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COMMENTARY

Implications of COVID-19 Infection on Medication Adherence with Chronic Therapies in Italy: A Proposed Observational Investigation by the Fail-to-Refill Project

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Luca Degli Esposti[1]
Stefano Buda[1]
Carmela Nappi[1]
Daniela Paoli[2]
Valentina Perrone[1]

On behalf of Network Health-DB

[1]CliCon S.r.l. – Health, Economics & Outcome Research, Ravenna, Italy; [2]Health-DB, Ravenna, Italy

Abstract: Poor medication adherence leads to worsening of clinical outcomes and increases healthcare costs, especially in the context of chronic conditions. The effects of new COVID-19 infection and the measures taken in response to the outbreak are further increasing the concerns about medication adherence. Patients with chronic diseases, many of whom are older adults, have been strongly recommended to stay at home and avoid social contacts even with family members, who often provide support for regular use of therapies. Moreover, the mobilization of health personnel to the frontline of the COVID-19 infection could limit access to healthcare services. Within the Health-DB project, the Fail-To-Refill monitoring system was designed to evaluate the lack of adherence to chronic therapies in Italian clinical practice settings. Considering the date and dose coverage of last prescription, all patients due to refill this prescription for a chronic therapy in the last month were identified, and it was verified if they had the refill. The proposed future analysis, based on the data linkage between the current administrative flows of the Italian Local Health Units involved, will be carried out on a monthly basis from the beginning of the infection, and the "post-Covid -19" results will be compared with "pre-COVID-19" results, calculated for the last three years for patients with chronic therapies. Preliminary data herein presented showed a trend of increased failed refill during the months of lockdown for lipid-lowering and biologic therapies. The pre-COVID-19 trend compared to that of post-COVID-19 in the next months will be useful to estimate the percentage of failure to refill truly related to COVID-19 and on the measures adopted. The identification of patients that do not refill their prescriptions allows healthcare professionals to put in place actions aimed to promptly correct the lack of adherence, thus reducing the associated negative outcomes.

Keywords: chronic disease, real-world data, SARS-CoV-2, treatment adherence

The World Health Organization (WHO) defines medication adherence to long-term therapies as "the extent to which a person's behavior (in taking medication) corresponds with agreed recommendations from a healthcare provider"[1] in terms of dosage, times and frequency of drug administration. In clinical practice settings, medication adherence, ie the utilization of drugs according to scientific recommendations, represents a determinant factor for the effectiveness of all pharmacological therapies.[2] It is indeed widely recognized that ensuring a proper adherence to medication regimens is related to better clinical as well as economical outcomes.[3]

Correspondence: Luca Degli Esposti
CliCon S.r.l., Health, Economics & Outcomes Research, Via Salara, 36, Ravenna 48100, Italy
Tel +39 (0)544 38393
Fax +39 (0)544 212699
Email luca.degliesposti@clicon.it

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The most frequent manifestations indicating a lack of adherence include treatment discontinuation, occasional use or use at wrong time, and administration of dosage lower than indicated in the summary of product characteristics.[4] Poor adherence to medications indicated for chronic conditions such as hypertension, hypercholesterolaemia, diabetes mellitus, osteoporosis, chronic kidney disease and chronic obstructive pulmonary disease is well-documented in literature.[5–11] Recent evidence demonstrated that the tendency of poor medication adherence is also reported for biologic therapies indicated for instance to manage rheumatoid arthritis, psoriasis or cancer.[12]

The conditions of use are also important for treatment success, as the administration of drugs without following provider recommendations compromises the effectiveness of the therapeutic regimen, leading to suboptimal clinical benefits and negative outcomes such as disease progression, reduced functional abilities and a lower quality of life.[13,14]

The worsening of clinical outcomes inevitably leads to increased morbidity, mortality, and a greater consumption of healthcare resources (and subsequently higher costs), thus representing a burden not only for the patients, but for National Healthcare Services and society as well.

