Respiratory Medicine 263 (2026) 109130

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Short communication

Adherence patterns and their determinants to CFTR modulators in France

Oriane Talabart [a,b], Elia Eid [a], Marie Viprey [a,b], Violaine Fernandez [a,b], Manon Belhassen [c], Antoine Bessou [d], Isabelle Durieu [a,e], Quitterie Reynaud [a,e], Cécile Payet [a,b,*], the French Cystic Fibrosis Centers Network

[a] Research on Healthcare Performance (RESHAPE), INSERM U1290, Université Claude Bernard Lyon 1, Lyon, France
[b] Hospices Civils de Lyon, Service des Données de Santé, Lyon, France
[c] PELyon, Lyon, France
[d] Association Vaincre la Mucoviscidose, Paris, France
[e] Cystic Fibrosis Reference Center. Department of Internal Medicine, Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France

A B S T R A C T

Cystic fibrosis transmembrane conductance regulator modulators (CFTRm) represent a major therapeutic advance for patients with cystic fibrosis (pwCF). Given their oral administration and high efficacy, they may be better suited than other cystic fibrosis treatments to optimize long-term adherence, which is crucial to ensuring effectiveness. To examine adherence patterns to CFTRm and their determinants, we conducted a population-based retrospective cohort study using data from the French CF Registry linked to the French National Health Data System. We included pwCF (>6 years) who initiated at least one CFTRm (ivacaftor or lumacaftor/ivacaftor) between 2012 and 2020 and were treated for at least six months. Implementation was measured using the continuous multiple-interval measure of medication availability version 7 (CMA-7), and longitudinal K-means clustering identified adherence trajectories based on monthly CMA-7 values over one-year follow-up. Multinomial logistic regression assessed associations between adherence patterns and sociodemographic and clinical characteristics. Among 1362 patients, three adherence trajectories were identified: optimal adherence (68%), gradual decline (16%), and initial drop-off followed by return to optimal adherence after 3-5 months (16%). Compared to optimal adherence, gradual decline trajectory was associated with age 15-25 years (reference: >25), while drop-off and rebound trajectory was linked to being younger than 15 and *P. aeruginosa* bronchial colonization. Socioeconomic disadvantage was also associated with nonoptimal adherence. This study highlights the need for age-tailored interventions to support long-term adherence, revealing a decline among adolescents and young adults, along with a specific pattern among children, which may relate to prescribing practices at treatment initiation.

1. Background

The development of cystic fibrosis transmembrane conductance regulator modulators (CFTRm) has significantly improved lung function and nutritional status as well as decreased pulmonary exacerbation in eligible patients with cystic fibrosis (pwCF). These results have led to an improved quality of life, a dramatic increase in life expectancy, and a reduction in the need for lung transplantation [1]. However, CFTRm effectiveness depends on medication adherence and, therefore, on how pwCF take their medication as prescribed [2]. Poor adherence leads to worse health outcomes, such as increased hospitalization and pulmonary exacerbations [3], and a systematic review demonstrated that CFTRm adherence was suboptimal, with adherence rates ranging from 0.62 to 0.99 [4]. However, studies included in this systematic review relied on average adherence levels during the follow-up period that did not consider the dynamic nature of the medication adherence process. This method can mask distinct underlying patterns, such as consistently low adherence, optimal adherence followed by interruption, or early non-adherence followed by recovery and eventual optimal adherence [5]. We evaluated medication adherence dynamics to identify the longitudinal patterns of adherence and to determine the sociodemographic and clinical determinants of these distinct adherence trajectories – an approach that, to our knowledge, has not yet been explored for CFTRm.

