VHPB TECHNICAL MEETING

# Viral hepatitis in Europe's Beating Cancer Plan

## Prevention and control of viral hepatitis as cancer prevention opportunities

*Background document*

27-28 March 2025

Antwerp, Belgium

Prepared by Sara Valckx, Sakshi Jindal & Greet Hendrickx

VHPB Scientific Secretariat

Executive VHPB Secretariat, Vaccine and Infectious disease Institute, University of Antwerpen, Campus Drie Eiken, Drie Eikenstraat 663, BE-2650 Edegem, Belgium, ☎ +32 (0)3 265 26 64, @ info@vhpb.org

# Table of Content

## LIST OF LEARNING OBJECTIVES FOR THIS ACTIVITY

- Discuss viral hepatitis in the **EU Beating Cancer Plan** and the latest **EU Council recommendations**, all in relation with WHO's viral hepatitis elimination goals for 2030
- Discuss how viral hepatitis focused health initiatives can **reduce liver cancer** and thereby identify opportunities to integrate viral hepatitis management as cancer prevention strategy at the level of **screening, vaccination, prevention and treatment**
- Identify ways to improve **health literacy** and **vaccine confidence** (communication)
- Discuss **data collection and sharing** strategies to monitor and report progress on hepatitis-related cancer outcomes
- Discuss resource needs and opportunities for EU and national **funding and collaborations** to support hepatitis-related cancer prevention initiatives

## PARTICIPANTS (± 50 PARTICIPANTS):

- Public health experts, policy makers, healthcare workers, civil society and academics/experts involved in prevention and control of viral hepatitis
- VHPB advisors
- Some selected observers

## EXPECTED IMPACT

Increase awareness of the importance of targeting viral hepatitis, as a major cause for liver cancer, by building on the EU council recommendations/Europe's Beating Cancer Plan.

## VENUE

Antwerp, Belgium

NOTE: This pre-meeting document contains general background information on the topic(s) of the VHPB meeting. It contains a list of selected abstracts/references from a Pubmed MEDLINE and web search on different search terms depending on the topics discussed in the session of the meeting.
The references are sorted by publication year. This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully, it will give an overview of what has been published on the topics of the meeting.

## List of organisations, focus on viral hepatitis related cancer

- **Cancer Prevention Europe (CPE)** – CPE is a collaborative research organization focused on preventing cancer through lifestyle and environmental interventions. Supported by major cancer research institutions across Europe, CPE works on evidence-based policies and strategies for cancer prevention, including vaccine advocacy and health education.
  - **Webpage**: Cancer Prevention – Cancer research for cancer prevention
  - Important publications:
    - Cancer Prevention Europe - Wild - 2019 - Molecular Oncology - Wiley Online Library
    - Time for a European initiative for research to prevent cancer: A manifesto for Cancer Prevention Europe (CPE) - ScienceDirect

- **CDA Foundation** - CDA Foundation (CDAF) is a non-profit organization that specializes in the study of complex and poorly-understood diseases.
  - **Webpage**: CDA Foundation – STUDY. MODEL. IMPACT.

- **Centers for Disease Control and Prevention (CDC)** – The CDC in the United States works on cancer prevention through vaccine promotion, education, and outreach for HPV and hepatitis B. The CDC's Division of Cancer Prevention and Control has specific programs targeting HPV vaccination as a means of preventing certain types of cancer.
  - **Webpage**: Preventing Cancer | Cancer | CDC; Vaccines (Shots) | Cancer | CDC

- **European Association for Cancer Research (EACR)** – EACR supports research into cancer causes, including preventable cancers. They fund and collaborate on projects that promote cancer prevention through vaccination, public awareness, and early detection across Europe.
  - **Webpage:** The European Association for Cancer Research
  - **Chief Executive officer –** Jane Smith (jane.smith@eacr.org)

- **European Cancer information System (ECIS)**: Managed by the Joint Research Centre of the European Commission, ECIS provides comprehensive data on cancer incidence, mortality, and survival trends across European countries. It is a vital tool for public health decision-making and includes detailed factsheets and projections
  - Homepage | ECIS - European Cancer Information System
  - Cancer Factsheets in EU-27 countries - 2022 | ECIS - European Cancer Information System
  - 2024-10-03_Factsheet_Liver-Cancer.pdf
  - The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers

- **European Cancer Organisation (ECO)** – ECO coordinates cancer prevention, research, and policy initiatives across Europe, supporting efforts to reduce cancer incidence. They focus on several key areas, including promoting HPV vaccination and preventive measures related to lifestyle factors.
  - **Webpage**: Home - European Cancer Organisation
  - Topic networks - HPV and Hep B Action Network - European Cancer Organisation
- **European Centre for Disease Prevention and Control (ECDC)** – ECDC works to strengthen Europe's defense against infectious diseases, including vaccine-preventable cancers like HPV-related cervical cancer and hepatitis B-associated liver cancer. They provide guidance, recommendations, and surveillance support for HPV vaccination programs in EU member states.

