

Hepatitis C

Heiner Wedemeyer

Medizinische Hochschule

Klinik für Gastroenterologie, Hepatologie & Endokrinologie

MHH

Medizinische Hochschule
Hannover

GHE

Gastroenterologie
Hepatology
Endocrinology

1

Transparenzfolie

GHE

Honorare für Beratung oder Vorträge:

Abbott, AbbVie, Abivax, Bayer, Biotest, BMS, BTG, Eiger, Esei, Falk Foundation, Gilead, JJ/Janssen-Cilag, MSD, MyrGmbH, Norgine, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, Vaccitec, Vir

Forschungsunterstützung:

Abbott, Abbvie, Biotest, BMS, Gilead, Merck, Novartis, Roche, Roche Diagnostics

2



Gemeinsamer Bundesausschuss

Beschluss

Gesundheitsuntersuchungs-Richtlinie:

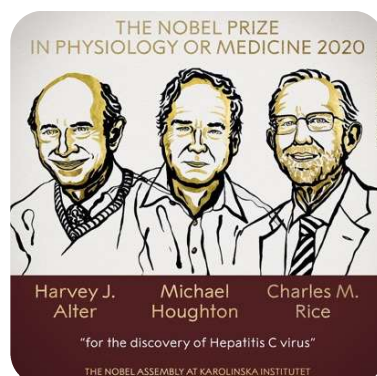
Einführung eines Screenings auf Hepatitis-B- und auf Hepatitis-C-Virusinfektion

Beschlussdatum: 20.11.2020

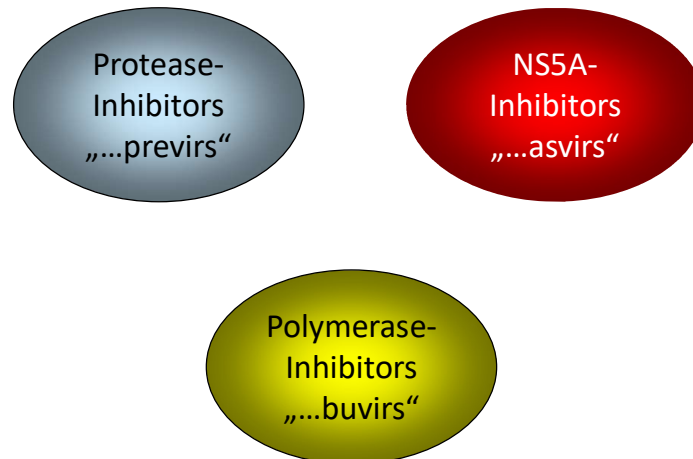
Inkrafttreten: 12.02.2021

Beschluss veröffentlicht: [BAnz AT 11.02.2021 B1](#)

