

SUPPLEMENTARY MATERIAL

METHODS

- Marginal structural models fitted with Inverse Probability of Treatment Weighting
 - To balance baseline and time-varying confounders between the persister and non-persister cohorts, creating a pseudo-population where the effect of non-persistence to treatment is disentangled from measured confounders and DMT switches.

Baseline confounders

Variables	Encoding
EDSS at index* (within 3-month time window)	Numerical
Relapses in pre-Index Year	0,1,>1
Number of DMTs pre-Index	0,1,>1
Index DMT group	Categorical
Sex	F/M
Annualized total costs in pre-Index Year	Numeric

Time-varying confounders measured over 4 years of follow-up

Variables	Encoding
Current disability (EDSS score)	Numerical
Change in disability in the year before	Yes, no
Current Pregnancy status	Yes, no
MRI progression in the year before	Yes, no
Current age	Numerical
Current Time since diagnosis	Numerical
Relapses in the year before	0,1,>1
Current DMT group	Categorical
Annualized total costs in the year before	Numerical

Confounders at baseline for Non-Persisters and Persisters before and after Propensity score weighting

	Prior to IPTW-ATT			After IPTW-ATT		
	Non-Persisters (N=648)	Persisters (N=1,522)	SMD	Non-Persisters (N=648*)	Persisters (N=1245*)	SMD
Age (years)	37.14 (10.45)	40.24 (10.80)	0.292	37.14 (10.45)	37.73 (10.67)	0.055
Female sex	519 (80.1)	1042 (68.5)	0.268	519.0 (80.1)	485.9 (77.3)	0.069
EDSS score	1.62 (1.43)	1.64 (1.46)	0.014	1.62 (1.43)	1.53 (1.42)	0.060
Number of previous relapses	0.66 (0.79)	0.58 (0.71)	0.097	0.66 (0.79)	0.62 (0.76)	0.050
Number of previous DMTs			0.139			0.053
0	280 (43.2)	608.(39.9)		280.0 (43.2)	274.0 (43.6)	
1	244 (37.7)	673 (44.2)		244.0 (37.7)	246.9 (39.3)	
>1	124 (19.1)	241 (15.8)		124.0 (19.1)	108.0 (17.2)	
Index DMT class			0.344			0.086
IV-Moderate/High	25 (3.9)	113 (7.4)		25.0 (3.9)	32.7 (5.2)	
SC-Low	256 (39.5)	403 (26.5)		256.0 (39.5)	229.4 (36.5)	
Oral-Moderate/High	54 (8.3)	231 (15.2)		54.0 (8.3)	58.3 (9.3)	
Oral-Low	313 (48.3)	775 (50.9)		313.0 (48.3)	308.5 (49.1)	
Time since diagnosis (years)	5.69 (6.11)	6.34 (6.70)	0.101	5.69 (6.11)	5.70 (6.25)	0.002
Total previous annualized costs (€)	1485.38 (2917.01)	1454.70 (3782.01)	0.009	1485.38 (2917.01)	1511.88 (4076.47)	0.007

Mean (SD) used for continuous and n(%) for categorical variables

*Effective sample after weighting the population

IPTW, Inverse probability of treatment weighting; ATT=Average treatment effect in the treated

DMT, disease modifying therapy; IV, infusion; SC, subcutaneous; EDSS, Expanded Disability Status Scale