- **European Commission (EC)** – The EC plays a significant role in cancer prevention through initiatives like Europe's Beating Cancer Plan. This plan emphasizes prevention through vaccination, tobacco control, healthy lifestyle promotion, and supports access to HPV vaccines across member states.

- Cancer - European Commission
- Europe's beating cancer plan
- European Code Against Cancer - International Agency for Research on Cancer (IARC). European Commission: 12 ways to reduce your cancer risk.

- **European Liver Patients' Association (ELPA)** – ELPA advocates for hepatitis B vaccination to prevent liver cancer, providing awareness campaigns, support services, and policy recommendations throughout Europe.
  - **Webpage**: ELPA
  - Working Groups – ELPA
    - ELPA working group on Primary Liver Cancer
    - ELPA worling group on Prevention
    - ELPA working group on Hepatitis B elimination

- **European Network of Cancer Registries (ENCR)**: the ENCR supports the harmonization and improvement of cancer data quality across Europe. Recent updates include standards for data collection, such as the 2023 "Common Data Quality Checks for European Cancer Registries" and recommendations on various cancer types
  - ENCR | European Network of Cancer Registries

- **European Society for Medical Oncology (ESMO)** – ESMO focuses on improving cancer prevention and treatment, with research, guidelines, and advocacy in areas like HPV vaccination. They work with healthcare providers and governments across Europe to integrate cancer prevention into healthcare services.
  - **Webpage**: European Society for Medical Oncology
  - ESMO Real World Data and Digital Health Working Group

- **Gavi, the Vaccine Alliance** – Gavi partners with countries to increase access to critical vaccines in lower-income countries, including HPV and hepatitis B vaccines. Their goal is to reduce the burden of cancer by increasing vaccine availability and affordability worldwide.
  - **Webpage**: Gavi, the Vaccine Alliance
  - Scaling up hepatitis B birth dose vaccination will save lives, and livers, experts say
  - Fighting liver cancer with vaccines in The Gambia

- **International Agency for Research on Cancer (IARC)** – Based in France and part of the WHO, IARC conducts research specifically on cancer causes and prevention, including the impact of HPV and hepatitis B vaccines. IARC collaborates with European governments and research institutions to develop guidelines for cancer prevention.
  - **Webpage**: IARC – INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
  - Liver cancer – IARC

- Institute for Health Metrics and Evaluation (IHME) – IHME works with collaborators around the world to develop evidence that informs health policy and practie
  - **Webpage**: Homepage | Institute for Health Metrics and Evaluation

- **PATH** – This global health nonprofit focuses on increasing HPV and hepatitis B vaccination through advocacy, policy, and partnerships. PATH works in low-resource settings to improve vaccination delivery systems and educate the public on vaccine benefits.
  - **Webpage**: Better health moves humanity forward | PATH

- **The Global Cancer Vaccine Collaborative (GCVC)** – A partnership focused on increasing access to preventive cancer vaccines, especially in underserved regions. GCVC works on policies and programs to promote HPV and hepatitis B vaccination.
  - The Cancer Vaccine Collaborative: a new model of coordinated discovery - PMC (Jill O'Donnell-Tormey, jtormey@cancerresearch.org)
  - Cancer vaccine research - Dr. Jedd D. Wolchok

- **Union for International Cancer Control (UICC)** – The UICC is a global organization that focuses on cancer control and prevention, including vaccine-preventable cancers. They work with governments, healthcare organizations, and NGOs to promote HPV and hepatitis B vaccination as a means of reducing cancer incidence.
  - **Webpage**: Leading global action on cancer | UICC
  - Cancer prevention | UICC
  - **Union for International Cancer Control (UICC) - European Region** – UICC works with local cancer societies, NGOs, and healthcare providers across Europe to promote cancer prevention strategies, including vaccine uptake, screening programs, and education campaigns to reduce cancer incidence.

- **World Health Organization (WHO)** – WHO runs the Global Cancer Initiative, focusing on cancer prevention strategies, including promoting vaccines against HPV and hepatitis B. They work with countries to strengthen immunization programs and promote policies for broader vaccine access.
  - World Hepatitis Day: reducing the risk of liver cancer
  - Cancer EURO
  - Cancer prevention
  - Cancer - Screening and early detection

# Literature review

## Introduction

Viral hepatitis, specifically hepatitis B virus (HBV) and hepatitis C virus (HCV), is widely recognized as a leading cause of liver cancer, particularly hepatocellular carcinoma (HCC), the most common type of liver cancer. This has become abundantly clear over the years:

1. **Global Cancer Statistics and WHO Reports**
   According to the World Health Organization (WHO), liver cancer ranks as the sixth most common cancer and the third leading cause of cancer deaths globally, with chronic hepatitis B and C infections being major causes. WHO reports that approximately 80% of liver cancers are attributable to chronic HBV and HCV infections.

2. **Chronic Hepatitis Infections as Primary Risk Factors**
   The International Agency for Research on Cancer (IARC) classifies both HBV and HCV as Group 1 carcinogens, meaning they are proven to cause cancer in humans. Chronic HBV and HCV infections lead to liver inflammation, which over time can progress to liver fibrosis, cirrhosis, and eventually HCC. Research shows that about 15-25% of people with chronic hepatitis B, and 10-15% of those with chronic hepatitis C, may develop liver cancer.