Although the issue of poor medication adherence and its consequences is well-established,[15] no substantial improvement of medication adherence was observed in clinical practice over the years.[16] Conversely, there are structural, organizational and economic barriers that can impair adherence interventions.[17]

In this historic period, the COVID-19 health crisis and the control measures taken to limit the spreading of the virus, eg, physical distancing and lockdowns, have increased concerns about medication adherence among physicians and healthcare systems. As for the Italian situation, after the COVID-19 outbreak, the Government has progressively introduced restrictive measures, that rapidly escalated after the first autochthonous cases were detected, thus creating the first "red-zones" in limited areas at the beginning of March 2020.[18] Within days, the lockdown was extended throughout the national territory; schools, public places and businesses were closed, and people could go out only to perform essential activities or if working in selected sectors (eg, healthcare and social care sectors, police and armed forces). Such containment measures were adopted to ensure physical distancing and to limit the movement of the population.[19]

These preventative measures may represent a major problem for the routine care and medicine management of special patient populations like those affected by chronic diseases.[20] Patients living with chronic conditions, mainly older adults, have been strongly advised to stay at home at all times and to avoid direct contact with family members, friends and acquaintances whose support is often necessary for regular use of therapies. Furthermore, the mobilization of healthcare professionals as specialist and general practitioners to the COVID-19 frontline could limit access to healthcare services. Scientific societies, patient associations, healthcare organizations and regulatory agencies are increasingly concerned about the possible implications of the COVID-19 infection and the measures taken to limit the spread of the epidemic on adherence to drug treatment in the context of chronic diseases.[21]

The Fail-to-Refill Project

In Italy, healthcare is provided to all citizens and residents by a mixed public–private system. The public part is the National Health System (NHS), which is based on the principle of universal coverage of all citizens. NHS is administered on a regional basis. Each region is divided into Local Health Units (LHUs), which are administrative bodies with the function of delivering health services and pharmaceutical care at local level. The LHUs manage the administrative databases that hold information meant to be used for administrative purposes in order to track the economic flows from the NHS to the healthcare providers for reimbursement purposes. Although administrative databases are primarily intended for administrative management, their use for healthcare research purposes is increasing, since they represent readily available sources of real-world healthcare data on a large population of unselected patients.

Health-DB is a business intelligence tool with data warehouse and dashboard functions. The data warehouse is based on the acquisition of data from the current administrative flows and/or other electronic archives available at LHUs and at regional level. The dashboard is based on a set of performance indicators designed to evaluate the compliance of medical prescriptions to therapeutic care standards.[22] Health-DB has been developed by CliCon S. r.l. with the goal to support different healthcare professionals in monitoring the compliance of prescribing methods with therapeutic care standards and in assessing the

effects of measures implemented to improve adherence to these standards.[22] Over the past years, Health-DB developed therapeutic appropriateness and adherence indicators used in the "National Report on Medicines use" in Italy (2012–2015).[22–25]

Within the Health-DB project and in partnership with a sample of Italian LHUs participating, the monitoring system named Fail-To-Refill was designed and developed with the aim to evaluate the lack of adherence to chronic therapies. All patients with chronic therapies who, based on the date and therapeutic coverage of last prescription, should refill a new one are identified and it is verified if they actually have the refill or, precisely, fail to refill. The analysis is carried out by integrating the administrative databases available from the LHUs sample involved in the project. In this context, we aim to explore the possibility to use such administrative data to gain insights into healthcare delivery during the COVID-19 pandemic in order to identify patients that, without refilling their prescription, could become non-adherent to chronic therapies. Therefore, we propose an observational retrospective analysis that will be performed monthly starting from the COVID-19 outbreak in Italy, in which the "post-COVID-19" results will be compared on a historical basis with "pre-COVID-19" findings.

The project evaluates the implications of COVID-19 infections and containment measures on the medication adherence to chronic therapies in terms of patients that, respect to "pre-COVID-19" period, became occasional users, interrupt their treatments, or take lower dosage, thus potentially becoming non-adherent.