2. Methods

We conducted a national retrospective cohort study using data from the French Cystic Fibrosis Registry linked to the French National Health Data System (SNDS), which included all reimbursement data for outpatient or inpatient care [6]. We included all French pwCF aged 6 years and older who initiated at least one CFTRm from 2012 to 2020, were treated for at least six months, and survived until the end of the 2-year follow-up period. CFTRm were ivacaftor (IVA) - available since 2012 in France, and lumacaftor/ivacaftor (LUM/IVA) - available since

* Corresponding author. Research on Healthcare Performance (RESHAPE), INSERM U1290, Université Claude Bernard Lyon 1, Lyon, France.
E-mail address: cecile.payet01@chu-lyon.fr (C. Payet).

https://doi.org/10.1016/j.rmed.2026.109130
Received 19 December 2025; Received in revised form 26 August 2026; Accepted 27 August 2026
Available online 29 August 2026

2015 in France. CFTR modulators were provided free of charge for all patients and data were available for CFTR modulators dispensed from both hospitals and pharmacies in the database (except during clinical trials). The extracted data included sociodemographic and clinical data, as well as dispensing records. Clinical data were assessed the year prior to CFTRm initiation including: best of the year percent predicted forced expiratory volume in 1 s (ppFEV1%), nutritional status (abnormal if Z-score<0 for children or BMI<18.5 for adults), bronchial colonization with *Pseudomonas aeruginosa* (*P. aeruginosa*), CF-related treated diabetes, number of intravenous antibiotic courses (proxy variable of the number of pulmonary exacerbations) all extracted from the French CF registry. Sociodemographic variables, assessed at the initiation year of CFTRm, consisted of age, gender, and the French Deprivation Index (FDep), an area-based socioeconomic indicator measuring social disadvantage (1: less disadvantaged socio-economic quartile, 5: most disadvantaged one), and dispensing records were extracted from the SNDS database. Age was categorized (<15, 15-25, > 25), along with FEV1 (low: first quartile within age category, high: fourth quartile within age category).

Adherence to the first CFTRm was measured with implementation using the continuous medication acquisition availability version 7 (CMA-7), calculated monthly (ratio of the number of days covered by dispensing events to 30 days) [7]. Longitudinal K-means clustering was conducted to identify adherence patterns on a monthly CMA-7 basis for the initial year of CFTRm treatment [8]. This method permits the identification of a pre-specified number of patient subgroups that follow similar patterns over time and considers missing values within individual trajectories. The algorithm was run 10 times with different starting points for each group number specification (2 to 8 groups) to identify the best partition. The best model was based on combined assessment: 1) the Calinski-Harabasz criterion; 2) the number of patients included in the smallest group (>5%); 3) the clinical meaningfulness of the trajectories. A multinomial logistic regression was then performed to determine the association between adherence patterns and the sociodemographic and clinical variables. Patients with at least one missing data were excluded from the multivariate analysis. Results were expressed as odds ratios (ORs) with their 95% confidence intervals (CIs).

3. Results

We included 1362 pwCF (Table 1) and identified three adherence trajectory patterns (Fig. 1). PwCF in the largest group (N = 921, 68%), defined as the «optimal adherence » group, had a high and consistent adherence rate during the year following treatment initiation (approximately 95% on average). PwCF in the second group (N = 224, 16%), had an adherence rate that showed a «gradual decline», from 100% to 50% over 12 months. PwCF in the last group (N = 217, 16%) initially showed their adherence rate, drop from 100% to 15% after two months, followed by a rebound to optimal adherence over the following four subsequent months, averaging approximately 95%, ("drop-off & rebound" group).

Determinants of these distinct adherence trajectories are presented in Fig. 2. PwCF in the «dropoff and rebound » group, compared to pwCF in the "optimal" group, were significantly younger (OR 2.70, IC95% [1.60-4.54] in children <15 years compared with adults >25 years) and had a significantly high risk of bronchial colonization by *P. aeruginosa* (1.94 [1.11-3.37]). However, they were less likely to have IVA (0.38 [0.15-0.98]) or low FEV1 (0.63 [0.40-0.99]). PwCF in the «gradual decline » group compared to pwCF in the "optimal" group, were more likely to be adolescents and young adults (1.74 [1.16-2.61] in 15-25 years compared with adults <25 years), more deprived (1.14 [1.01-1.28] for every unit increase in FDep) and less likely to be children (0.48 [0.31-0.76] in children <15 years compared with adults >25 years).

Table 1
Sociodemographic and clinical characteristics of the study population.