3. **Epidemiological Studies**
   Numerous studies have found strong epidemiological links between chronic hepatitis infections and liver cancer.

4. **Regional Burden of Liver Cancer Due to Viral Hepatitis**
   In regions with high rates of HBV infection, such as East Asia and sub-Saharan Africa, liver cancer incidence is particularly high. For instance, in China, where HBV is endemic, up to 60% of liver cancer cases are associated with HBV. In Western countries, where HCV infection is more common, it is estimated that about 50% of liver cancers are related to HCV.

5. **Preventive Impact of Vaccination and Antiviral Treatment**
   Studies on the impact of HBV vaccination have shown a significant reduction in liver cancer incidence in populations with widespread vaccination. For example, in Taiwan, where HBV vaccination was introduced in the 1980s, there has been a dramatic decline in liver cancer incidence among vaccinated age groups. Additionally, antiviral treatments that lower HBV and HCV viral loads have been shown to decrease the risk of liver cancer.

6. **Molecular Mechanisms**
   Research into the molecular biology of hepatitis viruses has shown that HBV DNA can integrate into host liver cells, potentially disrupting cellular functions and leading to cancerous changes. HCV, although it does not integrate into the host genome, causes oxidative stress and chronic inflammation, which also drive liver carcinogenesis.

Together, this evidence demonstrates that chronic viral hepatitis infections are major contributors to liver cancer globally. The strong link between hepatitis and liver cancer underscores the importance of preventive measures like HBV vaccination, HCV screening, and antiviral therapies as effective strategies for reducing the global burden of liver cancer.

WHO global health sector strategy on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030.

Europe's Beating Cancer Plan / A cancer plan for Europe - European Commission

Council recommendations on vaccine preventable cancers - Adoption

EASL Open Letter: 10 Asks to Improve Liver Cancer Care in Europe (2021)

World Code Against Cancer Framework: European Code

Lobbying, transparency and trust: power imbalances and the failure to implement Europe's Beating Cancer Plan - ScienceDirect

ECIR-inequalities-factsheet-liver-cancer-viral-hepatitis-May2024.pdf

EU4Health programme 2021-2027 – a vision for a healthier European Union - European Commission

EU Joint Action Networks of Expertise on Cancer (JANE): Shaping the EU Networksof Expertise on cancer!

Hepatitis, Liver Cancer and NCDs - World Hepatitis Alliance

## Pubmed speaker publication lists

Massimo Colombo

Maud Lemoine

Mojca Matičič

Francesco Negro

Heiner Wedemeyer

Paolo Bonanni

Erika Duffell

Philippa C Matthews

Nicola Cocco

Stanislas Pol

Rafael Esteban

Loreta Kondili

Maria Buti

Pierre Nahon

Jonel Trebicka

Silvia Romeo

Giorgia Randi

Otto Visser

Ivane Gamkrelidze

Harriet Rumgay

Stela Bivol

Maia Tsereteli

Milan Mishkovikj

David FitzSimons

## Literature search viral hepatitis related liver cancer (2017-current)

*2017*

Papatheodoridis, GV, R Idilman, GN Dalekos, M Buti, H Chi, F van Boemmel, JL Calleja, V Sypsa, J Goulis, S Manolakopoulos, A Loglio, S Siakavellas, O Keskın, N Gatselis, BE Hansen, M Lehretz, J de la Revilla, S Savvidou, A Kourikou, I Vlachogiannakos, K Galanis, C Yurdaydin, T Berg, M Colombo, R Esteban, HLA Janssen and P Lampertico (2017). "**The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B.**" Hepatology **66**(5): 1444-1453.

> Whether there is a change of hepatocellular carcinoma (HCC) incidence in chronic hepatitis B patients under long-term therapy with potent nucleos(t)ide analogues is currently unclear. We therefore assessed the HCC incidence beyond year 5 of entecavir/tenofovir (ETV/TDF) therapy and tried to determine possible factors associated with late HCC occurrence. This European, 10-center, cohort study included 1,951 adult Caucasian chronic hepatitis B patients without HCC at baseline who received ETV/TDF for ≥1 year. Of them, 1,205 (62%) patients without HCC within the first 5 years of therapy have been followed for 5-10 (median, 6.8) years. HCCs have been diagnosed in 101/1,951 (5.2%) patients within the first 5 years and 17/1,205 (1.4%) patients within 5-10 years. The yearly HCC incidence rate was 1.22% within and 0.73% after the first 5 years (P = 0.050). The yearly HCC incidence rate did not differ within and after the first 5 years in patients without cirrhosis (0.49% versus 0.47%, P = 0.931), but it significantly declined in patients with cirrhosis (3.22% versus 1.57%, P = 0.039). All HCCs beyond year 5 developed in patients older than 50 years at ETV/TDF onset. Older age, lower platelets at baseline and year 5, and liver stiffness ≥12 kPa at year 5 were independently associated with more frequent HCC development beyond year 5 in multivariable analysis. No patient with low Platelets, Age, Gender-Hepatitis B score at baseline or year 5 developed HCC. CONCLUSION: The HCC risk decreases beyond year 5 of ETV/TDF therapy in Caucasian chronic hepatitis B patients, particularly in those with compensated cirrhosis; older age (especially ≥50 years), lower platelets, and liver stiffness ≥12 kPa at year 5 represent the main risk factors for late HCC development. (Hepatology 2017;66:1444-1453).

