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Original Research

The impact of elexacaftor/tezacaftor/ivacaftor on cystic fibrosis health-related quality of life and decision-making about daily treatment regimens: a mixed methods exploratory study

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Abstract

Background: Elexacaftor/tezacaftor/ivacaftor (ETI) has reduced many symptoms of cystic fibrosis (CF).

Objectives: We sought to identify the impact of ETI on both symptoms and treatment decisions among adults with CF.

Design: Participants were enrolled in a cross-sectional study. Surveys were sent *via* a RedCap link. Semistructured interviews were administered remotely *via* Microsoft Teams. Interviews were audio recorded and professionally transcribed.

Methods: We assessed Cystic Fibrosis Questionnaire-Revised (CFQ-R) subscales for physical, respiratory, emotion, and treatment, and analyzed semistructured interviews covering CF treatment regimens and daily living. Quantitative and qualitative results were analyzed separately and via a mixed-methods convergence coding matrix.

Results: Twenty-four adults with CF taking ETI were included. CFQ-R subscale scores (mean scores/standard deviation) were physical (82.1/22.8), respiratory (83.7/11.2), emotion (65.3/14.2), and treatment (57.5/20.1). Three themes about decision-making for non-ETI-treatments emerged: (1) How I'm feeling, (2) Not noticing a difference, and (3) Uncertainty about long-term impact of modifying treatment regimens, and we found participants weighed each of these factors in their treatment decisions. Key findings from mixed-methods analysis show that among individuals experiencing higher CFQ-R scores for physical and respiratory compared to emotion and treatment, there were statements indicating that while those participants were experiencing better physical health, many continued their burdensome treatment regimens.

Conclusion: With little long-term data on the impact of reducing non-ETI treatments, participants weighed how they were feeling, treatment efficacy beliefs, and risk tolerance when making treatment decisions.

Plain language summary

The impact of Trikafta on CF health, health-related quality of life, and treatment adherence

People with cystic fibrosis may be experiencing many health benefits from taking Trikafta, leading some people to cut back on or stop their other non-Trikafta treatments. We explored the impact of Trikafta on CF health, health-related quality of life, and treatment

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adherence for people with CF currently taking Trikafta. We compared health-related quality of life subscales from the CF Questionnaire-Revised questionnaire focused on physical symptoms, respiratory symptoms, treatment burden, and emotional well-being to assess whether people with CF were experiencing improved physical and respiratory health compared to emotional health and feelings of treatment burden. We found that many people were feeling better physically, but were still experiencing poor mental health and high treatment burden. We then looked at results from open-ended interviews to see if our qualitative data could explain the differences in the health-related quality of life scores. We found that while people were feeling better physically, many people were still continuing with the pre-Trikafta treatment regimens which may explain why physical health and respiratory health scores were higher than emotional well-being and treatment burden scores. At this time, we believe that more research is needed to guide treatment decisions related to cutting back or stopping burdensome treatment regimens.

Keywords: adherence medication, cystic fibrosis, health-related quality of life, life quality, nonadherence medication, patients with cystic fibrosis, quality of life, symptom burden

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Introduction

Cystic fibrosis (CF) is a life-long progressive disease for which there is no cure. The most recent US-based figures estimate 'the 2020 prevalent CF population between 1968 and 2020 to be 38,8044'.[1] CF is associated with several distressing physical symptoms linked primarily to pulmonary function and decline, digestive issues, and pain.[2] Additionally, prior work also shows that for many people with CF, high treatment burden is associated with poor mental health.[2,3] To alleviate the multiple symptoms associated with CF and mitigate disease progression, long-standing guidelines for CF self-care recommend a daily treatment regimen that includes percussive chest physiotherapy and nebulized therapies for airway clearance, oral medications, and pancreatic enzymes taken with meals.[4–6] Further, to address symptoms associated with poor mental health, primarily anxiety and depression, psychotropic medications may be also prescribed.[7–9] In the past, people with CF reported completing, on average, 7 daily treatments, and spending ~108 min per day completing these treatments.[10] Prior work indicates that CF is similar to other chronic illnesses in terms of disease burden, and distressing symptoms,[11] and it has often been compared to sickle cell anemia in terms of its lifelong nature, disease progression, and frequent hospitalizations.[12] Therefore, CF and its associated treatment regimen may lead to prolonged treatment burden from an early age, impacting both individuals with CF and their families at various stages throughout their life-course.[13]

More recently, the widespread availability of highly effective modulator therapies (HEMTs) targeting the CF transmembrane conductance regulator (CFTR) – correcting the underlying molecular defect causing CF disease – has reduced many of the physical symptoms typically associated with CF and thereby led to improvements in health.[14,15] In particular, the triple combination therapy, elexacaftor/tezacaftor/ivacaftor commonly referred to as either ETI or Trikafta,[16,17] can be used in approximately 90% of people with cystic fibrosis (PwCF).[18] Among the recent short- and long-term studies showing a reduction in physical symptoms among people with CF on ETI, the vast majority of these studies evaluate the safety and efficacy of adding ETI to the regimen, with fewer studies specifically exploring stopping or reducing non-ETI pulmonary treatments such as pulmonary therapy or nebulizer treatments (non-ETI treatments will be referring to inhalational and airway clearance-related CF treatments throughout this study).[19] Additionally, recent studies have shown that mental health and treatment burden remain a concern even among those

reporting a reduction in physical symptoms on ETI.[19,20] As a result, there is a lack of standardization among CF providers in advising whether or not PwCF continue following the established self-care guidelines. Therefore, there is growing interest in studying the long-term effects of discontinuing non-ETI therapies on CF outcomes particularly for those doing well on ETI. However, there is little published long-term data to guide decisions about stopping or reducing non-ETI treatments, and a limited number of studies registered at ClinicalTrials.gov exploring this issue [ClinicalTrials.gov identifiers: NCT05392855, NCT05740618, NCT04378153, NCT04602468, NCT05519020, NCT04798014].

