**Title:** Severe hepatotoxicity is uncommon following ETI: A two-year study in Danish CF patients

**Lay Title:** Is ETI safe for the liver? A two-year study from Denmark offers reassuring results.

**Authors:** Christine Højte1,2,3, Mette Frahm Olsen1,2,4, Daniel Faurholt-Jepsen1,2,5, Marianne Hørby Jørgensen6, Tacjana Pressler1,2,3, Christian Leo-Hansen1,2, Thomas Bryrup1,2, Majbritt Jeppesen1,7, Hanne Vebert Olesen1,8, Janne Petersen9,10, Terese L. Katzenstein1,2, Bibi Uhre Nielsen1,2, Marianne Skov1,3, and the TransformCF Study Group\*.

**Affiliations:**

1The Danish Cystic Fibrosis Cohort; 2Department of Infectious Diseases, Copenhagen University Hospital - Rigshospitalet, Denmark; 3Department of Pediatrics and Adolescent Medicine, Copenhagen University Hospital - Rigshospitalet, Denmark; 4Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark; 5Department of Clinical Medicine, University of Copenhagen, Denmark; 6Department of Pediatric Gastroenterology, Copenhagen University Hospital - Rigshospitalet, Denmark; 7Department of Infectious Diseases, Aarhus University Hospital, Denmark; 8Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Denmark; 9Copenhagen Phase IV Unit, Department of Clinical Pharmacology and Center for Clinical Research and Prevention, University Hospital Bispebjerg-Frederiksberg, Denmark; 10Section of Biostatistics, Department of Public Health, University of Copenhagen, Denmark.

\* The TransformCF study group includes the following members: Thomas Bryrup1,2, Daniel Faurholt-Jepsen1,2,5, Esben Herborg Henriksen1,2, Christine Højte1,2,3, Majbritt Jeppesen1,5, Søren Jensen-Fangel1,5, Camilla Bjørn Jensen1,9, Terese L. Katzenstein1,2, Karlen Stade Bader Larsen1,2, Christian Leo-Hansen1,2, Inger Hee Mabuza Mathiesen1,2, Bibi Uhre Nielsen1,2, Hanne Vebert Olesen1,7, Mette Frahm Olsen1,2,4, Janne Petersen1,9,10, Tacjana Pressler1,2,3, Tavs Qvist1,2, Hans Kristian Råket1,9, Marianne Skov1,3, Espen Jimenez Solem1,9, Joanna Nan Wang1,9.

**What was your research question?**

What are the long-term impact and potential adverse effects of ETI (elexacaftor/tezacaftor/ivacaftor) on liver function?

**Why is this important?**

ETI or Trikaftor, has improved lung function and nutrition in people with cystic fibrosis (CF). ETI also affects the liver, although the impact is still not fully elucidated. Since CF liver disease is a leading cause of illness and death in CF, it is important to understand how ETI affects liver health over time, especially as people with CF live longer.

**What did you do?**

We studied 331 people with CF above 12 years of age in Denmark over two years after they started ETI. We looked at blood tests that show how well the liver is working and tracked individual cases where ETI had to be paused or stopped due to liver concerns.

**What did you find?**

ALT levels (a marker of liver cell stress) rose slightly at first but returned to normal within two years. GGT and ALP levels (markers of bile flow) decreased, suggesting ETI may improve bile duct function. Less than 1% of people showed signs of serious liver problems after starting ETI. Most people with liver issues after starting ETI were able to continue treatment after a short break, and five out of eight who paused treatment later tolerated the full dose. People who started ETI at a lower dose due to liver concerns often reached the full dose later without issues.

**What does this mean and reasons for caution?**

Overall, the changes in liver function were mild and temporary. Most people with CF, even those with liver problems, tolerated ETI well. Regular monitoring seemed to be enough to manage liver safety during ETI treatment. This study therefore finds that ETI is generally safe for the liver and in fact ETI may even improve certain liver functions in people with CF.

**What’s next?**

Future studies should include imaging of the liver as well as extended monitoring to better understand liver health in people with CF treated with ETI.

**Original manuscript citation in PubMed**

NA DATE