*2018*

Papatheodoridis, GV, V Sypsa, G Dalekos, C Yurdaydin, F van Boemmel, M Buti, J Goulis, JL Calleja, H Chi, S Manolakopoulos, A Loglio, S Siakavellas, N Gatselis, O Keskın, M Lehretz, S Savvidou, J de la Revilla, BE Hansen, A Kourikou, I Vlachogiannakos, K Galanis, R Idilman, M Colombo, R Esteban, HLA Janssen, T Berg and P Lampertico (2018). "**Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population.**" J Hepatol **68**(6): 1129-1136.

> BACKGROUND & AIMS: The effects of long-term antiviral therapy on survival have not been adequately assessed in chronic hepatitis B (CHB). In this 10-centre, ongoing cohort study, we evaluated the probability of survival and factors affecting survival in Caucasian CHB patients who received long-term entecavir/tenofovir therapy. METHODS: We included 1,951 adult Caucasians with CHB, with or without compensated cirrhosis and without hepatocellular carcinoma (HCC) at baseline, who received entecavir/tenofovir for ≥12 months (median, six years). Kaplan-Meier estimates of cumulative survival over time were obtained. Standardized mortality ratios (SMRs) were calculated by comparing death rates with those in the Human Mortality Database. RESULTS: The one-, five-, and eight-year cumulative probabilities were 99.7, 95.9, and 94.1% for overall survival, 99.9, 98.3, and 97.4% for liver-related survival, and 99.9, 97.8, and 95.8% for transplantation-free liver-related survival, respectively. Overall mortality was independently associated with older age and HCC development, liver-related

mortality was associated with HCC development only, and transplantation-free liver-related mortality was independently associated with HCC development and lower platelet levels at baseline. Baseline cirrhosis was not independently associated with any type of mortality. Compared with the general population, in all CHB patients mortality was not significantly different (SMR 0.82), whereas it was lower in patients without HCC regardless of baseline cirrhosis (SMR 0.58) and was higher in patients who developed HCC (SMR 3.09). CONCLUSION: Caucasian patients with CHB and compensated liver disease who receive long-term entecavir/tenofovir therapy have excellent overall and liver-related eight-year survival, which is similar to that of the general population. HCC is the main factor affecting their overall mortality, and is the only factor affecting their liver-related mortality. LAY SUMMARY: Caucasian patients with chronic hepatitis B with or without compensated cirrhosis who receive long-term entecavir or tenofovir therapy have excellent overall eight-year survival, which is similar to that of the general population. Hepatocellular carcinoma is the main factor affecting their overall mortality, and is the only factor affecting liver-related mortality in this setting.

Safreed-Harmon, K, KL Hetherington, S Aleman, H Alho, O Dalgard, T Frisch, M Gottfredsson, N Weis and JV Lazarus (2018). "**Policy responses to hepatitis C in the Nordic countries: Gaps and discrepant reporting in the Hep-Nordic study**." PLoS One **13**(1): e0190146.

BACKGROUND AND AIMS: In the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden), the prevalence of chronic hepatitis C virus (HCV) infection is relatively low in the general population, but is much higher among people who inject drugs (PWID). We conducted an exploratory study to investigate the extent to which these countries have policies supporting key elements of the public health response that is necessary to achieve the global goal of eliminating HCV as a public health threat. METHODS: Fourteen stakeholders representing government agencies, medical societies, and civil society organisations (CSOs) in the Nordic countries completed a cross-sectional online survey that included 21 policy questions related to national coordination, prevention, testing, linkage to care, and treatment. We summarised the findings in a descriptive analysis, and noted discrepant responses from stakeholders within the same country. RESULTS: Stakeholders reported that three of the five study countries have national viral hepatitis strategies, while only Iceland has a national HCV elimination goal. The availability of harm reduction services varies, with opioid substitution therapy provided for the general population throughout all countries, but not needle and syringe programmes. No country has access to anonymous HCV testing in all parts of the country. National HCV treatment guidelines are available in all countries except Finland, and all countries provide publicly funded direct-acting antiviral treatment. Disagreement regarding policies was observed across countries, and CSOs were the stakeholder group that most frequently answered survey questions incorrectly. CONCLUSION: The Nordic region as a whole has not consistently expressed its commitment to tackling HCV, despite the existence of large HCV epidemics among PWID in these countries. Stakeholder alignment and an established elimination goal with an accompanying strategy and implementation plan should be recognised as the basis for coordinated national public health efforts to achieve HCV elimination in the Nordic region and elsewhere.