Herein, we present results of a secondary analysis of data exploring treatment adherence, decision-making about daily treatment regimens, and the impact of ETI on physical health, mental health, and treatment burden among a sample of adults with CF on ETI. Data for this secondary analysis were taken from a wider, unpublished, mixed-methods study assessing the impact of personal-level (egocentric) social networks on treatment adherence among adults with CF. Our secondary analysis includes cross-sectional results from the CF Questionnaire-Revised (CFQ-R)[21] sub scales for physical and respiratory symptoms, emotion (well-being/mental health), and treatment (burden), as well as data from a semistructured interview exploring treatment adherence among adults with CF. Our study contributes to prior work exploring the extent to which ETI may be positively impacting physical symptoms at a higher degree than mental health and treatment burden.[11,22]

We also apply to our discussion, extant work on the *health belief model*, which suggests that beliefs about treatment efficacy are associated with treatment adherence,[23,24] phenomenology which explores how individual-level experiences, feelings, emotions, and memories, may effect perceptions of health and subsequent treatment decisions,[25–27] and risk and prognostic uncertainty which explores how individuals understand probabilistic data, and apply it when weighing benefits of short-term treatment burden against the long-term risks of poor outcomes.[28,29] These theoretical frameworks will inform our discussion about how, in the absence of revised guidelines for care, PwCF are negotiating their beliefs about treatment efficacy, subjective experiences of improved physical health since starting ETI, and individual-level risk tolerance amid clinical uncertainty regarding the long-term impact of modifying treatment regimens when making decisions about whether or not to adhere to existing pre-ETI standards of care. Finally, to further situate our work, we also discuss the landscape of recent research on ETI safety and efficacy, and the reduction of non-ETI treatments on lung function for people with CF.

Methods

Recruitment and enrollment

Eligible participants for the wider study were recruited for a cross-sectional study from the Northwell Health CF Center and through social media sites using Institutional Review Board (IRB)-approved remote recruitment flyers. All members of the study team were female. PwCF aged 18 years or older who had not previously undergone a lung transplant were eligible to participate in the study.

Primary data collection

Enrolled participants were e-mailed a link to RedCap surveys, which included the Cystic Fibrosis Questionnaire-Revised (CFQ-R).[21] After completing the RedCap surveys, each participant was given an egocentric network interview, followed by a qualitative interview [the McGill Illness Narrative Interview (MINI), modified for CF adherence]. The MIN has been validated in multiple studies.[30] However, the MINI modified for CF adherence was not pretested for this study. The MINI was audio recorded and transcribed for qualitative analysis. All interviews were conducted by MB, a PhD-level medical anthropologist and Assistant Professor. All interviews were conducted remotely *via* Microsoft Teams and lasted ~60 min. The interviewer had no prior relationship to the participants. Participants were provided with details of the study *via* a detailed written informed consent form, and were told that they could ask questions about the study at any point during their participation.

Subanalysis

For the subanalysis, we included only those individuals who had indicated that they were

currently taking ETI. Those taking a different HEMT or those not taking an HEMT were excluded. While all participants included in this subanalysis had at least one genetic mutation that was responsive to ETI (i.e. making them eligible for ETI), we only asked participants whether or not they were on ETI (i.e. 'Are you taking Trikafta?') as part of the semistructured interview, without specifically asking about which genetic mutation(s) they had. For the subanalysis, we included results from CFQ-R subscales for symptoms related to physical, respiratory, emotion (well-being), and treatment (burden). The CFQ-R also contains basic demographics questions which are presented in Table 1.[21] Each CFQ-R domain is scored from 0 to 100, with higher scores indicating better health-related quality of life (HRQoL) for each domain. For this subanalysis, CFQ-R-derived demographics were analyzed descriptively and reported as mean and %, and the four included subscales are initially aggregated and reported as mean and standard deviation (StD) in Table 2, using SPSSv29 statistical software, IBM®. Further, for the subanalysis, two domains from the interview transcripts that focused specifically on treatment regimens and the impact of CF on daily HRQoL underwent a secondary initial deductive analysis by two coders, to identify portions of text specifically addressing the following deductively driven areas of interest: (1) descriptions of current daily treatment regimens and daily treatment adherence specifically for their non-ETI treatments; (2) the impact of ETI on symptoms, treatment burden, and HRQoL; and (3) descriptions of ETI side effects which may also impact HRQoL. From our initial deductive analysis, we then inductively identified three themes which are presented in our results below. Finally, to integrate the qualitative data and quantitative data, a mixed-methods convergent coding matrix[31] was created to include CFQ-R subscale scores and deductive domains of interest from the qualitative interview. For each participant, CFQ-R and qualitative data were placed into each respective field in the matrix. For this mixed-methods analysis, we were interested in understanding whether there were differences in physical functioning and respiratory health *versus* treatment burden and mental health symptoms as has been seen in other studies, and the extent to which participants' lived experiences concerning the impact of ETI could help explain their CFQ-R sub-scale responses. To further elaborate on our qualitative methods, we have included the COREQ checklist in our Supplemental Files.[32]

Results

Demographics

Thirty people were recruited and completed the full data collection as part of the wider study between 9 June 2020 and 7 December 2021. Of these, 24 people were currently taking the triple combination CFTR modulator therapy ETI (Trikafta) and were included in the subanalysis. Results presented herein represent 24 participants. Table 1 shows the cohort of participants representing a diverse age range [mean age 34 (StD 9.97)]; there was an even split between male and female participants, half were never married, almost all were white, the majority had at least a college degree or higher, and most worked full- or part-time.

HRQoL, symptom burden, and adherence to treatment regimens in the era of HEMT

Results from the CFQ-R show that mean scores, which could range from 0 to 100, were higher among physical functioning (82.1) and respiratory symptoms (83.7), compared to emotional health (65.3) and perceived treatment burden (57.5). Table 2 provides mean scores with standard deviation for the four CFQ-R subscales.

Overview of content analysis

Qualitative content analysis of transcripts from the 24 participants, explored the impact of ETI on physical and respiratory symptoms, mental health, and treatment burden, including side effects of ETI as an additional marker of treatment burden, participants' current daily treatment regimens, and their adherence to recommended treatment for non-ETI therapies (e.g. vest and other chest percussive therapies and nebulizer treatments). In general, most participants experienced positive effects of ETI including higher energy levels, reduced cough and mucus production, and weight gain. Several participants had described the introduction of ETI as life changing. However, there were a limited number of participants who had experienced negative side effects including poor sleep, abdominal pain, rashes, and heartburn which also negatively

Table 1. Participant demographics.