	Adherence groups			
	Total	Optimal	Drop-off & rebound	Gradual decline
	N = 1362	N = 921	N = 217	N = 224
Sociodemographic characteristics				
Sex, n (%)				
Male	717 (52.6%)	489 (53.1%)	109 (50.2%)	119 (53.1%)
Female	645 (47.4%)	432 (46.9%)	108 (49.8%)	105 (46.9%)
Age (in years), n (%)	19.2 ± 10.8	19.7 ± 11.4	15.2 ± 9.4	20.8 ± 8.1
<15	684 (50.2%)	464 (50.4%)	152 (70.0%)	68 (30.3%)
15-25	315 (23.1%)	192 (20.8%)	33 (15.2%)	90 (40.2%)
>25	363 (26.7%)	265 (28.8%)	32 (14.8%)	66 (29.5%)
FDep[a], n (%)				
Quintile 1 (least deprived)	259 (19.5%)	178 (19.8%)	42 (19.8%)	39 (18.1%)
Q2	318 (23.9%)	243 (27.0%)	33 (15.6%)	42 (19.4%)
Q3	299 (22.5%)	198 (22.0%)	50 (23.6%)	51 (23.6%)
Q4	241 (18.1%)	147 (16.2%)	53 (25.0%)	41 (19.0%)
Q5 (most deprived)	212 (16.0%)	135 (15.0%)	34 (16.0%)	43 (19.9%)
Clinical characteristics				
FEV1[c], mean ± SD	83.7 ± 25.2	82.6 ± 25.6	93.1 ± 22.1	78.7 ± 24.3
Nutritional status[b], n (%)				
Abnormal (Z-score<0 or BMI<18.5)	544 (40.5%)	353 (38.8%)	100 (46.7%)	91 (41.2%)
P. aeruginosa bronchial colonization, n (%)	142 (10.4%)	85 (9.2%)	24 (11.1%)	33 (14.7%)
CF-related diabetes, n (%)	208 (15.3%)	151 (16.4%)	19 (8.8%)	38 (17%)
Number of IV-antibiotics courses, mean ± SD	0.7 ± 1.4	0.8 ± 1.4	0.4 ± 1.0	0.8 ± 1.7
Type of CFTR modulator, n (%)				
Ivacaftor	95 (7.0%)	78 (8.5%)	8 (3.7%)	9 (4.0%)
Lumacaftor/ivacaftor[d]	1267 (93.0%)	843 (91.5%)	209 (96.3%)	215 (96.0%)

[a] Missing data: 33.
[b] Missing data: 18.
[c] Missing data: 78.
[d] Homozygous for F508*del*.

4. Discussion

This study described adherence patterns, considering the dynamic nature of the medication adherence process in pwCF after initiating CFTRm and explored their determinants in a French nationwide cohort. We identified distinct and previously unknown adherence trajectories. The « optimal adherence » group, which represented the majority of pwCF, showed a consistently high trajectory that exceeded previously reported adherence rates [4]. Nevertheless, our results for gradual decliners were consistent with the literature on high adherence rates in children, which subsequently decline in adolescents and young adults [9]. We also showed that children were more likely to belong to the «drop-off and rebound » group. Given that the adherence rate was calculated assuming a fixed dosage, this pattern could be explained by a gradual dose escalation during CFTRm initiation in some pwCF. A