*2019*

Carrat, F, H Fontaine, C Dorival, M Simony, A Diallo, C Hezode, V De Ledinghen, D Larrey, G Haour, JP Bronowicki, F Zoulim, T Asselah, P Marcellin, D Thabut, V Leroy, A Tran, F Habersetzer, D Samuel, D Guyader, O Chazouilleres, P Mathurin, S Metivier, L Alric, G Riachi, J Gournay, A Abergel, P Cales, N Ganne, V Loustaud-Ratti, L D'Alteroche, X Causse, C Geist, A Minello, I Rosa, M Gelu-Simeon, I Portal, F Raffi, M Bourliere and S Pol (2019). "**Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study**." Lancet **393**(10179): 1453-1464.

BACKGROUND: Although direct-acting antivirals have been used extensively to treat patients with chronic hepatitis C virus (HCV) infection, their clinical effectiveness has not been well reported. We compared the incidence of death, hepatocellular carcinoma, and decompensated cirrhosis between patients treated with direct-acting antivirals and those untreated, in the French ANRS CO22 Hepather cohort. METHODS: We did a prospective study in adult patients with chronic HCV infection enrolled from 32 expert hepatology centres in France. We excluded patients with chronic hepatitis B, those with a history of decompensated cirrhosis, hepatocellular carcinoma, or liver transplantation, and patients who were treated with interferon-ribavirin with or without first-generation protease inhibitors. Co-primary study outcomes were incidence of all-cause mortality, hepatocellular carcinoma, and decompensated cirrhosis. The association between direct-acting antivirals and these outcomes was quantified using time-dependent Cox proportional hazards models. This study is registered with ClinicalTrials.gov, number NCT01953458. FINDINGS: Between Aug 6, 2012, and Dec 31, 2015, 10 166 patients were eligible for the study. 9895 (97%) patients had available follow-up information and were included in analyses. Median follow-up was 33·4 months (IQR 24·0-40·7). Treatment with direct-acting antivirals was initiated during follow-up in 7344 patients, and 2551 patients remained untreated at the final follow-up visit. During follow-up, 218 patients died (129 treated, 89 untreated), 258 reported hepatocellular carcinoma (187 treated, 71 untreated), and 106 had decompensated cirrhosis (74 treated, 32 untreated). Exposure to direct-acting antivirals was associated with increased risk for hepatocellular carcinoma (unadjusted hazard ratio [HR] 2·77, 95% CI 2·07-3·71) and decompensated cirrhosis (3·83, 2·29-6·42). After adjustment for variables (age, sex, body-mass index, geographical origin, infection route, fibrosis score, HCV treatment-naive, HCV genotype, alcohol consumption, diabetes, arterial hypertension, biological variables, and model for end-stage liver disease score in patients with cirrhosis), exposure to direct-acting antivirals was associated with a decrease in all-cause mortality (adjusted HR 0·48, 95% CI 0·33-0·70) and hepatocellular carcinoma (0·66, 0·46-0·93), and was not associated with decompensated cirrhosis (1·14, 0·57-2·27). INTERPRETATION: Treatment with direct-acting antivirals is associated with reduced risk for mortality and hepatocellular carcinoma and should be considered in all patients with chronic HCV infection. FUNDING: INSERM-ANRS (France Recherche Nord & Sud Sida-HIV Hépatites), ANR (Agence Nationale de la Recherche), DGS (Direction Générale de la Santé), MSD, Janssen, Gilead, AbbVie, Bristol-Myers Squibb, and Roche.

Rinaldi, L, A Perrella, M Guarino, M De Luca, G Piai, N Coppola, PC Pafundi, F Ciardiello, M Fasano, E Martinelli, G Valente, R Nevola, C Monari, L Miglioresi, B Guerrera, M Berretta, FC Sasso, F Morisco, A Izzi and LE Adinolfi (2019). "**Incidence and risk factors of early HCC occurrence in HCV patients treated with direct acting antivirals: a prospective multicentre study.**" J Transl Med **17**(1): 292.

BACKGROUND: An unexpected increased HCC recurrence and occurrence rate among HCV patients treated with direct acting antivirals combination has been reported. Aim of the study was the evaluation of early HCC occurrence rate and its risk factors in a HCV infected population, treated with direct-acting-antivirals. METHODS: According to the Italian ministerial guidelines for direct-acting-antivirals treatment, 1022 consecutive HCV patients treated with direct-acting-antivirals were enrolled. Patients either with active HCC at imaging or history of previous treated HCC, HBV or HIV co-infection, or liver transplant recipients were excluded. The SVR, defined as the persistent absence of detectable serum HCV-RNA 12 weeks after the end of treatment (SVR12), was assessed for all enrolled patients. Abdominal ultrasound was performed before starting antiviral therapy, and repeated every 6 months. HCC was diagnosed according to the international guidelines. Patients showing either nodular patterns suggestive of HCC or with uncertain dynamic vascular behaviour were excluded from a further follow-up. RESULTS: Nine hundred and eighty-five patients completed the 48 weeks follow-up after the end of treatment. A Sofosbuvir-based regimen was administered in the 74.9% of patients, among whom, the 71.6% underwent a simultaneous Ribavirin administration. A sustained