Characteristics	*N* = 24 (%)
Age	34/StD 9.97
Gender	
Female	12 (50%)
Male	12 (50%)
Marital status	
Single/never married	12 (50%)
Married	8 (33.3%)
Widowed	0
Divorced	1 (4.2%)
Separated	1 (4.5%)
Remarried	0
With a partner	2 (8.3%)
Racial background	
Caucasian	23 (96.8%)
African American	0
Hispanic	1 (4.2%)
Asian or Pacific Islander	0
Native American or Native Alaskan	0
Other	0
Prefer not to answer this question	0
Education	
Some high school or less	0
High school diploma/GED	1 (4.2%)
Vocational school	0
Some college	7 (29.1%)
College degree	9 (37.5%)
Professional or graduate degree	7 (29.1%)
Work/school status	
Attending school outside the home	3 (12.5%)
Taking home educational courses	1 (4.2%)
Seeking work	1 (4.2%)
Working full- or part-time	17 (70.8%)
Full-time homemaker	0
Not attend school/work due to health	1 (4.2%)
Not working for other reasons	1 (4.2%)

GED, General Educational Development/High School Equivalency; StD, standard deviation.

affected their HRQoL. However, among those study participants experiencing negative side effects, all had continued taking ETI because of the positive effects on their respiratory health.

Generally, in addition to ETI, most participants had continued their pre-ETI regimens either fully or at a reduced number of treatments, typically based on how they were feeling. Some participants discussed cutting back on wearing their vests or conducting their nebulizer therapies as needed rather than daily. Some participants indicated that they had made decisions to modify their treatment regimens in consultation with their CF pulmonologists, while others indicated that they had not informed their CF providers about these decisions. There were several participants who believed that their non-ETI-treatments offered no additional benefit above what they were already experiencing on ETI, leading them to either cut back on treatments, or continue anyway. Finally, some participants expressed concern about the long-term impact of modifying their treatment regimens. Based on our initial deductive analysis, three themes regarding treatment decision making and adherence emerged inductively: (1) How I'm feeling, (2) Not noticing a difference, and (3) Uncertainty about long-term impact of modifying treatment regimens, with some overlap among each of these themes (e.g. feeling better, but continuing due to long-term uncertainty).

Health, HRQoL, and side effects on ETI

The majority of participants discussed the positive effects of ETI. The most common benefits experienced were reduced coughing and mucus production, greater mobility, and less fatigue. For example, the positive impact of ETI were expressed by one participant as follows:

> Within the first two weeks I could feel the difference. Before I was on it, like there was talks of about putting a feeding tube in, I had a couple of PICC lines because of lung infections, and next thing I know I'm on [Trikafta], I'm on this and my [lung function] went from like 60% to almost like 70. I put on like maybe 10 pounds in like four months. (Participant PID-8)

While the majority of participants mentioned a reduction in physical symptoms since beginning ETI, some participants placed greater emphasis

Table 2. Summary of CFQ-R physical, respiratory, emotion, and treatment subscales ($N = 24$).

Reported as	Physical	Respiratory	Emotion (mental health)	Treatment burden
Mean	82.1	83.7	65.3	57.5
StD	22.8	11.2	14.2	20.1

CFQ-R, Cystic Fibrosis Questionnaire-Revised; StD, standard deviation.

on mental health or financial concerns impacting their quality of life as described in the following transcript excerpt:

> My parameters for taking care of myself are switched . . . Like back then [pre-Trikafta], it would be like doing all my meds, but now it's like, my care is motivated by what will help like [my] mental health. (PID-5)

Among participants experiencing negative side effects of ETI, all were continuing to take it because the positive effects on their respiratory health and lung function outweighed the negative side effects. One participant described having to regularly start and stop ETI to balance the positives, which included reduced abdominal and pancreatic pain, and negatives which included poor sleep, and lower abdominal tension:

> There's a whole litany of minuses to taking the Trikafta. I'll take it, then I come off of it for a little while if I can't tolerate it. Then, I go back on it when I can't tolerate the abdominal pain anymore. So, [Trikafta] had my heart rate racing. It's like I've had too much caffeine – I can't sleep. It also causes a lot of lower abdominal tension. It kills my appetite. And there's a lot of stress around the financial part of it. But it really reduces the pancreatic pain to the point where I almost can't not take it. (Participant PID-10)

Current daily treatment regimens and treatment adherence for non-ETI treatments

In providing detailed descriptions of their daily treatment regimens since starting ETI, we inductively identified three themes that described how treatment decisions were being made: (1) How I'm feeling, (2) Not noticing a difference, and (3) Uncertainty about long-term impact of modifying treatment regimens.

Theme 1: How I'm feeling. Several participants described doing the same types of treatments, though they spent less time each day, based on how they were feeling. Here decisions about treatment were guided by how they were feeling and deliberation with a provider. For example, one participant had reduced the number of treatments from twice daily to once daily in consult with her provider:

> After a conversation with my pulmonologist, she was like, 'You're doing well, you're fully functional, and if you're doing it once a day [non-ETI treatments] and you feel good, then great. If you don't feel so great, then do it twice a day.' So as long as I'm getting it done once a day, I'm not concerned. (Participant PID-1)

In contrast some participants had reduced treatments, without consulting their pulmonologists of their decisions. For example, one participant had stated,

> Since Trikafta, I've pulled back more than I should on my nebulized treatments. . . . I did not consult my care team. (Participant PID-19)

Another area where adherence was affected by how a participant was feeling as a result of ETI was on skipped or missed treatments. Whereas some participants had deliberately either cut back on the amount of time spent on treatment, or eliminated specific treatments altogether, some participants mentioned that, although they were maintaining their regimens, they were less concerned about missing a treatment occasionally without an immediate decline in their health. For example:

> It used to be that I was religious about doing breathing treatments. And now with Trikafta, I don't have to be. It used to be that if I missed one [treatment], my day was affected, if not ruined. I don't have it like I used to, and that's wonderful. It's

> liberating. I've been tied to this nebulizer my entire life, and I don't have to do it, and I still do it, but if I miss one, if I miss three, it doesn't matter anymore. Two, three years ago, it would have been inconceivable that I would leave the house without doing the treatment. Breaking that chain mentally, that's something that Trikafta has allowed me to do that I couldn't do before. (Participant PID-11)

Theme 2: Not noticing a difference. Several participants discussed that they were no longer seeing a benefit in continuing their non-ETI treatments. For some, while this was the case, they continued doing these treatments anyway. For example, as described by one participant whose respiratory symptoms had improved on ETI, but who had maintained her pre-ETI treatment regimen.