In this context, we provide here a first "glimpse" of the proposed investigation by describing the failed refill of selected therapeutic classes in the three years prior COVID-19 spreading (pre-COVID-19 period) and in the very first months of post-COVID-19 period. Preliminary data focused on therapies indicated for chronic cardiovascular (hypercholesterolemia) conditions and for chronic autoimmune diseases, in which higher prevalence of COVID-19 infections are observed.[26] The classes of chronic therapies herein reported were chosen to reflect two different scenarios of distribution: lipid-lowering drugs dispensed in community pharmacy and biologic therapies dispensed by NHS hospitals for outpatients use (direct distribution). The demographic characteristics of patients were given in Table 1. The mean percentage of

Table 1 Demographic Characteristics of Patients Included in the Preliminary Analysis Belonging to (a) Lipid-Lowering and (b) Biological Therapies

	2017	2018	2019	2020
(a) Lipid-lowering therapy				
N	401,523	415,749	431,892	389,191
Male, n (%)	197,212 (49.1)	204,246 (49.1)	212,001 (49.1)	192,533 (49.5)
Age range (years), n (%)				
≤ 45	13,923 (3.5)	14,128 (3.4)	14,267 (3.3)	10,064 (2.6)
46–65	131,153 (32.6)	135,558 (32.6)	141,105 (32.6)	120,134 (30.9)
66–75	131,267 (32.7)	134,560 (32.4)	138,898 (32.2)	128,640 (33.0)
>75	125,180 (31.2)	131,503 (31.6)	137,622 (31.9)	130,353 (33.5)
(b) Biologic therapy				
N	1420	1515	1708	1627
Male, n (%)	674 (45.6)	743 (49.0)	847 (49.6)	820
Age range (years), n (%)				
≤ 45	444 (31.3)	460 (30.4)	500 (29.3)	478 (29.4)
46–65	737 (51.9)	804 (53.1)	916 (53.6)	858 (52.7)
66–75	185 (13.0)	184 (12.1)	215 (12.6)	222 (13.6)
>75	54 (3.8)	67 (4.4)	77 (4.5)	69 (4.2)
Psoriasis*, n (%)	774 (54.5)	865 (57)	980 (57.4)	922 (56.7)
Rheumatoid arthritis*, n (%)	460 (32.4)	468 (30.9)	477 (27.9)	440 (27)
Crohn's disease* n (%)	256 (18)	252 (16.6)	322 (18.8)	321 (19.7)

Note: *Not mutually exclusive.