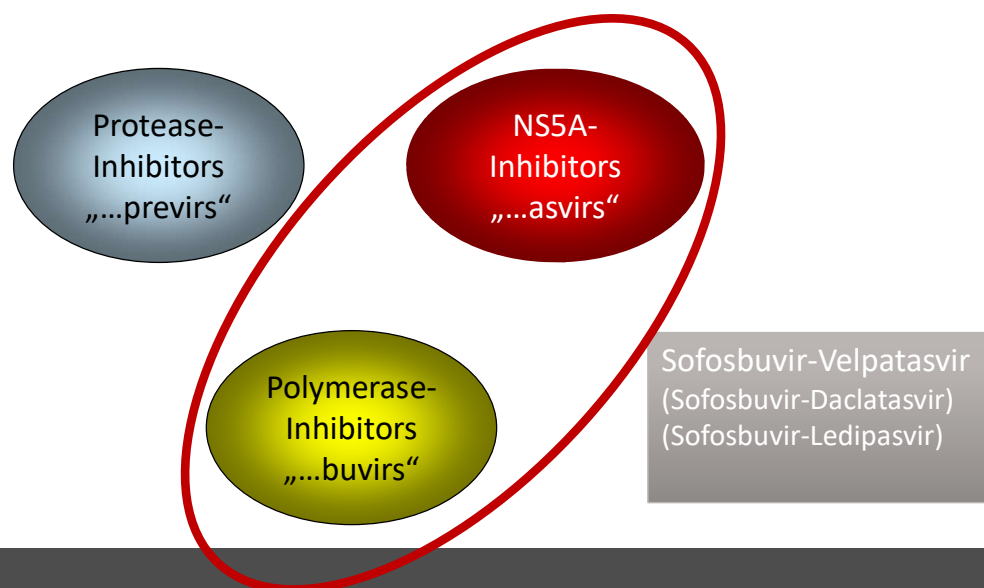
Hepatitis C



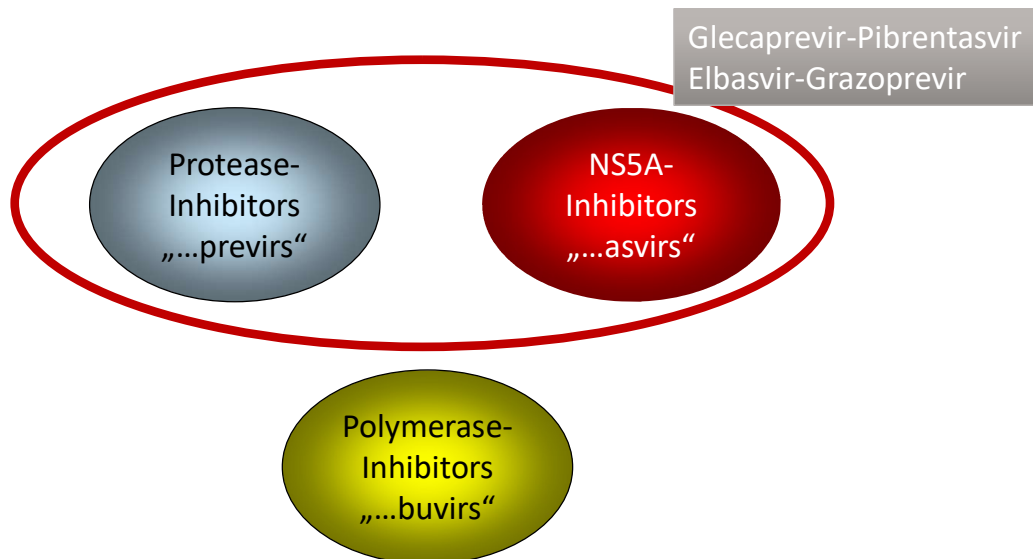
IFN-freie Kombinationstherapien für die Hepatitis C



IFN-freie Kombinationstherapien für die Hepatitis C



IFN-freie Kombinationstherapien für die Hepatitis C



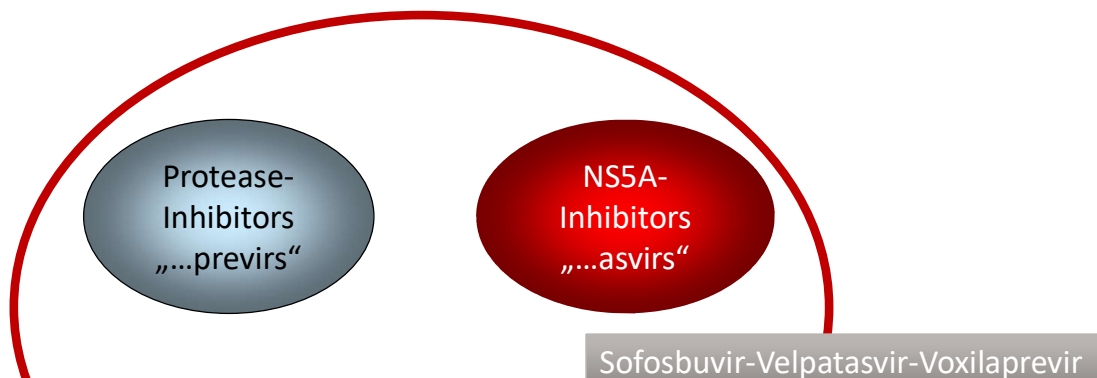
Metaanalysen von Real-World-Kohorten

- Sofosbuvir/Velpatasvir (Mangia et al., Liver International 2020):
5552 Patienten
SVR:98,9%
- Glecaprevir/Pibrentasvir (Lampertico et al., J Hepatol 2020):
12531 Patienten
SVR ITT: 98,1%%

>18.000 patients

- HCV-Genotyp 1: Höner zu Siederdisen, Mauss et al. UEG Journal 2017
- HCV-Genotyp 2: Tacke, Mauss et al. Liver International 2017
- HCV-Genotyp 3: Cornberg, Nierderau et al. Aliment Pharmacol Ther. 2017
- OBV/PTV/r + DBV: Welzel, Wedemeyer et al., J Viral Hepatitis 2017
- 8 Wochen LDV/SOF: Buggisch, Zeuzem et al. J Hepatol 2018
- OST Patienten: Christensen, Wedemeyer et al. Addiction 2018
- HIV-koinfizierte Patienten: Bischoff, Rockstroh et al., HIV-Medicine 2018
- Ältere Patienten >70 Jahre: Dutz, Welzel et al., J Viral Hepatitis 2018
- HIV-koinfizierte - Rolle von CD4+ Zellen: Bischoff, Rockstroh et al., HIV-Clinical Trials 2018
- Transplantationslistungen und HCV: Herzer, Wedemeyer et al., J Hepatol 2018
- Gesundheitsökonomie: Krüger, Rossol, Krauth, Stahmeyer et al., EJGH 2018
- Nicht-invasive Fibrosemarker: Knop, Hoffmann, Friedrich-Rust et al. J Viral Hepatitis 2018
- HCV-RNA+ am Ende der Therapie: Maasoumy, Vermehren et al. Liver International 2018
- Gesamtkohorte 4 Jahre: Hüppe, Wedemeyer et al., Z Gastroenterol 2019
- Glecaprevir/Pibrentasvir: Berg, Niederau et al., Aliment Pharmacol Ther. 2019
- Alcohol & Cannabis: Christensen, Wedemeyer et al., Substance Abuse: Research and Treatment 2019
- Erhöhte Leberwerte trotz Ausheilung: Tacke, Mauss et al., Liver International 2020