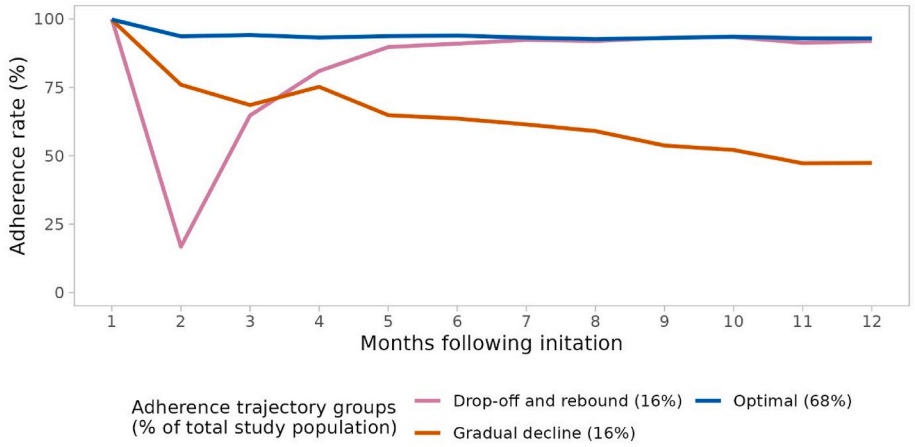

Fig. 1. Mean adherence trajectories for each of the 3-group partitions in the year following initiation of CFTR modulator (IVA or IVA/LUM). 74 patients had at least one missing data point in their trajectory.

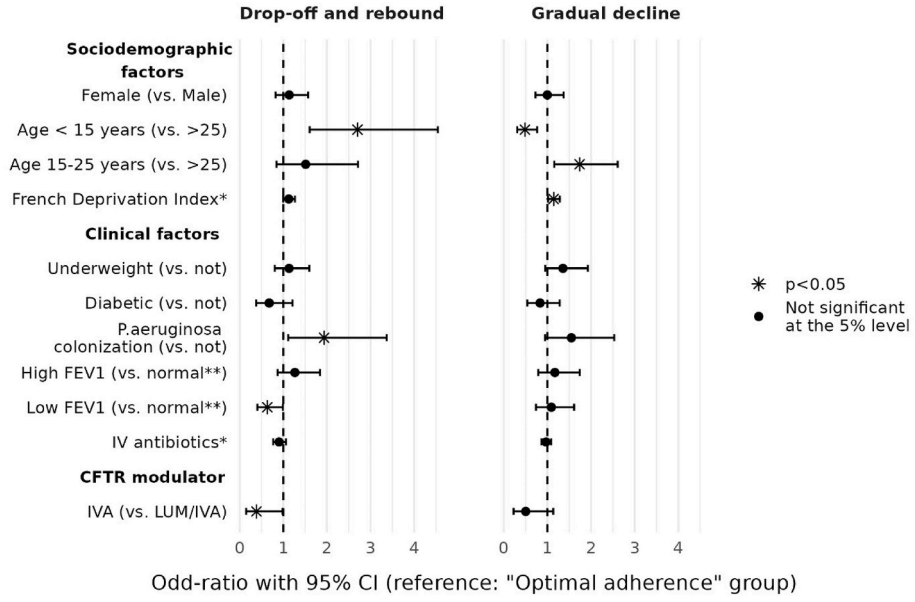

Fig. 2. Odd-ratios of belonging to the groups « Gradual decline» and «Drop-off and rebound » compared to the group with optimal adherence, for several socio-demographic, clinical and medication (type of CFTR modulator) factors. * For French Deprivation Index and IV antibiotics, the value of the odds ratios is the value for a 1-unit augmentation (one more IV antibiotic course, being one quartile of FDep higher). ** Having a FEV1 in the highest or lowest quartile versus FEV1 in range for each age class. The model was fitted based on 1241 patients (121 had at least one missing value: missing data were equally distributed across groups).

gradual dose escalation is recommended for patients initiating LUM/IVA while taking a strong inhibitor of cytochrome P450 superfamily member CYP3A, starting with a quarter of the full dose during the first week of treatment. This pattern could also be explained by a temporary dose reduction or short discontinuation of CFTRm during the first weeks of treatment due to initial adverse effects [10]. These adjustments made by clinicians, allowed patients to maintain their treatment while improving tolerability, with most individuals subsequently resuming the full recommended dose.

