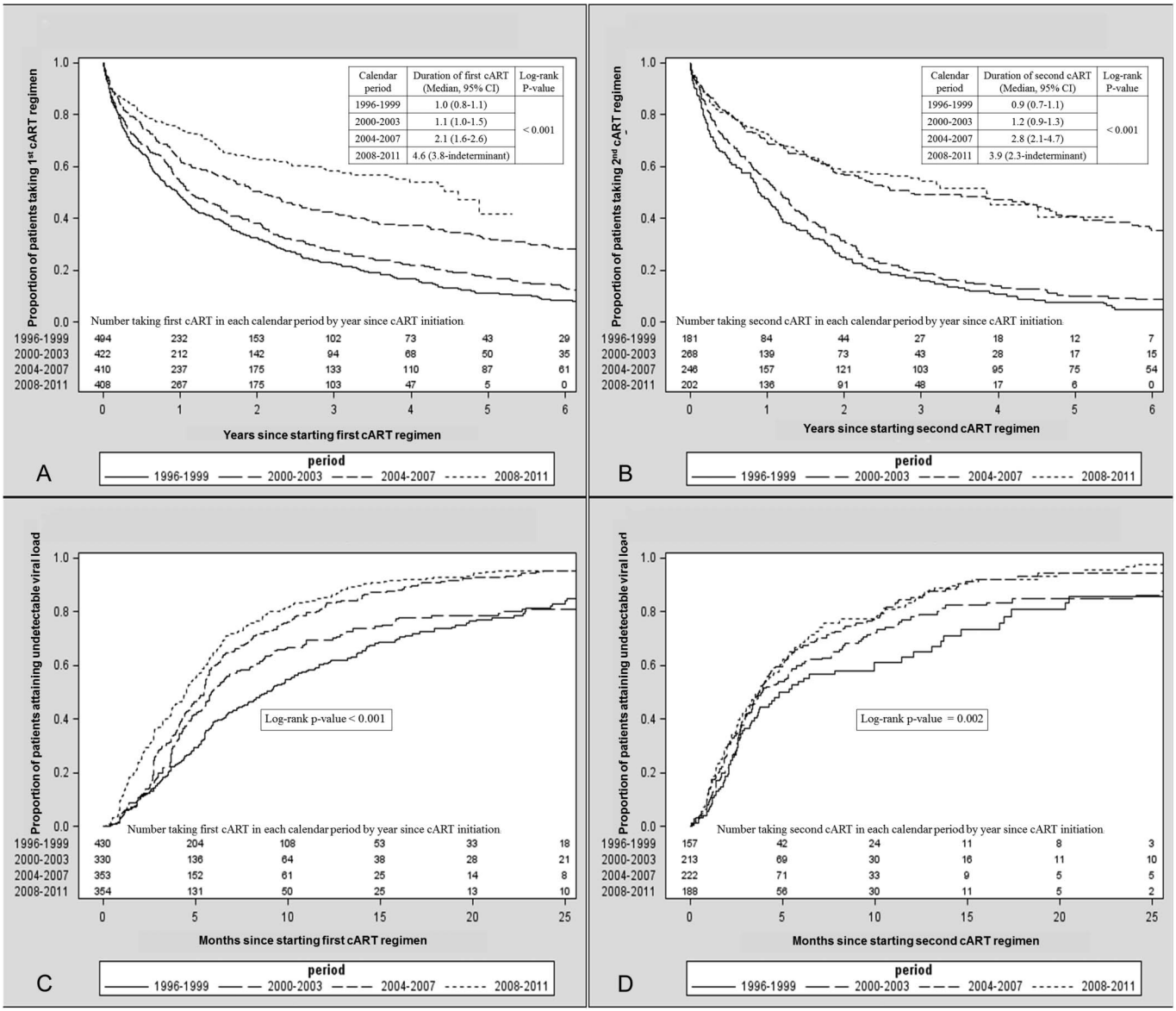

FIGURE 1. Years to the first (A) and second (B) regimen discontinuation and months to attaining undetectable viral load for the first (C) and second (D) cART regimen, by cART initiation calendar period (Kaplan–Meier curves), the HOPS, 1996–2011.

viral load was associated with not achieving virological suppression (aHR 0.73 per 1 $\log_{10}$ copies/mL).