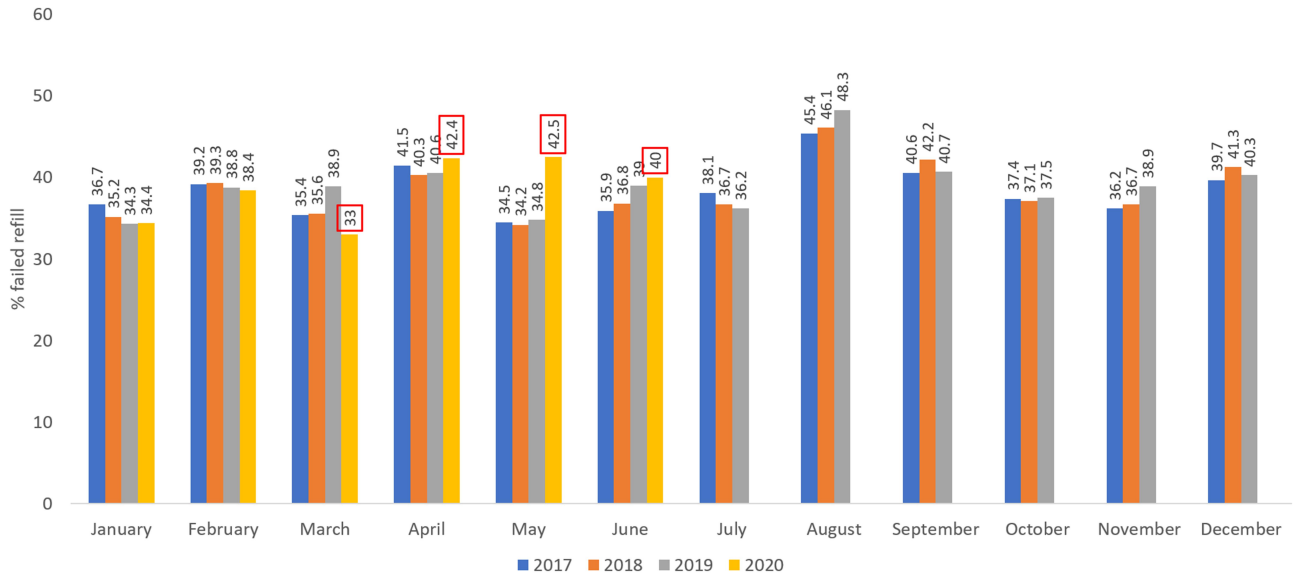

Figure 1 Percentage of failed refill of lipid-lowering therapies prior to COVID-19 outbreak and in the first months afterwards (highlighted in red boxes).
Notes: ATC code of treatment analysed: C10A and C10B.

failure to refill during the pre-COVID-19 period was 38.6% for lipid-lowering drugs and 33.6% for biologic therapies. Although only preliminary data are reported, we were able to observe a tendency of increased failed refill after COVID-19 outbreak in Italy when the most restricted measures (ie, lockdown throughout the territory) were applied. Specifically, for April and May 2020 high proportions of failed refill of lipid-lowering drugs (42.4 and 42.5%, respectively) were reported (Figure 1). Among the biologic-treated patients, higher percentages of failed refill were observed in May (37.9%) and June 2020 (38.8%), therefore more than two months from the outbreak (Figure 2). Interestingly, this trend appeared more evident for patients with chronic conditions, aged over 65 years (Table 2). The data herein reported are preliminary and descriptive, and further analysis will be performed in due time. The failed refill in the observed months could be underestimated in the case of lipid-lowering drugs, as until