IFN-freie Kombinationstherapien für die Hepatitis C



Sofosbuvir, velpatasvir, and voxilaprevir for patients with failure of previous direct-acting antiviral therapy for chronic hepatitis C: Results from the German Hepatitis C-Registry (DHC-R)
Vermehren J, Serfert Y, Cornberg M, Stoehr A, Klinker H, Simon KG, Teuber G, Deterding K, Schulze Zur Wiesch J, Jung MC, Manns MP, Zeuzem S, Wedemeyer H, Sarrazin C. Z Gastroenterol. 2020 Sep;58(9):841-846.

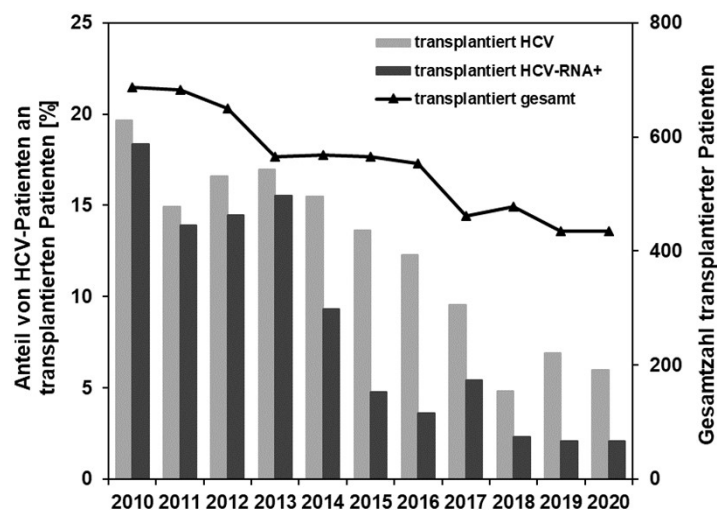
[Glecaprevir/Pibrentasvir + Sofosbuvir + Ribavirin as a salvage regimen after Sofosbuvir + Velpatasvir + Voxilaprevir re-treatment failure].

Tergast TL, Kordecki N, Ohlendorf V, Beier C, Sandmann L, Wedemeyer H, Cornberg M, Maasoumy B.

Z Gastroenterol. 2021 Oct 19. doi: 10.1055/a-1649-8931. Online ahead of print.

Two patients with genotype 3 chronic HCV infection, liver cirrhosis and virological failure after re-treatment with SOF/VEL/VOX that successfully achieved SVR with the combination of SOF+G/P ± RBV. Importantly, one patient had Child B cirrhosis to the time of treatment initiation. No adverse events were reported.

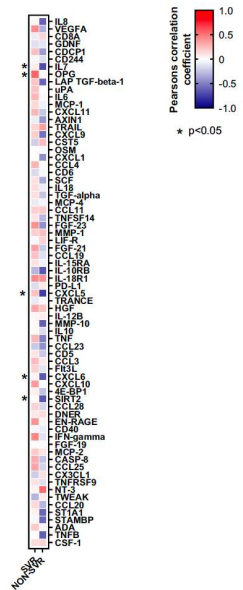
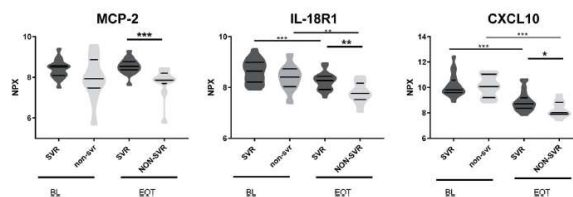
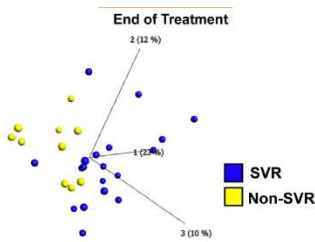
Lebertransplantation und Hepatitis C in Deutschland



Wedemeyer et al. Deutsches Ärzteblatt 2021, Nov 19;118(46):797-798

Soluble inflammatory mediators identify HCV patients who may be cured with four weeks of antiviral treatment