virological response at 12 weeks off treatment was documented in 966 patients (98.2%). During the post treatment follow-up HCC was detected in 35 patients, with a cumulative incidence rate of the 3.55%. At multivariate analysis, four variables resulted independently associated with HCC development, both in a cirrhosis based and a class B Child based model, respectively: cirrhosis/class B Child, therapeutic schedule including Sofosbuvir without Ribavirin, liver stiffness values, male gender and presence of diabetes. A multivariate analysis performed on Child A cirrhotic patients, showed that Sofosbuvir based therapeutic treatment without Ribavirin had a HCC occurrence 5.7 higher than Ribavirin-based schedules with or without Sofosbuvir ($p < 0.0001$, OR: 5.686, 95% CI 2.455-13.169). CONCLUSIONS: Our data suggest that early HCC occurrence appears more frequently related to Sofosbuvir-based therapy without Ribavirin which, indeed, seems to play a protective role on HCC onset. Therefore, a careful follow-up should be mandatory, especially in those regimens including Sofosbuvir without Ribavirin.

*2020*

Ebel, F, K Deterding, K Port, B Schlevogt, MP Manns, B Maasoumy, M Cornberg and H Wedemeyer (2020). "**Letter: a 5-year long-term follow-up study after DAA treatment confirms a reduced HCC risk in a central European cohort of HCV patients with liver cirrhosis.**" Aliment Pharmacol Ther **51**(1): 194-195.

Marrone, A, G Franci, A Perrella, R Nevola, A Chianese, LE Adinolfi, FC Sasso and L Rinaldi (2020). "**Editorial - HCC in HCV patients and the direct acting antivirals: is there really a link?**" Eur Rev Med Pharmacol Sci **24**(2): 983-987.

Nakitanda, AO and E Duffell (2020). "**Hospital discharges of hepatocellular carcinoma and non-alcohol related cirrhosis in the EU/EEA and United Kingdom: a descriptive analysis of 2004-2015 data.**" Infect Dis (Lond) **52**(11): 816-827.

BACKGROUND: Viral hepatitis is a leading cause of mortality globally, comparable to that of HIV and TB. Most hepatitis deaths are related to liver cirrhosis and hepatocellular carcinoma (HCC) associated with chronic hepatitis B and C infections. To examine the progress towards the elimination goals set in the global health sector strategy for viral hepatitis, we aimed to assess the impact of mortality-indicative morbidity. METHODS: We retrieved inpatients and day cases hospital discharges data from the Eurostat hospital activities database, and analysed ICD-10 and ICD-9 specific codes related to primary HCC and non-alcohol related cirrhosis registered by European Union/European Economic Area (EU/EEA) countries and United Kingdom (UK) for 2004 to 2015. RESULTS: In 2015, 20 countries (45.7% of total EU/EEA/UK population) reported 13,236 (Range 0-6294) day cases and 36,012 (4-9097) inpatients discharges of HCC. Romania, Croatia, Luxembourg and UK reported increasing day cases discharge rates between 2004 and 2015; while HCC inpatients discharge rates increased overall during this period. There were 13,865 (0-5918) day cases and 56,176 (3-29,118) inpatients discharges reported for cirrhosis across the 20 countries in 2015. Over the 12 years, day cases discharge rates for cirrhosis increased in Romania, Croatia and UK. Though higher than for day cases, cirrhosis inpatients discharge rates remained stable. CONCLUSIONS: The hospital burden of HCC and cirrhosis is high, with considerable inpatient load including sustained increasing trends in HCC discharge rates. Further interpretation in light of local health system contexts, and more robust harmonised data are needed to better understand the impact of the viral hepatitis epidemic in the region.

Papatheodoridis, GV, GN Dalekos, R Idilman, V Sypsa, F Van Boemmel, M Buti, JL Calleja, J Goulis, S Manolakopoulos, A Loglio, M Papatheodoridi, N Gatselis, R Veelken, M Lopez-Gomez, BE Hansen, S Savvidou, A Kourikou, J Vlachogiannakos, K Galanis, C Yurdaydin, R Esteban, HLA Janssen, T Berg and P Lampertico (2020). "**Similar risk of hepatocellular carcinoma during long-term entecavir or tenofovir therapy in Caucasian patients with chronic hepatitis B.**" J Hepatol **73**(5): 1037-1045.