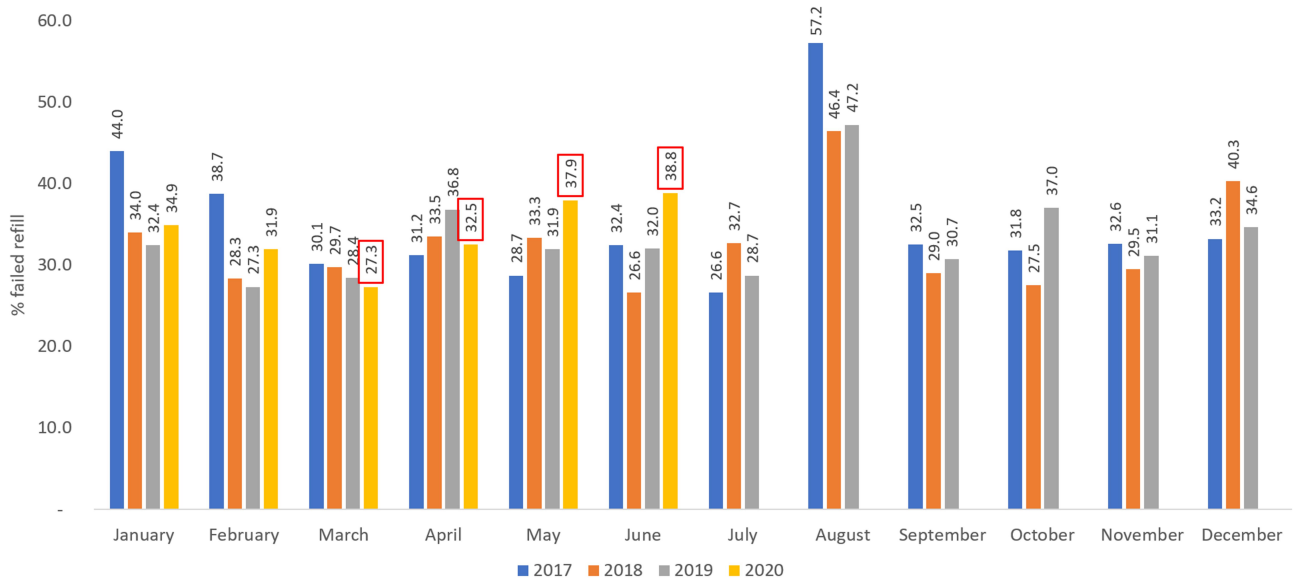

Figure 2 Percentage of failed refill of biologic therapies prior to COVID-19 outbreak and in the first months afterwards (highlighted in red boxes).
Notes: The analysis referred to patients treated with biologic therapies indicated for rheumatoid arthritis, psoriasis and Crohn's disease, ATC code: L04AA24, L04AA33, L04AB01, L04AB02, L04AB04, L04AB05, L04AB06, L04AC03, L04AC05, L04AC07, L04AC08, L04AC10.

Table 2 Proportion of Patients That Failed to Refill (a) Lipid-Lowering and (b) Biologic Therapies Stratified by Age Range

Age Range	≤ 45 years				46–65				66–75				>75 years			
	2017	2018	2019	2020	2017	2018	2019	2020	2017	2018	2019	2020	2017	2018	2019	2020
(a) Lipid-lowering drugs																
January (%)	44.6	42.3	41.4	43	37.3	36	35.1	35.5	35.1	33.3	32.5	32.5	37.1	35.7	34.8	34.6
February (%)	48.2	47.9	48.1	48.4	40.8	40.9	40.8	40.3	37.1	37.5	36.8	36.3	39.3	39.1	38.4	38
March (%)	43.6	43.2	47.9	**42.8**	36.7	37.1	40.2	**35.1**	33.8	33.7	37.3	**31.1**	35.3	35.7	38.7	**32.4**
April (%)	50.1	49.7	52.1	**49.9**	44	42.3	43.1	**43.3**	39.1	37.8	38.4	**41**	40.9	40.2	39.7	**42.7**
May (%)	44.8	44.5	45	**48.6**	36	36.2	36.4	**43.4**	32.6	31.9	32.9	**41.1**	34.2	34	34.7	**42.7**
June (%)	44.3	45.5	49.3	**48.1**	37.1	38.6	41	**41.5**	34.3	34.8	37.2	**38.2**	35.7	36.7	38.5	**39.8**
July (%)	45.5	45.7	45		38.6	37.7	37.1		37	35	34.7		38.1	37	36.2	
August (%)	53.1	53.1	56.5		46.4	47.2	49.5		44	45	47		45.3	45.6	48	
September (%)	46.5	48.2	47.6		41.5	43.3	41.8		38.9	40.3	39		41	42.6	40.8	
October (%)	45.7	45.2	47.6		38.7	38.4	38.9		35.3	35.3	35.5		37.5	37.2	37.4	
November (%)	44.6	44.7	46.8		37.4	38.3	40.2		34.4	34.7	37		36.2	36.8	39.1	
December (%)	47.9	48.9	49		41	42.7	41.9		37.8	39.3	38.3		39.8	41.3	40.2	
(b) Biologic therapies																
January (%)	49.5	34.1	38.2	35.6	40.9	34.6	30.2	36.5	43.2	34.2	29.3	25.2	47.1	25	29.4	35.7
February (%)	39.3	30.8	25.9	33	38.1	28.8	27.6	31.6	39.1	20.2	29.9	32.3	40	28.6	25	27.3
March (%)	28.5	36.3	27.1	**26.6**	31.3	27.3	30.2	**28.7**	30.8	28.8	26.4	**21.4**	22.2	23.7	18.9	**33.3**
April (%)	34	36.8	36.4	**30.9**	30.6	33.9	38.6	**31.5**	25.5	25	30.6	**36**	40	34.2	35	**46.7**
May (%)	28.4	38.1	28.1	**38.3**	29.5	32.4	33.9	**38.1**	21.6	28.3	31.7	**37.5**	45.5	29	30.3	**33.3**
June (%)	34.7	24.3	29.7	**41**	31.2	29.7	33.6	**40.5**	34.4	20.4	31.5	**28**	21.1	21.1	28.6	**34.5**
July (%)	25.5	33.3	26.7		27.5	32.1	30.4		25.3	32	24.1		26.7	39.4	33.3	
August (%)	58.5	53	47.5		59	46.3	48.9		50	38.8	42		43.5	37.8	39.3	
September (%)	36.7	28.4	28.5		31.6	26.6	33.6		29	35.9	25.2		23.8	41.9	21.2	
October (%)	34.8	29.8	41.9		31.4	26.3	35.5		29.5	30.8	35		24.2	18.4	26.5	
November (%)	34.7	30.9	36.9		30.9	27.3	31.1		37.1	33	23.1		25	38.9	18.9	
December (%)	35.3	41.6	35.8		33.1	42.4	33.9		29.1	33.7	35		31.3	31.4	34.6	