Tanvi Khera^{1,2} | Lone Wulff Madsen^{3,4} | Yanqin Du² | Søren Thue Lillevang^{4,5} | Peer Brehm Christensen^{3,4} | Heiner Wedemeyer^{1,2,6}

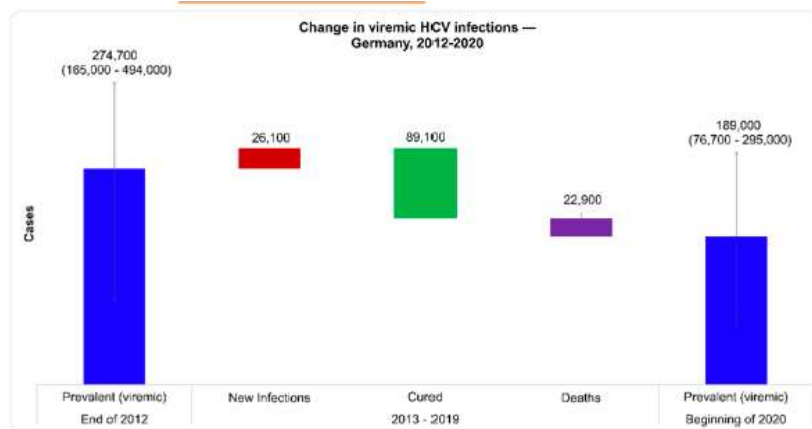


H. Wedemeyer 06-2022
Virushepatitis C

Updated epidemiology of hepatitis C virus infections and implications for hepatitis C virus elimination in Germany

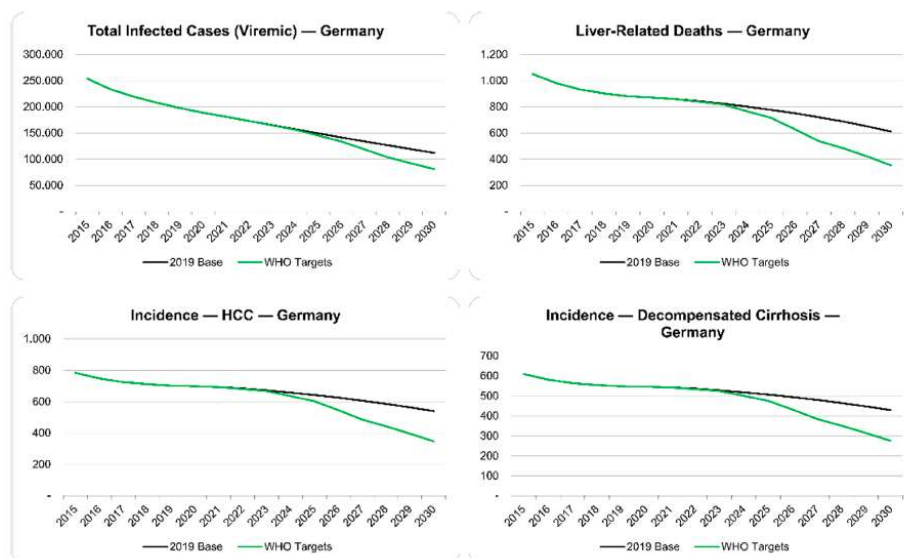
Tammo L. Tergast¹ | Sarah Blach² | Frank Tacke³ | Thomas Berg⁴ | Markus Cornberg^{1,5} | Achim Kautz⁶ | Michael Manns^{1,5} | Homie Razavi² | Christoph Sarrazin^{7,8} | Yvonne Serfert⁵ | Ingo van Thiel⁹ | Stefan Zeuzem¹⁰ | Heiner Wedemeyer^{1,5}