> Before and after [Trikafta], it's mostly the same. I was on Pulmozyme, now, I am still on Pulmozyme. I still do the vest. Even though I don't feel mucus anymore or bring anything up, they have indicated that the vest can still be shaking up things internally. So, I continue to do it even though I can't feel effects from it anymore. (Participant PID-23)

Others had cut back since they no longer believed that the non-ETI treatments were having an impact:

> It's more or less become to the point where I don't see the benefits [of non-ETI treatments], right where I was before, I would get more up, and that just doesn't happen. So continuing those treatments doesn't seem to make sense. You know, the doctor would tell you otherwise, right? (PID-18)

Theme 3: Uncertainty about long-term impact of modifying treatment regimens. Finally, some participants continued with their prior non-ETI treatments after starting ETI due to uncertainty about the long-term consequences of changing their regimens or whether ETI would continue to work for them long-term, as discussed by one participant:

> For me, I do the same as I did a year ago. Just because I want to stay stable, I don't want to slip just because I'm relying on this pill, at this point, this is what works, so I'll just do it. (Participant PID-7)

Overall, most of participants indicated that they had maintained their pre-ETI treatment, with several indicating that they occasionally missed treatments without noticing an immediate decline in their health. Therefore, among most participants, the overall daily treatment burden remained high even if physical health had improved. Therefore, it is vital to understand the impact of these treatment decisions on participants' health and HRQoL.

Mixed-methods analysis

For our mixed-methods analysis, we further explored how individual-level participant's scores for the CFQ-R subscales corresponded to statements made during their interviews. We were interested in examining qualitative data that could help contextualize recent findings[11,22] which showed improvements in physical and respiratory health at greater levels than mental health and treatment burden among people taking ETI. Table 3 shows the results for the four CFQ-R subscales with statements made regarding treatment regimens and impact of ETI on health for each participant.

Among our 24 participants, there were 14 who discussed that they were feeling better physically since starting ETI, but were continuing most of their pre-ETI treatment regimens, who also had CFQ-R scores that were higher for physical and respiratory health, compared to either emotional health or treatment burden. For those participants, while they were feeling better on ETI, they were still experiencing the treatment burden associated with their pre-ETI regimens. For example, one participant reporting high scores for respiratory health but moderate scores for treatment burden described a treatment regimen that had not changed since starting ETI:

> With Trikafta, I didn't change my routine I wake up, I take my inhaled medications while I utilize the vest. On the way home from work, I take more inhaled medications, and some medications I require three times a day. And then at night, I take another round of meds depending on what course of medication I'm on. (PID-6)

Among our 24 participants, there are 5 who were either cutting back on treatments despite poor

Table 3. Mixed-Methods convergent analysis.

Participant	CFQ-R subscales				Illustrative quotes from transcript analysis
	Physical	Respiratory	Emotion	Treatment burden	
PID-1[a]	75	77.8	40	66.7	- Probably like 40 minutes in the morning, which I don't have, but I would definitely try and get them done at least four times a week. - My friends usually tend to swoop in or even my mom, my sister, my stepdad, they kind of push me in a good way to get out of my own head and just, you know, move forward.
PID-2[b]	100	66.7	66.7	55.5	- So the first thing I do is I take my antiacid medicine, then I have to wait half an hour until I can eat, so I would do my treat my breathing treatment and usually, I'm tired at that point anyway. About an hour a day. It's about a half an hour to do treatments and then half an hour to do the Vest. - The most interesting thing that I found recently is that I'm on Trikafta, and I have not had that huge jump that everyone else has.
PID-3[a]	100	94.4	66.7	11.1	- I'll rush out of bed. I'll go downstairs, eat something, I'll take my meds. Uh, then I will rush out the door, 6:00 am work, until 6:00 p.m. So then I'll get home. So, I want to hang out with my friends. And then before I know it, whatever I fall asleep or whatever, and it's 9:00 p.m. I still have to do my therapy and I still have stuff to write up for school and I have to shower still and I'm exhausted, and I kind of, most of the time I get to do my therapy. - So, before Trikafta if I missed one treatment, I would definitely feel it, nowadays, and I hate to say it, I won't feel it after missing one or something . . . I mean, just not coughing every five minutes of every day is awesome. I hated that so much.
PID-4[a]	95.8	94.4	46.6	66.6	- I usually wake up and I try to work out, and then I'll have breakfast, I try to do [my treatments] right after dinner, so that I can still hang out before I go to bed. I do my vest. I do saline solution and I'm on Pulmozyme. Usually, it takes like 25 minutes. - I used to notice if I skipped more than like two days I would get like a super bad cough, like quick, like within two days. But now since I started Trikafta, like I broke my nebulizer and they couldn't get me a new one for like a week, and I didn't even have the slightest cough for the whole week.

(Continued)

Table 3. (Continued)