Our study has several limitations. The data source used to assess medication adherence and its determinants was the SNDS, which is a claims database. Consequently, dispensing data does not necessarily reflect actual medication intake, and medication adherence may be overestimated. Furthermore, because the SNDS does not contain psychosocial or behavioral data, several determinants of medication adherence could not be assessed. “Another limitation is a potential survival bias, as patients who died during the study period were excluded. Since patients with poorer adherence may also have worse clinical outcomes, their exclusion could lead to an overestimation of adherence at the cohort level. However, this effect is expected to be minimal, as only 9 patients died during the follow-up period. Moreover, the findings may not be generalizable to all CFTRm, as patients treated with elexacaftor/tezacaftor/ivacaftor (ETI) were excluded because ETI was not available in France during the study period. However, our findings regarding medication adherence to IVA and LUM/IVA may provide useful insights for understanding adherence to ETI, as the methods we used to assess medication adherence can be fully applicable to ETI and may guide future analyses once sufficient data are available. Although ETI has demonstrated clinical benefits greater than those of previous CFTR modulators, it remains a lifelong treatment, making medication adherence a critical aspect to monitor and address.

To conclude, adherence to CFTRm was generally high. However, lower adherence was observed among adolescents, young adults and socially disadvantaged individuals, including a distinct pattern that was particularly pronounced among children. The evaluation and implementation of targeted interventions may help to optimize long-term

CFTRm adherence within these subgroups, especially among adolescents and young adults.

CRediT authorship contribution statement

Oriane Talabart: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Elia Eid:** Writing – original draft, Methodology, Conceptualization. **Marie Viprey:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Violaine Fernandez:** Writing – review & editing, Software, Data curation. **Manon Belhassen:** Writing – review & editing, Data curation. **Antoine Bessou:** Writing – review & editing, Data curation. **Isabelle Durieu:** Writing – review & editing, Validation, Funding acquisition, Conceptualization. **Quitterie Reynaud:** Writing – review & editing, Validation, Conceptualization. **Cécile Payet:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Ethics declaration

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was approved by the Ethical approval for this study was obtained from the Expert Committee for Research, Studies, and Evaluations in the Field of Health (CEREES) n°TPS 2719090 and from the French data protection authority (National Commission on Informatics and Liberty, CNIL n° 920463). (Approval No. CEREES: n°TPS 2719090/CNIL n° 920463)

Funding

This project was funded through a call for proposals issued by the Direction Générale de l'Offre de Soins (DGOS, French Ministry of Health) under the Programme hospitalier de recherche clinique (PHRC National) PHRC N-19-0186 (ClinicalTrials.gov NCT05663255).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Isabelle Durieu reports financial support was provided by Direction Générale de l'Offre de Soins (DGOS, French Ministry of Health). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge the Caisse Nationale de l'Assurance Maladie (CNAM) and the Vaincre la Mucoviscidose (VLM) registry for granting access to the data used in this study.

Participating Investigators of the French CF Reference Network Study Group

RAMES Cinthia (AMIENS); TROUSSIER Françoise (Angers); RICHAUD THIRIEZ Bénédicte, DALPHIN

Marie-Laure (BESANCON); BUI Stéphanie, MACEY Julie (BORDEAUX); LAURANS Muriel (CAEN);

MONTCOUQUIOL Sylvie (CLERMONT-FERRAND); EPAUD Ralph (CRETEIL); HUET Frédéric (DIJON);

SCALBERT Manuela (DUNKERQUE); MELY Laurent (GIENS); HAMIDFAR Rébecca, LLERENA

Catherine (LA TRONCHE); AUDOUSSET Camille, WIZLA-DERAMBURE Nathalie (LILLE); LANGUEPIN

Jane (LIMOGES); REIX Philippe (BRON); DUBUS Jean-Christophe, REYNAUD GAUBERT

Martine (MARSEILLE); CHIRON Raphaël (MONTPELLIER); TATOPOULOS Aurélie, GUILLAUMOT

Anne (VANDOEUVRE-LES- NANCY); DANNER BOUCHER Isabelle, BIHOUEE Tiphaine (NANTES); LEROY.

Sylvie (NICE); BURGEL Pierre-Régis, SERMET Isabelle, HOUDOUIN Véronique, CORVOL.

Harriet (PARIS); BESSACI-KABOUYA Katia (REIMS); BELLEGUIC Chantal (RENNES).