H. Wedemeyer 06-2022
Virushepatitis C



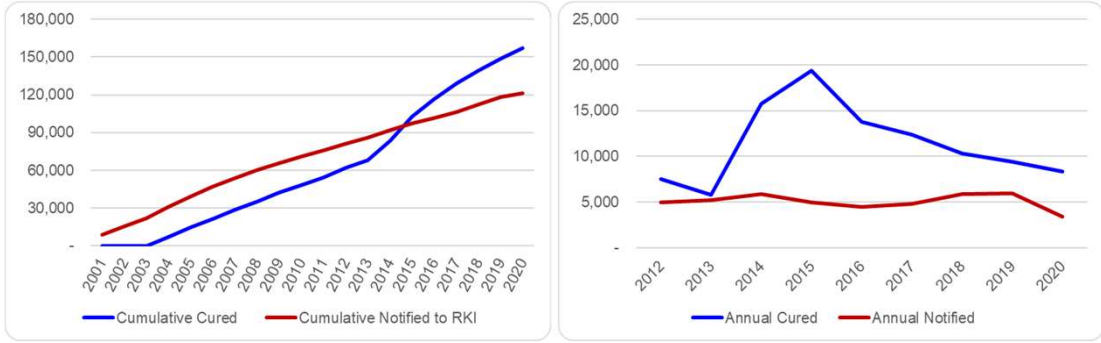
H. Wedemeyer 06-2022
Virushepatitis C

Tergast et al., Journal of Viral Hepatitis, 2022 epub 31. März



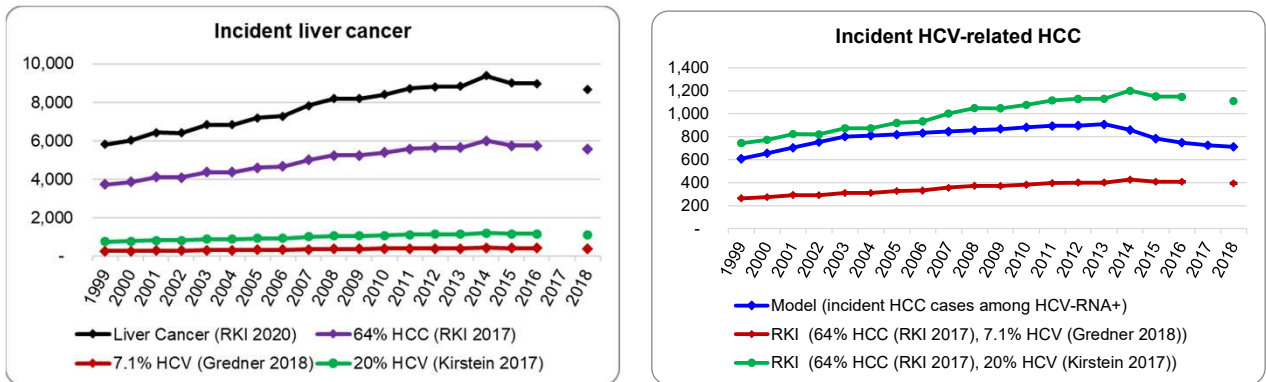
H. Wedemeyer 06-2022
Virushepatitis C

Tergast et al., Journal of Viral Hepatitis, 2022 epub 31. März



H. Wedemeyer 06-2022
Virushepatitis C

Tergast et al., Journal of Viral Hepatitis, 2022 epub 31. März



H. Wedemeyer 06-2022
Virushepatitis C

Tergast et al., Journal of Viral Hepatitis, 2022 epub 31. März

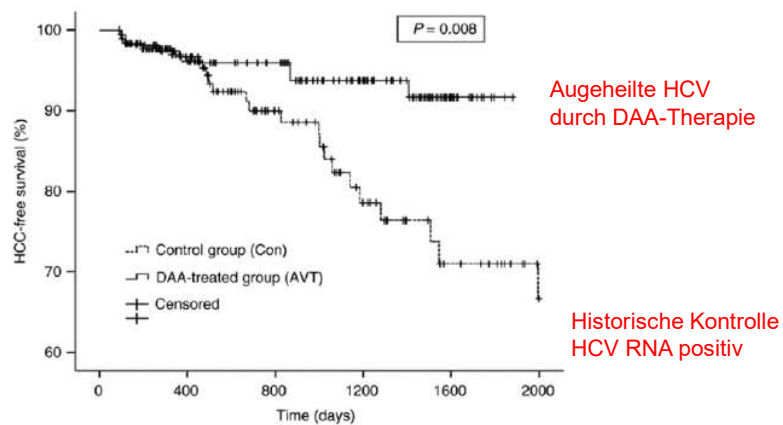
Ausheilung der Hepatitis C – alles gut?