BACKGROUND & AIMS: A recent study in Asian patients with chronic hepatitis B (CHB) reported that the incidence of hepatocellular carcinoma (HCC) was lower in patients treated with tenofovir disoproxil fumarate (TDF) than entecavir (ETV), but this finding remains controversial. We aimed to identify any differences in HCC incidence, or other patient outcomes, between patients receiving TDF or ETV in the well monitored, multicenter European PAGE-B cohort. METHODS: We included 1,935 Caucasians with CHB, with or without compensated cirrhosis, treated with ETV (n = 772) or TDF (n = 1,163) monotherapy. Mean follow-up was 7.1 ± 3.0 years from ETV/TDF onset. RESULTS: The 5-year cumulative HCC incidence was 5.4% in ETV- and 6.0% in TDF-treated patients (log-rank, p = 0.321), with no significant difference in any patient subgroup (with or without cirrhosis, naïve or experienced to oral antiviral(s) [total, with or without cirrhosis]). In multivariable Cox regression analyses, the hazard of HCC was similar between ETV- and TDF-treated patients after adjustment for several HCC risk factors. ETV- and TDF-treated patients had similar rates of on-therapy biochemical and virological remission, HBsAg loss, liver transplantation and/or death. Elastographic reversion of cirrhosis at year 5 (liver stiffness <12 kPa) was observed in 245/347 (70.6%) patients with pretreatment cirrhosis, being more frequent in TDF- than ETV- treated patients (73.8% vs. 61.5%, p = 0.038). CONCLUSION: In Caucasian patients with CHB, with or without cirrhosis, long-term ETV or TDF monotherapy is associated with similar HCC risk, rates of biochemical/virological remission, HBsAg loss and liver transplantation or death, but elastographic reversion of cirrhosis at year 5 was more frequent with TDF. LAY SUMMARY: In a large cohort of Caucasians with chronic hepatitis B treated with entecavir (ETV) or tenofovir disoproxil fumarate (TDF) monotherapy, cumulative rates of hepatocellular carcinoma did not differ (up to 12 years). Nor did rates of biochemical/virological remission, HBsAg loss and liver transplantation or death. However, elastographic reversion of cirrhosis at year 5 was more frequent in TDF- than ETV-treated patients with pretreatment cirrhosis.

Phan, DV, CL Chan, AA Li, TY Chien and VC Nguyen (2020). "**Liver cancer prediction in a viral hepatitis cohort: A deep learning approach**." Int J Cancer **147**(10): 2871-2878.

Viral hepatitis is the primary cause of liver diseases, among which liver cancer is the leading cause of death from cancer. However, this cancer is often diagnosed in the later stages, which makes treatment difficult or even impossible. This study applied deep learning (DL) models for the early prediction of liver cancer in a hepatitis cohort. In this study, we surveyed 1 million random samples from the National Health Insurance Research Database (NHIRD) to analyze viral hepatitis patients from 2002 to 2010. Then, we used DL models to predict liver cancer cases based on the history of diseases of the hepatitis cohort. Our results revealed the annual prevalence of hepatitis in Taiwan increased from 2002 to 2010, with an average annual percentage change (AAPC) of 5.8% (95% CI: 4.2-7.4). However, young people (aged 16-30 years) exhibited a decreasing trend, with an AAPC of -5.6 (95% CI: -8.1 to -2.9). The results of applying DL models showed that the convolution neural network (CNN) model yielded the best performance in terms of predicting liver cancer cases, with an accuracy of 0.980 (AUC: 0.886). In conclusion, this study showed an increasing trend in the annual prevalence of hepatitis, but a decreasing trend in young people from 2002 to 2010 in Taiwan. The CNN model may be applied to predict liver cancer in a hepatitis cohort with high accuracy.

Shiha, G, I Waked, R Soliman, M Elbasiony, A Gomaa, NNH Mikhail and M Eslam (2020). "**GES: A validated simple score to predict the risk of HCC in patients with HCV-GT4-associated advanced liver fibrosis after oral antivirals**." Liver Int **40**(11): 2828-2833.

BACKGROUND & AIMS: Hepatocellular carcinoma (HCC) risk persists after hepatitis C virus (HCV) eradication with direct-acting antivirals (DAAs), particularly in patients with cirrhosis. Identifying those who are likely to develop HCC is a critical unmet medical need. Our aim is to develop a score that offers individualized patient HCC risk prediction. METHODS: This two-centre prospective study included 4400 patients, with cirrhosis and advanced fibrosis who achieved a sustained virologic response (SVR), including 2372 patients (derivation cohort). HCC-associated factors were identified by multivariable Cox regression analysis to develop a scoring model for prediction of HCC risk; and subsequently internally and externally validated in two independent cohorts of 687 and 1341 patients. RESULTS: In the derivation cohort, the median follow-up was 23.51 ± 8.21 months, during which 109 patients (4.7%) developed HCC. Age, sex, serum albumin, α fetoprotein and pretreatment fibrosis stage were identified as risk factors for HCC. A simple predictive model (GES) score was constructed. The 2-year cumulative HCC incidence using Kaplan-Meier method was 1.2%, 3.3% and 7.1% in the low-risk, medium-risk and high-risk groups respectively. Internal and external validation showed highly significant difference among the three risk groups ($P < .001$) with regard to cumulative HCC risk. GES score has high predictive ability value (Harrell's C statistic 0.801), that remained robustly consistent across two independent validation cohorts (Harrell's C statistic 0.812 and 0.816). CONCLUSION: GES score is simple with validated good predictive ability for the development of HCC after eradication of HCV and may be useful for HCC risk stratification in those patients.