; DENEUVILLE Éric (SAINT-BRIEUC); RAMEL Sophie (ROSCOFF); MARGUET

Christophe (ROUEN); ALLOU Nathalie (SAINT DENIS – LA RÉUNION); PERISSON Caroline (SAINT.

PIERRE – LA RÉUNION); RENAUD-PICARD Benjamin, WEISS Laurence (STRASBOURG); GRENET.

Dominique (SURESNES); RODITIS Léa (TOULOUSE); MURRIS ESPIN.

Marlène (TOULOUSE); MANKIKIAN Julie (TOURS); COSSON Laure (TOURS); ARNOUAT

Baptiste (VANNES); GABSI Asma (LE CHESNAY).

References

[1] M.D. Pastor-Vivero, J. Costa I Colomer, C. Martín De Vicente, S. Vicente-Santamaria, R. Garcia Romero, D. González Jiménez, C. Luna Paredes, Advances in the treatment of cystic fibrosis: CFTR modulators, Anales de Pediatría (English Edition) 102 (2025) 503857, https://doi.org/10.1016/j.anpede.2025.503857.

[2] B. Vrijens, S. De Geest, D.A. Hughes, K. Przemyslaw, J. Demonceau, T. Ruppar, F. Dobbels, E. Fargher, V. Morrison, P. Lewek, M. Matyjaszczyk, C. Mshelia, W. Clyne, J.K. Aronson, J. Urquhart, for the ABC Project Team, A new taxonomy for describing and defining adherence to medications, Br. J. Clin. Pharmacol. 73 (2012) 691–705, https://doi.org/10.1111/j.1365-2125.2012.04167.x.

[3] M.N. Eakin, K.A. Riekert, The impact of medication adherence on lung health outcomes in cystic fibrosis, Curr. Opin. Pulm. Med. 19 (2013) 687–691, https://doi.org/10.1097/MCP.0b013e3283659f45.

[4] C.M.E. Hansen, A.J. Breukelman, P.M.L.A. Van Den Bemt, A.M. Zwitserloot, L. Van Dijk, J.F.M. Van Boven, Medication adherence to CFTR modulators in patients with cystic fibrosis: a systematic review, Eur. Respir. Rev. 33 (2024) 240060, https://doi.org/10.1183/16000617.0060-2024.

[5] M. Alhazami, V.M. Pontinha, J.A. Patterson, D.A. Holdford, Medication adherence trajectories: a systematic literature review, JMCP 26 (2020) 1138–1152, https://doi.org/10.18553/jmcp.2020.26.9.1138.

[6] P. Tuppin, J. Rudant, P. Constantinou, C. Gastaldi-Ménager, A. Rachas, L. de Roquefeuil, G. Maura, H. Caillol, A. Tajahmady, J. Coste, C. Gissot, A. Weill, A. Fagot-Campagna, Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France, Revue d'Épidémiologie et de Santé Publique 65 (2017) S149–S167, https://doi.org/10.1016/j.respe.2017.05.004.

[7] W.M. Vollmer, M. Xu, A. Feldstein, D. Smith, A. Waterbury, C. Rand, Comparison of pharmacy-based measures of medication adherence, BMC Health Serv. Res. 12 (2012) 155, https://doi.org/10.1186/1472-6963-12-155.

[8] C. Genolini, B. Falissard, KmL: k-means for longitudinal data, Comput. Stat. 25 (2010) 317–328, https://doi.org/10.1007/s00180-009-0178-4.

[9] G.S. Sawicki, K.S. Heller, N. Demars, W.M. Robinson, Motivating adherence among adolescents with cystic fibrosis: youth and parent perspectives: adherence perspectives in Cystic Fibrosis, Pediatr. Pulmonol. 50 (2015) 127–136, https://doi.org/10.1002/ppul.23017.

[10] J.L. Taylor-Cousar, M. Jain, T.L. Barto, T. Haddad, J. Atkinson, S. Tian, R. Tang, G. Marigowda, D. Waltz, J. Pilewski, VX14-809-106 investigator group, Lumacaftor/Ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for F508del-CFTR, J. Cyst. Fibros. 17 (2018) 228–235, https://doi.org/10.1016/j.jcf.2017.09.012.