H. Wedemeyer 06-2022
Virushepatitis C

19

Verringertes Risiko für De-novo-HCCs durch DAA-basierte Therapien

Ebel et al., *Aliment Pharmacol Ther.* 2020; 51: 194-195



Number of patients at risk

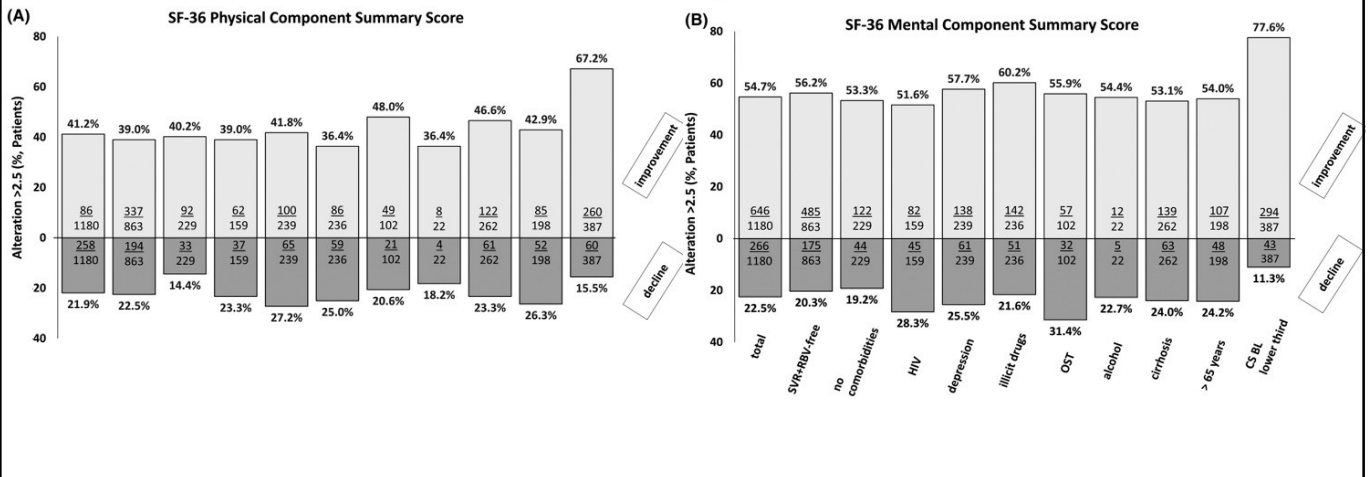
Days	0	400	800	1200	1600	2000
AVT	158	134	105	66	12	
Con	184	124	73	50	34	23

H. Wedemeyer 06-2022
Virushepatitis C

141

20

Nicht alle Patienten verbessern Symptome nach Ausheilung

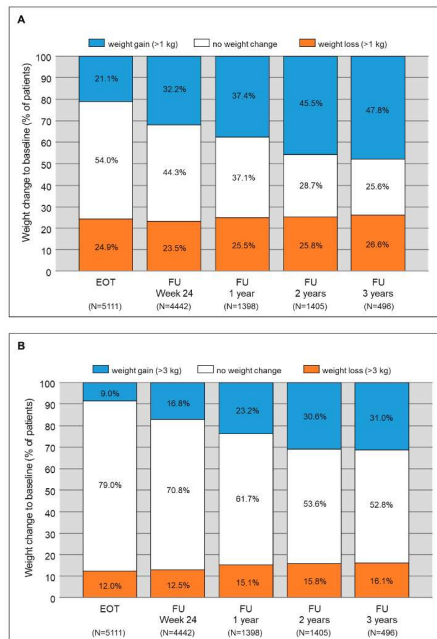


H. Wedemeyer 06-2022
Virushepatitis C

Ohlendorf et al., Journal of Viral Hepatitis, 2021 Aug;28(8):1206-1218

21

Gewichtszunahme nach Ausheilung der Hepatitis C



H. Wedemeyer 06-2022
Virushepatitis C

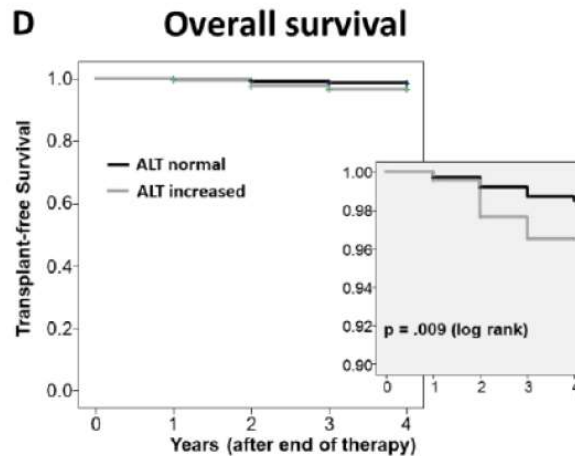
Schlevogt et al., Biomedicines 2021 Oct 19;9(10):1495.

22

Erhöhtes Langzeitrisiko bei weiter erhöhter ALT nach HCV Heilung

Tacke et al., *Liver Int.* 2020; 40: 539-48 & Mauss et al., *Hepatology* 2022 in press

Monitoring nach Ausheilung weiter notwendig



„Long-HepC“?

> *J Infect Dis.* 2016 Dec 15;214(12):1965-1974. doi: 10.1093/infdis/jiw457. Epub 2016 Sep 28.