Participant	CFQ-R subscales				Illustrative quotes from transcript analysis
	Physical	Respiratory	Emotion	Treatment burden	
PID-5[c]	100	100	46.6	89.8	- So before Trikafta, my care was at a point where it was exhausting. I would wake up and probably do hour and a half of treatments in the morning, hour and a half at night, so many pills, so many antibiotics so my life was pretty much consumed by IVs, sinus surgeries, aerosols, nebulizers, chest PT, like I was consumed. I was lucky enough to be in the Trikafta trial and then everything flipped. So, now I literally don't even feel like I have CF. - My parameters for taking care of myself are switched . . . Like back then [pre-Trikafta], it would be like doing all my meds, but now it's like, my care is motivated by what will help like mental health.
PID-6[a]	95.8	88.8	53.3	44.4	- With Trikafta, I didn't change my routine I wake up, I take my inhaled medications while I utilize the vest. On the way home from work, I take more inhaled medications, and some medications I require three times a day. And then at night, I take another round of meds depending on what course of medication I'm on. - So, you know, the Trikafta helps because I'm not getting as sick. My lungs are clearer. You're not burning as much calories throughout the day fighting off constant infection. Less infection, less calorie intake, less wear and tear on the body, less cognitive fatigue.
PID-7[b]	21.17	61.11	60	55.56	- For me, I do the same as I did a year ago. Just because I want to stay stable, I don't want to slip just because I'm relying on this pill, at this point, this is what works, so I'll just do it. - My lung function really hasn't gone up tremendously, but I will say that my endurance is a lot stronger. I'm definitely stronger than I was a year ago. So it definitely was something beneficial to me.
PID-8[a]	100	88.3	77.3	33.3	- I have a brand new one [vest], like it is a portable one, so that makes that makes it so much better honestly. Nebulizers, inhaler I have with me throughout the day. Just my medications are just kind of organized pill cases in the morning, so it is just easy get it over with while I eat. - Within the first two weeks, I could feel the difference. Before, I was on it, like there was talks of about putting a feeding tube in I had a couple of PICC lines because of lung infections, and next thing I know I'm on [Trikafta] I'm on this and my [lung function] went from like 60% to almost like 70. I put on like maybe 10 pounds in like four months

(Continued)

Table 3. (Continued)

Participant	CFQ-R subscales				Illustrative quotes from transcript analysis
	Physical	Respiratory	Emotion	Treatment burden	
PID-9[a]	95.8	100	77.3	66.67	- In the morning, I have a 15-minute vest treatment. And during that vest treatment, I do two nebulizers; I do albuterol and Pulmozyme. Then once I finish that, I'll take my Trikafta, which is two tablets in the morning. Then I'll take my enzymes with that as well. I'll do my night pill with dinner plus my enzymes. And then later on at night, I'll do my last treatment of vest, which is just 15 minutes but no nebulizer with that. - Within a month of me doing it [Trikafta], my cough automatically disappeared. My lung function improved greatly. The way like I breathe and the way I work out just as well as people without it. I can run just as long. I don't get out of breath anymore. I do gain weight as well a little bit faster, not at the same rate as other people do but faster than what I used to. So I am able to keep weight on, and now, I can like work out without worrying that I'm going to lose too much weight.
PID-10[b] Non-lung physical symptoms	54.1	77.8	46.6	33.3	- But it's [Trikafta] caused me to be like extraordinarily wakeful, so that I've to take a heavy sedative to sleep. So, it had my heart rate racing, it's like I've had as much caffeine So, there's a whole litany of like – like minuses to taking the Trikafta. - So, like taking it, then I can come off of it for a little while if I can't tolerate it. Then, I go back on it, when I can't tolerate the abdominal pain any more, you know. So, it's helped with the level of abdominal pain. It really reduces the pancreatic pain to the point where I almost can't not take it.
PID-11[a]	87.5	88.8	53.3	55.5	- I have a small handful of pills I take every morning, but it's 10 seconds. You take the pills – then you're done. I do have a vest. I wear it a lot less than I used to, my evening breathing treatment is probably the most stalwart part of my day. I do bronchodilator and Pulmozyme, 13 nights out of 14. - The things that Trikafta has allowed me to do, which are significant, even though they're not physical, temporarily breaking that bond, that chain between me and my nebulizer. Breaking that chain is mentally, that's something that Trikafta has allowed me to do that I couldn't do before.
PID-12[d]	65.5	88.8	40	33.3	- I will go on my exercise bike or go for a run in the neighborhood. Then, I do the vest right after. I do Pulmozyme at the same time. I do my night pills, head to bed. I'm not too proud to admit I've become a little more lenient [since] Trikafta. - My FEV1 has only been going steadily up when I started Trikafta, I jumped by like 40 pounds. I put a lot of weight on. I don't cough at all throughout the day, unless like I'm doing Xopenex or something. My appetite's been bigger. I used to be used to be admitted [to the hospital] every other year, every year or so. I haven't been admitted in two years.

(Continued)

Table 3. (Continued)

Participant	CFQ-R subscales				Illustrative quotes from transcript analysis
	Physical	Respiratory	Emotion	Treatment burden	
PID-13[a]	100	94.4	86.6	66.7	- [I] get up and I do my vest right when I get up and hypertonic saline while I'm on my vest and then, you know, take my Trikafta and other medications with breakfast. And then in the evening, I do Pulmozyme, but I don't do my vest anymore in the evening. - I'm not bringing pretty much anything up with Trikafta so yeah, my CF Clinic told me that I could just drop one of the vest times if I wanted to and just see how it went and I didn't notice any kind of difference. I do feel like a little bit before Trikafta that I was very slowly going downhill, like you know as time went on, just coughing more and needing more antibiotics and you know that kind of stuff.
PID-14[a]	91.67	88.8	66.6	66.6	- I do albuterol, and TOBI every other month, I take my pills with breakfast including Trikafta. Come home, I have dinner with my pills and then sometime before bed, I neb with albuterol, Pulmozyme, TOBI. - When I was getting sicker, it was annoying because I'd still have to get up early even though like I coughed all night. Growing up, I had a lot of strep throat like So I would cough all night. I do the same thing from before Trikafta. I just don't have as many symptoms.
PID-15[a]	83.3	88.8	73.3	77.7	- I do a nebulizer and then every other month, I do antibiotics. I take my Trikafta and I take another asthma med I do my vest. two or three hours. I do my vest and my nebs and then do the same thing at night. I actually started peeling off some of my meds, which a lot of people have done. - I had like a little bit of a purge, my body was just getting used to it [Trikafta] and like, there was so much mucus and it came out and it was great. it was such a relief. Like it was truly such a relief to get it out.
PID-16[b] Side effects from ETI	55.1	77.7	60	66.67	- CPT therapy with the vest. Pulmozyme and saline and they gave me tobramycin, and Trikafta. - I'm thankful for Trikafta because it was amazing within so to the point of me not even knowing that I had a genetic lung condition that – that limited the function of my lungs. [But] my time on Trikafta has been really rough. There are some rough side effects. I've been so sick on the Trikafta and there's days where like I just don't, you know, don't want to get out of bed. So, it was like flu like symptoms. Then, it was like the major headaches from out of nowhere and I think it was like maybe my body was regulating the saltwater balance and it could have had something to do with dehydration because I noticed before Trikafta, I was never thirsty . . . I have some rashes and I think it's due – it's like dry skin type stuff and I think it's due to like the saltwater regulation.