DISCUSSION

In the HOPS, median durations of the first and second cART regimens have increased significantly over time during the 15-year period represented in this analysis, corroborating reports from earlier cohorts that included regimens initiated up to 2009.[5–7,15,16] These changes in cART regimen duration were temporally coincident with the availability of more tolerable, less complex cART regimens that required less frequent dosing. Although median regimen durations were only approximately 1 year for both the first and second cART among HOPS patients who initiated these regimens during the first 2 calendar periods of our study (1996–2003), they exceeded a median of 2 years in the latter 2 calendar periods (2004–2011) and approached 5 years for the first cART in the most recent calendar period ending in 2011. For the earlier periods, the first cART regimen durations were similar to those recently reported for other U.S. cohorts,[4–6] but the 4.6-year median duration of the first cART that we observed during the most recent calendar period (2008–2011), exceeded cART regimen durations recently reported from the Multicenter AIDS Cohort Study.[7] As the duration of the first and second cART regimens increased over time, the percentage of persons who achieved viral suppression within 6 months of regimen initiation likewise increased markedly

TABLE 3. Multivariable Cox Proportional Hazards Regression Models by Calendar Period of cART Initiation for Factors Associated With Time to the First cART Regimen Modification/Discontinuation, the HOPS, 1996–2011 [N = 1734; n = 1231 (71%) Observed to Discontinue the First ART Regimen During Follow-up Period]

Calendar Period of the First cART Initiation	1996–1999, N = 494		2000–2003, N = 422		2004–2007, N = 410		2008–2011, N = 408	
Number Observed to Modify/ Discontinue the First cART Regimen (%)	n = 453 (91.7)		n = 349 (82.7)		n = 271 (66.1)		n = 158 (38.7)	
Baseline Characteristic	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*
Age in years <40 (vs. ≥40 yrs)	1.16 (0.95 to 1.41)	0.15	0.99 (0.79 to 1.23)	0.91	1.35 (1.05 to 1.73)	0.020	1.07 (0.78 to 1.47)	0.69
Female sex (vs. male sex)	0.92 (0.71 to 1.18)	0.50	1.02 (0.80 to 1.30)	0.89	1.06 (0.77 to 1.48)	0.71	1.27 (0.86 to 1.87)	0.23
Black, non-Hispanic/Latino race/ ethnicity (vs. other race/ ethnicities)	1.30 (1.06 to 1.60)	0.012	1.25 (0.99 to 1.58)	0.06	1.31 (0.99 to 1.72)	0.06	1.64 (1.16 to 2.33)	0.006
IDU HIV transmission risk (vs. other HIV transmission risks)	1.08 (0.78 to 1.49)	0.66	1.00 (0.67 to 1.50)	0.99	1.59 (1.01 to 2.52)	0.047	0.97 (0.39 to 2.43)	0.95
Public/no insurance (vs. private insurance)	1.32 (1.08 to 1.62)	0.007	0.89 (0.71 to 1.12)	0.33	0.95 (0.72 to 1.26)	0.72	0.82 (0.57 to 1.17)	0.28
Baseline $CD4^+$ cell count <200 cells/mm^3 (vs. ≥200 cells/mm^3)	1.25 (1.03 to 1.51)	0.022	1.10 (0.89 to 1.37)	0.38	0.78 (0.61 to 1.01)	0.06	0.81 (0.58 to 1.14)	0.23
Twice-or-more daily dosing (vs. once-daily dosing)	n/a		1.50 (1.07 to 2.10)	0.020	1.58 (1.21 to 2.06)	<0.001	1.72 (1.05 to 2.81)	0.032
Boosted PI-containing cART (vs. NNRTI cART)	1.01 (0.55 to 1.85)	0.97	1.22 (0.91 to 1.63)	0.19	1.57 (1.19 to 2.08)	0.002	1.40 (0.96 to 2.05)	0.08
Unboosted PI-containing cART (vs. NNRTI cART)	1.27 (1.03 to 1.56)	0.026	1.23 (0.94 to 1.62)	0.13	1.12 (0.65 to 1.92)	0.69	1.38 (0.59 to 3.24)	0.46
Integrase or entry inhibitor-containing cART (vs. NNRTI cART)	n/a		n/a		n/a		0.56 (0.30 to 1.02)	0.06