Direct-Acting Antiviral-Induced Hepatitis C Virus Clearance Does Not Completely Restore the Altered Cytokine and Chemokine Milieu in Patients With Chronic Hepatitis C

Julia Hengst¹, Christine Susanne Falk^{2 3 4}, Verena Schlaphoff¹, Katja Deterding¹,
Michael Peter Manns^{1 3 4}, Markus Cornberg^{1 4}, Heiner Wedemeyer^{1 2 3}

- + MAIT Cells: Hengst et al., *EJI* 2016
- + NK Cells: Strunz et al., *Nat Comm* 2018
- + gd T cells: Ravens et al., *Front Immunol* 2018
- + HCV-specific T cells, Aregay et al., *J Hepatol* 2019
- + post-liver transplantation, Aregay et al., *Liver Transplantation* 2021
- + soluble molecules after acute HCV infection, *J Infect Dis* 2021
- + unconventional T cells after acute HCV infection, *Eur J Immunol* 2022

Memory-like HCV-specific CD8⁺ T cells retain a molecular scar after cure of chronic HCV infection

Nina Hensel^{1,2,3,5}, Zuguang Gu^{6,5}, Sagar^{1,5,15}, Dominik Wieland^{1,7}, Katharina Jechow⁴, Janine Kemming^{1,2,3}, Sian Llewellyn-Lacey⁷, Emma Gostick⁷, Ozlem Sogukpinar^{1,2}, Florian Emmerich^{2,4}, David A. Price^{8,9}, Bertram Bengsch^{1,2,10}, Tobias Boettler^{1,2}, Christoph Neumann-Haefelin^{1,2}, Roland Eils^{4,11}, Christian Conrad⁴, Ralf Bartenschlager^{12,13,14}, Dominic Grün^{1,5,16}, Naveed Ishaque^{6,16}, Robert Thimme^{1,2,16,17} and Maïke Hofmann^{1,2,16,18}

Single-cell transcriptomics implicated that memory-like cells are maintained and terminally exhausted cells are lost after DAA-mediated cure, resulting in a memory polarization of the overall HCV-specific CD8⁺ T cell response. However, an exhausted core signature of memory-like CD8⁺ T cells was still detectable, These results identify a molecular signature of T cell exhaustion that is maintained as a chronic scar in HCV-specific CD8⁺ T cells even after the cessation of chronic antigen stimulation.

Epigenetic scars of CD8⁺ T cell exhaustion persist after cure of chronic infection in humans

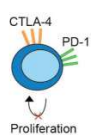
Kathleen B. Yates^{1,2,3}, Pierre Tonnerre^{4,5}, Genevieve E. Martin^{6,7}, Ulrike Gerdemann¹, Rose Al Abosy¹, Dawn E. Comstock^{1,4}, Sarah A. Weiss^{1,8}, David Wolski⁴, Damien C. Tully^{9,10}, Raymond T. Chung¹, Todd M. Allen⁹, Arthur Y. Kim¹¹, Sarah Fidler^{12,13}, Julie Fox^{14,15}, John Frater^{6,16}, Georg M. Lauer⁴, W. Nicholas Haining^{1,17,18,19} and Debattama R. Sen^{1,2,18,20}

Here we show that the epigenetic state of exhaustion is largely irreversible, even after curative therapy. Analysis of chromatin accessibility in HCV- and HIV-specific responses identifies a core epigenetic program of exhaustion in CD8⁺ T cells, which undergoes only limited remodeling before and after resolution of infection. Moreover, canonical features of exhaustion, including super-enhancers near the genes TOX and HIF1A, remain 'epigenetically scarred.'

Yates et al., *Nat Immunol.* 2021 Aug;22(8):1020-1029.



A Immune exhaustion in chronic HCV infection



CD8 T cells
Elevated inhibitory receptors (PD-1, CTLA-4, etc)
Mitochondrial dysfunction
Lack of proliferation

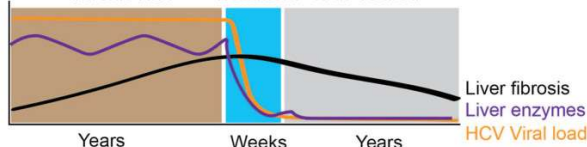
MAIT cells
Reduced frequency
Altered phenotype
Dysfunction

NK cells
Activated phenotype
IFN α response
Reduced NK cell diversity

Regulatory T cells
Altered phenotype
Elevated frequency

Soluble inflammatory markers
Proinflammatory signature and diminished Th2 and Th17 responses

B Chronic HCV Treatment Virus cleared

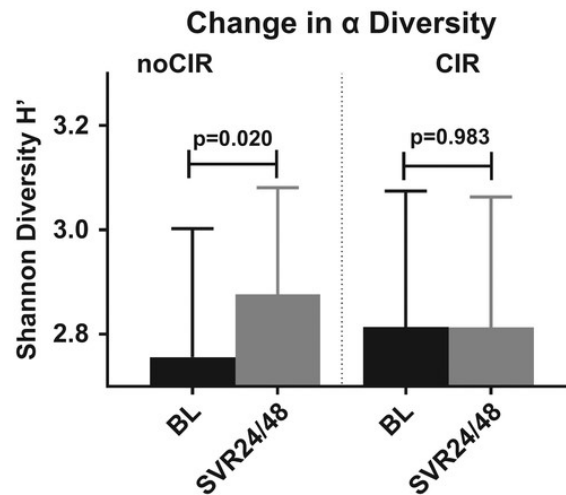


C Modulation of immunity after viral clearance

	Frequency	Diversity	Phenotype	Function	Proliferation
HCV specific CD8 T cells	++		+	+/-	++
HCV specific CD4 T cells		+++	+	+	
$\gamma\delta$ T cells			+	+	
MAIT cells	+/-		+/-	+/-	
Tregs	+/-		+/-	+/-	
NK cells	++	+/-	++	+++	



Wedemeyer et al.,
Front Immunol. 2020 Oct 8;11:571166.