(Continued)

Table 3. (Continued)

Participant	CFQ-R subscales				Illustrative quotes from transcript analysis
	Physical	Respiratory	Emotion	Treatment burden	
PID-17[a]	70.8	83.3	77.3	22.2	- I, start my day with my nebs and then after that, I wait till about lunchtime, I eat and then I take my Trikafta and then I take other pills and then before bed, I take my pills and then I start doing my nebulizers. I don't use the vest, no. I prefer to use things like Acapella. - I'm on Trikafta and feeling great and my life is better than ever. Travel is just something that has recently come up because I wasn't really able to do it much without Trikafta.
PID-18[c] CFRD	25	72.2	66.6	100	- Prior to [Trikafta], I was doing the vest twice a day. I used to do hypertonic It's probably due to Trikafta because I also used to do the vest with the hyper, and I don't do that either. I haven't touched the vest in probably about six months. I stopped doing vest and I reduced the hypertonic saline . . . The diabetes is complex because that's a pain in the ass, and that's not just, you know, take it and forget about it. - It's more or less become to the point where I don't see the benefits, right where I was before, I would get more up, and that just doesn't happen. So continuing those treatments doesn't seem to make sense. You know, the doctor would tell you otherwise, right?
PID-19[a]	100	83.3	73.3	55.5	- Get up in the morning, immediately take my oral meds. I do like a metered dose inhaler or Advair, nasal spray, nasal saline, and then like a Nasacort – I did transition from nebulized TOBI to the TOBI inhaled powder – which is fast and quick and easy to use. And then breakfast – got to – get breakfast to have some fat intake in order to take a morning dose of Trikafta, enzymes with all my meals. No evening treatment right now. Since Trikafta, I've pulled back more than I should on my nebulized treatments. - Trikafta made a big difference in my day to day regimen, I was getting more like PICC lines per year – it was getting to the point of like, we could be getting two PICC lines in a year, and a PICC line is a major interruption to your life.
PID-20[d] Non-lung related treatment burden	83.3	83.3	73.3	56.5	- Yeah, I'm on Trikafta. I take my ursodiol. I take my vitamins and my calcium supplement and I do my feeding tube, Allegra if I need it, I have my Xanax and my Soma. That's about it. That's literally all I do now. - My regimen used to be it was like hours and hours of treatments back to back all day long. I was at the point where my baseline was in the 1960s and 1970s, and now it's in the 1990s again, because of Trikafta. Ever since Trikafta, they were like, 'You can go off of this, you can safely go off of this, this' and you know what I mean? So my life has gotten so much easier because all I do is just take pills. and it's been a roller coaster the last eight years, up until Trikafta.

(Continued)

Table 3. (Continued)

Participant	CFQ-R subscales				Illustrative quotes from transcript analysis
	Physical	Respiratory	Emotion	Treatment burden	
PID-21[d]	100	66.6	80	66.6	- So honestly since Trikafta, I was able to get the Monarch vest, the one I can walk around in I do that once a day. And then in terms of the Pulmozyme, I haven't done that in a long time. I've just done the hypertonic saline solution. And that's pretty much been the only nebulizer I take. 30 minutes – 30 minutes or 45. The whole day. - We went from an hour a day, twice, twice a day to just 30 minutes. I've been on it for a while. I mean, I noticed a huge difference. You know, the first time I started taking it and even if I do miss it, I miss a day or in the next day I start it back, like I'm just like starting to cough up stuff – it definitely has helped out a lot.
PID-22[b]	66.6	66.6	77.3	66.6	- I take antiacid 30 minutes before I eat. I eat breakfast, take my Trikafta, and my Creon and when I'm on an 'on month', I do a breathing treatment, I do Cayston nebulizer, I do that three times a day. And then, you know, I eat another meal, take all those pills. I usually eat like five meals a day, and any type of airway clearance, it's usually exercise, I try to go on hikes as much as I can. I can't really go on like strenuous ones or long ones or, you know, like really uphill ones, for example, but I – I try to just walk in some type of nature forest, that seems to help my lungs. - I stopped coughing like to a high degree. Not completely, but like it – I don't know 1/5th to 1/10th of how much I used to cough, I cough now. [FEV1] went up like 20%.
PID-23[a]	100	100	73.3	66.6	- Before and after]Trikafta] it's mostly the same. I was on Pulmozyme. Now, I am still on Pulmozyme I still do the vest. Even though I don't feel mucus anymore or bring anything up, they have indicated that the vest can still be shaking up things internally. So, I continue to do it even though I can't feel effects from it anymore. Other than not taking enzymes, my treatments are unchanged. - These days I just feel like I got a second life with Trikafta. I have so much more energy. I don't have to waste my energy on – on coughing and not sleeping.
PID-24[a]	100	83.3	86.6	56.5	- I haven't removed anything. so, I've just kept doing what I'm doing as a like a preventive thing until you tell the, like, I've been told that studies show this doesn't change it. - I had gotten a cold, and the day that I started it [Trikafta], it felt like I had started antibiotics, like, that was the – the change that I felt. . I was like, wow! this is amazing. So, and then I noticed I don't clear my throat as much, just didn't like the daily. So those were the two – two big things that I noticed now that I'm taking it.