Baseline characteristics listed in the table were included in all models except where noted.
n/a, not applicable (variable not included in the model because not relevant in the specific calendar period of interest); NNRTI, nonnucleoside reverse transcriptase inhibitor.

over time, corroborating randomized clinical trial-generated data that report improved potency, tolerability, and adherence associated with more contemporary regimens.[17]

Understanding cART regimen characteristics that were associated with increased rates of the first cART modification and viral nonsuppression in the most recent calendar period may inform regimen selection for contemporary patients. As in reports from other cohorts,[5] we found that twice or more daily dosing was associated with increased rates of cART regimen modification and decreased rates of achieving viral suppression. Once-daily cART regimens are preferred in current HIV treatment guidelines for initial therapy.[17] Furthermore, our findings concur with those from other cohorts suggesting that the use of NNRTI-containing regimens has been associated with decreased rates of cART modification compared with the use of some RTV-boosted PI-containing regimens.[5,7,15,18]

We found that black non-Hispanic race/ethnicity was a demographic associated with discontinuing or modifying cART for regimens initiated during 2008–2011. This could reflect lower regimen adherence among this patient group[19–22] or other ART-related factors such as financial cost, tolerability, or toxicity. Notably, during this same time, black non-Hispanic race/ethnicity was not associated with diminished likelihood of achieving viral suppression.

There are important methodological issues relevant to the interpretation of our results. Earlier analysis from the HOPS cohort demonstrated that first cART regimens tend to be more durable than subsequent ones,[2] which is consistent with clinical experience. However, no such trend emerged in our present multiyear study. We could not perform direct statistical comparisons of the first and second cART regimen durations because many patients included in the analyses of the first cART were not included in the analyses of the second cART, and by definition, observation on the second cART follows observation on the first cART, resulting in correlated data for some patients. Our analysis nonetheless indicates that effective and tolerable cART treatment options exist for treatment-experienced patients. In the most contemporary period evaluated, the likelihood of achieving treatment success (ie, remaining on durable, virally suppressive, and tolerable cART) did not seem to differ substantially for cART-treated patients compared with patients newly initiating cART.

The findings from our study are subject to additional limitations and caveats. First, we analyzed data abstracted from medical records of patients in routine HIV care; specific reasons for regimen modification or discontinuation were not uniformly charted or were missing for many patients, and cART adherence data, which may have impacted regimen

TABLE 4. Multivariable Cox Proportional Hazards Models by Calendar Period of cART Initiation for Factors Associated With Achieving an Undetectable HIV Viral Load Test Result* With the First cART Regimen, the HOPS, 1996–2011 [N = 1467; n = 996 (66%) Achieved an Undetectable Viral Load With the First cART Regimen]