Impfung gegen Hepatitis C

Randomized Trial of a Vaccine Regimen to Prevent Chronic HCV Infection.

Page K, Melia MT, Veenhuis RT, Winter M, Rousseau KE, Massaccesi G, Osburn WO, Forman M, Thomas E, Thornton K, Wagner K, Vassilev V, Lin L, Lum PJ, Giudice LC, Stein E, Asher A, Chang S, Gorman R, Ghany MG, Liang TJ, Wierzbicki MR, Scarselli E, Nicosia A, Folgori A, Capone S, Cox AL.

N Engl J Med. 2021 Feb 11;384(6):541-549.

Hepatitis C reference viruses highlight potent antibody responses and diverse viral functional interactions with neutralising antibodies. Bankwitz D, Bahai A, Labuhn M, Doepke M, Ginkel C, Khera T, Todt D, Ströh LJ, Dold L, Klein F, Klawonn F, Krey T, Behrendt P, Cornberg M, McHardy AC, **Pietschmann T**. *Gut*. 2021 Sep;70(9):1734-1745.

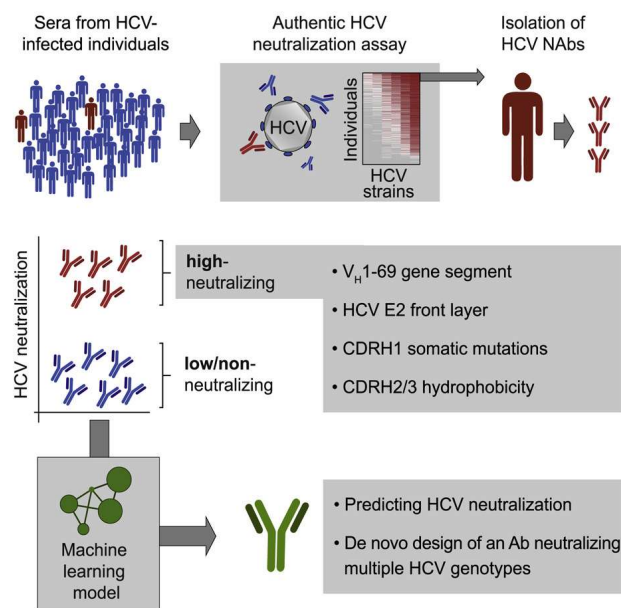
A pan-genotype hepatitis C virus viral vector vaccine generates T cells and neutralizing antibodies in mice. Donnison T, McGregor J, Chinnakannan S, Hutchings C, Center RJ, Pountourios P, Klenerman P, Drummer HE, **Barnes E**. *Hepatology*. 2022 Mar 21. doi: 10.1002/hep.32470.

Neutralization and receptor use of infectious culture-derived rat hepatitis virus as a model for HCV. Wolfisberg R, Thorselius CE, Salinas E, Elrod E, Trivedi S, Nielsen L, Fahnøe U, Kapoor A, Grakoui A, Rice CM, **Bukh J**, Holmbeck K, Scheel TKH. *Hepatology*. 2022 Apr 21

Analysis of antibodies from HCV elite neutralizers identifies genetic determinants of broad neutralization.

Weber T, Potthoff J, Bizu S, Labuhn M, Dold L, Schoofs T, Horning M, Ercanoglu MS, Kreer C, Gieselmann L, Vanshylla K, Langhans B, Janicki H, Ströh LJ, Knops E, Nierhoff D, Spengler U, Kaiser R, Bjorkman PJ, Krey T, Bankwitz D, Pfeifer N, Pietschmann T, Flyak AI, Klein F.

Immunity. 2022 Feb 8;55(2):341-354.e7



Controlled Human Infection Model - Fast Track to HCV Vaccine?

Liang TJ, Feld JJ, Cox AL, Rice CM.

N Engl J Med. 2021 Sep 23;385(13):1235-1240

Hepatitis C: Zusammenfassung

- Standardtherapie über 8-12 Wochen führt fast immer zur Ausheilung
- Restrisiko für HCCs erfordert weiteres Screening
- Symptome können nach Ausheilung persistieren
- Erhöhte Leberwerte trotz Ausheilung ernst nehmen!
- Hepatitis C Impfung: neue Ansätze auf dem Weg!

Was kann der Patient noch tun?

**Kaffee ist gut
für die Leber**



Virushepatitis C