[a]CFQ-R scores higher for physical and/or respiratory compared to emotion and/or treatment, and correspond to qualitative statements made.
[b]CFQ-R scores high for both physical and/or respiratory, and emotion and/or treatment, and correspond to qualitative statements made.
[c]CFQ-R scores low for both physical and/respiratory and emotion and/or treatment, and correspond to qualitative statements made.
[d]CFQ-R scores for physical and respiratory, and emotional and treatment do not correspond to qualitative statements made.
CFRD, CF-related diabetes; CFQ-R, Cystic Fibrosis Questionnaire-Revised.

health or maintaining their prior regimens without feeling the benefit of improved health. In this group, CFQ-R scores were similarly both lower to moderate for either physical or respiratory health and lower to moderate for either for emotional health or treatment burden. For example, one participant who was moderate to low for respiratory health, emotional health, and treatment burden but who had not changed their regimen had stated:

> The most interesting thing that I found recently is that I'm on Trikafta, and I have not had that huge jump that everyone else has. (PID-2)

Among our 24 participants, there were 2 who had discussed reducing non-ETI treatments while also experiencing better physical health and less treatment burden, and who reported CFQ-R scores that were both high for either physical or respiratory health and either emotional health or treatment burden. For example, one participant who had reported moderate to high scores across all four subscales stated:

> Prior to [Trikafta], I was doing the vest twice a day. I used to do hypertonic. It's probably due to Trikafta because I also used to do the vest with the hyper, and I don't do that either. I haven't touched the vest in probably about six months. I stopped doing vest and I reduced the hypertonic saline. (PID-18)

Finally, we also found that among 3 of our 24 participants there was no clear link between CFQ-R sub scores and statements made during their interviews. For example, one participant described cutting back on treatments and feeling better, but who still reported high treatment burden. However, for this specific participant, this could possibly be explained by descriptions of nonrespiratory treatments that were resulting in continued treatment burden:

> My regimen used to be it was like hours and hours of treatments back to back all day long. I was at the point where my baseline was in the 60s and 70s, and now it's in the 90s again, because of Trikafta. Ever since Trikafta, they were like, 'You can go off of this, you can safely go off of this, this' and you know what I mean? So my life has gotten so much easier because all I do is just take pills. and it's been a roller coaster the last eight years, up until Trikafta. (PID-20)

Discussion

Among our study participants, CFQ-R subscales scores were higher for physical and respiratory symptoms than for emotional and treatment burden symptoms, with qualitative results indicating that the majority of participants were continuing their pre-ETI regimens or slightly reducing the amount of time spent on their treatments, even though they were feeling better. Other recent work supports findings concerning the impact of ETI on physical health compared to mental health for PwCF. For example, one study exploring the impact of a CF primary palliative care screening intervention showed that among study participants, symptom burden was high, and that anxiety and depression were a greater source of symptom burden than physical symptoms.[11,22] Another study showed nonsignificant change in scores for depression Patient Health Questionnaire-9 (PHQ-9)[33] and anxiety scores Generalized Anxiety Disorder-7 (GAD-7)[34] among a cohort of participants pre and post their starting ETI.[35] Our study adds to this work by placing CFQ-R scores alongside qualitative descriptions of treatment regimens, treatment burden, and physical health. Results from our mixed-methods analysis show that among the majority of participants who had higher CFQ-R physical and respiratory scores compared to emotion and treatment burden scores, there were clear statements made by these participants about feeling physically better on ETI, *and* statements describing treatment regimens that were the same or only slightly altered from their pre-ETI regimens (e.g. occasionally missing a treatment) so that treatment burden remained high despite better physical health. Therefore, at this time it is imperative to understand the long-term impact of reducing treatments for those who are doing well or who are stable on ETI so that they may make evidenced-based decisions that may improve quality of life.

ETI was approved by the FDA for people with CF ages 12 and older in October 2019,[36] with many people with CF having earlier access to the therapy through participation in clinical trials. As a result, there have been multiple short and long-term studies exploring ETI pharmacodynamics, safety, and efficacy. These studies have explored respiratory outcomes such the impact of ETI on lung function,[37,38] sputum production,[39] and mucociliary clearance,[40,41] as well as on nonrespiratory outcomes such as the impact of ETI on

the intestinal microbiome,[42] liver injury,[43] and lipid and fat soluble vitamin levels.[44] However, there are fewer studies that are specifically exploring stopping or reducing non-ETI pulmonary treatments for people on ETI, so it is too soon to assess the long-term impact of reducing or eliminating non-ETI treatments such as airway clearance therapies or nebulizers on respiratory health. One important short-term study known as SIMPLIFY conducted among people with CF on ETI showed that at 6 weeks, discontinuing hypertonic saline and Pulmozyme was noninferior to continuing these treatments.[20] As seen among our sample, it was the case that many of our study participants were not noticing a difference in their health when eliminating their non-ETI treatments, which would support the SIMPLIFY findings in a real-world context.

There are other studies assessing stopping or reducing non-EI therapies, or exploring the impact of nonadherence to non-ETI therapies currently underway. For example, a ClinicalTrials.gov search of elexacaftor–tezacaftor–ivacaftor conducted on 10 February 2024 revealed a total of 58 studies. Of those, there were six registered studies with *explicit* information about study design or study outcomes that indicated a focus on the impact of modifying non-ETI treatments on outcomes such as lung function [ClinicalTrials.gov identifiers: NCT05392855, NCT05740618, NCT04378153] or the impact of treatment adherence/nonadherence on a health outcome for people on ETI [ClinicalTrials.gov identifiers: NCT04602468, NCT05519020, NCT04798014]. Results from these and future studies assessing the impact of reducing or discontinuing non-ETI treatment on both HRQoL and disease progression are critical for ensuring that treatment decisions are guided by evidence rather than subjective experience. To that end, the Cystic Fibrosis Foundation has also recently issued a funding announcement soliciting multicentered studies exploring therapy initiation and modification on ETI known as the TIME initiative.[45]

In the absence of evidence-based longitudinal data specifically regarding stopping or reducing non-ETI treatments, it is important to consider how treatment decisions are being made. In our analysis, we identified three specific themes related to treatment decision-making and adherence that may shed light on this process: (1) How I'm feeling, (2) Not noticing a difference, and (3) Uncertainty about long-term impact of modifying treatment regimens. To better understand these themes, we situate them within the extant literature focused on phenomenology, the Health Belief Model (HBM), and risk and prognostic uncertainty.