Calendar Period of the First cART Initiation	1996–1999, N = 430		2000–2003, N = 330		2004–2007, N = 353		2008–2011, N = 354	
Number Achieving Undetectable Viral Load With the First cART (%)	n = 227 (52.8)		n = 190 (57.6)		n = 265 (75.1)		n = 284 (80.2)	
Baseline Characteristic	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*
Age in years <40 (vs. ≥40 yrs)	0.86 (0.65 to 1.12)	0.26	0.98 (0.73 to 1.33)	0.90	1.01 (0.79 to 1.31)	0.92	1.05 (0.82 to 1.33)	0.72
Female sex (vs. male sex)	0.88 (0.58 to 1.34)	0.55	0.74 (0.51 to 1.09)	0.13	1.11 (0.76 to 1.61)	0.60	1.08 (0.79 to 1.49)	0.62
Black, non-Hispanic/Latino race/ethnicity (vs. other race/ethnicities)	0.88 (0.63 to 1.23)	0.44	0.57 (0.40 to 0.81)	0.002	0.69 (0.49 to 0.95)	0.024	1.22 (0.93 to 1.59)	0.15
IDU HIV transmission risk (vs. other HIV transmission risks)	0.32 (0.17 to 0.62)	<0.001	1.24 (0.68 to 2.24)	0.48	1.58 (0.93 to 2.69)	0.09	2.18 (0.98 to 4.86)	0.06
Public/no insurance (vs. private insurance)	0.66 (0.49 to 0.89)	0.006	0.95 (0.69 to 1.29)	0.72	0.88 (0.65 to 1.20)	0.42	0.86 (0.67 to 1.11)	0.25
Viral load (per 1 $\log_{10}$ c/mL)†	0.91 (0.75 to 1.12)	0.37	0.88 (0.72 to 1.09)	0.24	0.75 (0.61 to 0.91)	0.005	0.73 (0.61 to 0.87)	<0.001
Baseline $CD4^+$ cell count <200 cells/mm^3 (vs. ≥200 cells/mm^3)	0.79 (0.59 to 1.08)	0.14	0.74 (0.53 to 1.03)	0.07	0.89 (0.67 to 1.17)	0.39	0.78 (0.58 to 1.04)	0.09
Twice-or-more daily dosing (vs. once-daily dosing)	n/a		n/a		0.71 (0.53 to 0.95)	0.022	1.23 (0.83 to 1.82)	0.30
Boosted PI-containing cART (vs. NNRTI cART)	0.95 (0.45 to 2.00)	0.89	0.82 (0.55 to 1.21)	0.32	1.09 (0.83 to 1.42)	0.55	1.04 (0.77 to 1.42)	0.79
Unboosted PI-containing cART (vs. NNRTI cART)	0.77 (0.58 to 1.02)	0.06	0.84 (0.56 to 1.27)	0.42	0.46 (0.24 to 0.87)	0.017	1.38 (0.69 to 2.76)	0.36
Integrase or entry inhibitor-containing cART (vs. NNRTI cART)	n/a		n/a		n/a		1.17 (0.76 to 1.78)	0.48

Baseline characteristics listed in the table were included in all models except where noted.
*Undetectable viral load was defined as one below the limit of detection for each given viral load assay.
†Values were imputed for patients with missing pre-cART viral load (Table 2).
c/mL, copies per milliliter; n/a, not applicable (variable not included in the model because not relevant in the specific calendar period of interest); NNRTI, nonnucleoside reverse transcriptase inhibitor.

duration, were not systematically gathered. Second, because of patient aging and other demographic shifts occurring over time among HOPS participants initiating cART, it is possible that changes in cART regimen durations could be influenced by these shifts and were not due solely to improvements in cART potency, tolerability, and regimen dosing during the time frame of the study. Third, because we assessed percentages of patients who achieved viral suppression based on prevailing lower thresholds of detection for viral load, which were relatively higher in earlier calendar years, our findings related to temporal improvements in virological suppression may be conservative. Fourth, despite the fact that the HOPS includes a large number of patients drawn from multiple and diverse HIV specialty clinics, our findings may not be generalizable to HIV-infected persons receiving cART in other care settings in the U.S. A recent analysis comparing the characteristics of HOPS patients to all HIV-infected persons included in the national HIV Surveillance System revealed that HOPS patients tended to be older, and more frequently non-Hispanic white, noninjection drug using, and diagnosed with AIDS.[23]

In summary, among HOPS participants, the duration of first and second cART regimens has increased substantially over time, particularly in the most recent (2008–2011) calendar period studied. Likewise, time to the achievement of viral suppression after cART initiation decreased over time for both the first and second cART recipients. Our findings likely reflect the benefits of newer cART regimens in terms of improved efficacy, tolerability, and simplicity (with once-daily dosing for many regimens). We identified a patient group for whom regimen modification was more likely during the most recent calendar period (ie, persons of black, non-Hispanic/Latino race/ethnicity), suggesting that interventions aimed at improving ART adherence and tolerability in this patient group are justified to extend cART regimen longevity. Trends in cART regimen use, regimen durability, and reasons for regimen modification warrant ongoing surveillance to better inform regimen selection for persons receiving initial and subsequent cART.

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