Note: The cells referring to post-COVID-19 period are in bold.

August 2020 in Italy chronic therapies distributed in community pharmacies could be prescribed with "multi-month prescription", which covered up to 6 months of therapy. Moreover, in response to the emergency, the Government adopted digital solutions for the transmission of medical prescriptions (to cover a maximum of 2 months of therapy) at national scale, so that the prescriber is allowed to send the electronic prescription number via email, telephone or text messaging to the patient.[27] This measure avoids unnecessary exposure of patients within clinical settings, however it could be potentially complicated for older patients not familiar with electronic devices. As for biologic therapies, the failed refill could reflect the temporal trend of the measure introduced to manage the accesses to outpatient services for the administration of these therapies.

From a statistical standpoint, an interrupted time series analysis could be performed, that will also take into account possible seasonal variations if constant through the years. In this case, the historical data could be a valid control group, as they referred to patients that did not experience the COVID-19 consequences in terms of disease, physical distancing, psychological implications.

We acknowledge the presence of some limitations of the analysis, mainly due to the type of data sources. The main limitation is linked with the traceability of drugs: since data on the use of pharmacological treatments were retrieved from medical prescriptions and dispensing, the actual use by the patients who had the refill is not available, as well as the reason behind potential interruption of treatments. Moreover, pharmacological databases do not provide information on drugs prescribed during hospitalizations. Other limitations are represented by lack of detailed information on lifestyle habits, social status, self-isolation status, presence of family members/relatives infected by COVID-19.

The update of this analysis will provide a quantification of the effects of the measures adopted to contain the pandemic on the adherence to chronic treatments. The comparison between pre-COVID-19 and post-COVID-19 trend will be useful to estimate the percentage of failure to refill truly depending on COVID-19 and on the measures adopted.

The Fail-To-Refill project will also allow the LHUs to identify the patients that do not refill their prescriptions and, together with the involvement of their attending physicians, to implement actions aimed to promptly correct the lack of adherence and to avoid/reduce the associated negative outcomes. The stakeholder engagement will be in the interpretation of the findings of the project and in the subsequent actions to put in place: specifically, the LHUs will set clinical audit processes with clinicians that in turn will recall their patients in order to optimize the adherence to treatments and the therapeutic appropriateness.

Moreover, by using the same administrative flows and analysis systems, each identified patient can be characterized by variables such as treatment duration and interruption, type and number of chronic conditions, presence of specific risk factors for COVID-19 infection and progression. These could represent useful information for physicians for a complete assessment of the patient and to the LHUs to stratify the health-assisted population according to risk factors and therapeutic needs and for the next phases of care interventions planning to optimize patients management during the pandemic.

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Disclosure

The authors report no conflicts of interest in this work.

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