Theme 1: How I'm Feeling

Phenomenology explores subjective experiences, perceptions, feelings, emotions, and memories related to specific events, including those experiences related to bodily change.[25] Many people may be drawing on their own physical experiences (i.e. how they are feeling) in what has also been referred to as 'embodied knowledge'.[46] This describes personal-level knowledge of the body connected to how a person is feeling physically at any moment. In the case of our study participants, references to improved health, fewer breathing exacerbations, and higher energy levels are the embodied knowledge of how a person experiences their illness physically, serving as one component of the decision-making equation. In our study, qualitative analysis highlights the individual-level experiences of health before and after the introduction of ETI. For PwCF, disease progression and decline is often marked by changes in lung function with Forced expiratory volume in 1 second (FEV1) frequently used as a marker of CF health.[47] For many study participants, changes in health were often illustrated by references to a stabilization or increase in their FEV1 as well as a reduction in symptoms such as coughing and shortness of breath. We also saw that this was often accompanied by feelings of being liberated or no longer being tied to their treatments. Phenomenology may thus explain the emotional reaction to the improvements in health ('being liberated') as well as the fear of going back to the way things were prior to beginning ETI (i.e. the fear of 'feeling the way I used to' or reverting to a prior illness state).

Theme 2: Not noticing a difference

The HBM, shows how people will engage in a positive health behavior when they feel susceptible to disease or worsening health if they believe engaging in the health behavior would be beneficial.[48] Among PwCF, prior work done before the era of ETI supports this model. One study showed that beliefs about efficacy of airway clearance were associated with adherence.[49]

Another study found that some PwCF only took their medications when they were feeling poorly.[50] Finally, a qualitative study showed that among those participants who reported doing nebulizer treatments regularly was a belief that it would prevent hospitalization.[51] Currently, many of our participants were finding little or no benefit to continuing daily Pulmozyme, hypertonic saline, or percussive chest therapy, and some were questioning the benefit of these treatments over and above taking ETI. Among our participants, some had continued their prior regimens, while others had modified or discontinued treatments. Here, efficacy beliefs rooted in subjective experience were leading people to question the benefits of pre-ETI treatments, resulting in a range of adherence decisions described by our participants.

Theme 3: Uncertainty about long-term impact of modifying treatment regimens

Prior work on prognostic uncertainty has mainly focused on how patients and providers understand probabilistic uncertainty and the factors contributing to this uncertainty.[52–54] In our study, participants were also negotiating prognostic uncertainty related to both the impact of stopping treatment (e.g. due to not experiencing a benefit) and concerns that ETI effects may wane over time (e.g. questioning long-term efficacy of ETI). In the face of uncertainty, individuals must also assess their own risk tolerance.[54] Specifically relevant to our study is the 'scientific uncertainty'[29] that arises during times when novel illnesses first appear (e.g. coronavirus disease 2019)[52] or when novel treatments are first implemented on a wide scale (e.g. ETI), and there is little data on which to draw to guide treatment decisions. Additionally, there is prognostic uncertainty that stems from sociocontextual and personal level factors that are frequently not included in prognostic models.[55] For example, one mixed-methods study in which people with chronic obstructive pulmonary disease and their caregivers were shown prognostic data about the likelihood of experiencing a future breathing exacerbation, found that some participants put greater value on knowledge drawn from prior lived experiences and how they were feeling in the moment over probabilistic data due to its perceived uncertainty or direct relevance to themselves.[56]

Among our study participants, embodied knowledge, beliefs about treatment efficacy, and risk tolerance amid uncertainty about future health outcomes were all part of the decision-making process among our participants. For some participants, long-term uncertainty and anxiety about future health drove them to continue with their treatments even though they no longer experienced the benefits or believed the treatment were working, resulting in continued high treatment burden, and to some extent poor mental health. Those who were discontinuing treatment may have been doing so due to how they were feeling in the moment, despite the future risks. In both instances, personal risk tolerance may be driving these decisions, which will impact HRQoL in the short term but may also have long-term impact on health for people with CF. While decisions about modifying treatments regimens may be focused on subjective experiences of improved health and beliefs that other treatments may not be offering additional benefits to justify the time spent, the long-term impact of reducing or discontinuing treatment is unknown; therefore, long-terms studies assessing the impact of modifying non-ETI treatments are needed.

Limitations and strengths

This case study has two primary limitations:

1. Homogeneity of our study sample. Our study sample was primarily White, and the majority had completed college. However, our sample comprised individuals from within our health system and *via* recruitment *via* social media incorporating a nationwide sample that varied by age, which allowed for greater diversity of experiences.
2. Our cross-sectional study design limited our ability to assess HRQoL *via* the CFQ-R scale prior to the introduction of ETI among our sample. Overall, however, our qualitative interviews compensate for this in their detailed description of participants' treatment regimens both before and after the introduction of ETIs.

The primary strengths of the study are

1. Our mixed-methods analysis linking outcomes for the CFQ-R subscales to specific statements made about treatment regimens,

symptoms, and HRQoL adds to current literature concerning impact of ETI on treatment burden, physical and mental health symptoms.
2. The use of established theoretical frameworks guiding the discussion and
3. Each participant's receipt of an open-ended interview (rather than solely a proportion). This allowed for a broad spectrum of experiences to be included in the qualitative and mixed-methods analyses without reliance on assumptions that data saturation was reached.

Conclusion

Currently, little long-term data exist to provide evidence for modifying treatment regimens in response to improvements in physical health. Results from our study show that most participants in our study were continuing their non-ETI treatments resulting in continued high treatment burden. In the absence of long-term clinic data to inform treatment decisions, patients are weighing their subjective experiences of their health and beliefs about treatment efficacy against personal-level risk tolerance amid uncertainty when making decisions about their current daily treatment regimens. Results from ongoing and future longitudinal studies are needed to help guide decision-making. We wish to emphasize that the participant experiences shared within this study may be unique to our study participants and not reflective of all patients' experiences or outcomes. Therefore, CF care teams should be involved in individual-level conversations with patients about decision-making regarding treatment regimens and decisions to modify them.

Declarations

Ethics approval and consent to participate

This study was approved by the Northwell Health IRB #: 20-0010. All participants completed written informed consent as part of their enrollment in the study.

Consent for publication

Not applicable.

Author contributions

Melissa Basile: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Writing – original draft.

Jennifer Polo: Formal analysis; Investigation; Project administration; Writing – review & editing.

Katherine Henthorne: Conceptualization; Investigation; Writing – review & editing.

Joan DeCelie-Germana: Conceptualization; Formal analysis; Writing – review & editing.

Susan Galvin: Conceptualization; Writing – review & editing.

Janice Wang: Conceptualization; Methodology; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data and materials may be requested by written e-mail to the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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