Yotsuyanagi, H, T Takano, M Tanaka, K Amano, M Imamura, K Ogawa, T Yasunaka, Y Yasui, K Hayashi, Y Tanaka and H Tajiri (2020). "**Hepatitis B virus-related hepatocellular carcinoma in young adults: Efficacy of nationwide selective vaccination**." Hepatol Res **50**(2): 182-189.

AIM: Hepatitis B vaccination in infancy was carried out in Japan only when the mother was persistently infected from 1986 to 2016. The aim of the present study was to elucidate the results of vaccination for the prevention of hepatocellular carcinoma in young adults. METHODS: We studied the number of patients who had liver cancer and died from 1976 to 2017 using a national database. Furthermore, we carried out a nationwide survey focusing on patients with hepatitis B virus-related hepatocellular carcinoma who were diagnosed when aged <40 years from 2007 to 2016. RESULTS: The national database showed that the number of deaths of patients aged <40 years decreased from 337 in 1986 to 61 in 2016. Among the 122 patients with hepatocellular carcinoma (HCC) who were registered in the survey, just three patients were born after the start of the vaccination in 1986. Liver cirrhosis, defined by a high Fib-4 index (≥3.25), was found in just 12.5% of the patients at the time of the survey. HCC was incidentally diagnosed in 85 of the 122 (69%) patients. More than 60% of the patients (54/88) were dead at the time of the study, which may be attributed to the delay in diagnosis. CONCLUSIONS: Selective vaccination was effective for the prevention of hepatitis B virus-related HCC. In contrast, many young adults who missed the chance of hepatitis B vaccination and HCC surveillance developed HCC and died. Hepatitis B virus screening in young adults and careful follow up of infected patients are important to prevent HCC development.

*2021*

Ahumada, A, L Rayon, C Uson, R Banares and S Alonso Lopez (2021). "**Hepatocellular carcinoma risk after viral response in hepatitis C virus-advanced fibrosis: Who to screen and for how long?**" World J Gastroenterol **27**(40): 6737-6749. (https://www.ncbi.nlm.nih.gov/pubmed/34790004)

Hepatitis C virus (HCV) chronic infection is associated with fibrosis progression, end-stage liver complications and HCC. Not surprisingly, HCV infection is a leading cause of liver-related morbidity and mortality worldwide. After sustained virological response (SVR), the risk of developing hepatocellular carcinoma is not completely eliminated in patients with established cirrhosis or with advanced fibrosis. Therefore, lifelong surveillance is currently recommended. This strategy is likely not universally cost-effective and harmless, considering that not all patients with advanced fibrosis have the same risk of developing HCC. Factors related to the severity of liver disease and its potential to improve after SVR, the molecular and epigenetic changes that occur during infection and other associated comorbidities might account for different risk levels and are likely essential for identifying patients who would benefit from screening programs after SVR. Efforts to develop predictive models and risk calculators, biomarkers and genetic panels and even deep learning models to estimate the individual risk of HCC have been made in the direct-acting antiviral agents era, when thousands of patients with advanced fibrosis and cirrhosis have reached SVR. These tools could help to identify patients with very low HCC risk in whom surveillance might not be justified. In this review, factors affecting the probability of HCC development after SVR, the benefits and risks of surveillance, suggested strategies to estimate individualized HCC risk and the current evidence to recommend lifelong surveillance are discussed.

Alqahtani, SA and M Colombo (2021). "**Treatment for Viral Hepatitis as Secondary Prevention for Hepatocellular Carcinoma.**" Cells **10**(11).

Chronic infections with either hepatitis B or C virus (HBV or HCV) are among the most common risk factors for developing hepatocellular carcinoma (HCC). The hepatocarcinogenic potential of these viruses is mediated through a wide range of mechanisms, including the induction of chronic inflammation and oxidative stress and the deregulation of cellular pathways by viral proteins. Over the last decade, effective anti-viral agents have made sustained viral suppression or cure a feasible treatment objective for most chronic HBV/HCV patients. Given the tumorigenic potential of HBV/HCV, it is no surprise that obtaining sustained viral suppression or eradication proves to be effective in preventing HCC. This review summarizes the mechanisms by which HCV and HBV exert their hepatocarcinogenic activity and describes in detail the efficacy of anti-HBV and anti-HCV therapies in terms of HCC prevention. Although these treatments significantly reduce the risk for HCC in patients with chronic viral hepatitis, this risk is not eliminated. Therefore, we evaluate potential strategies to improve these outcomes further and address some of the remaining controversies.

Allaire, M, W El Hajj, S Brichler, K Diallo, D Fanica, L Blaise, G Nkontchou, V Grando, F Arbadi, P Nahon, M Ziol, JC Nault and N Ganne-Carrié (2021). "**Prior surveillance and antiviral treatment improve the prognosis of HCC developed in HBV patients in the West.**" Clin Res Hepatol Gastroenterol **45**(1): 101436.

BACKGROUND: In Western countries, hepatocellular carcinoma (HCC) in hepatitis B (HBV) patients without cirrhosis was poorly studied. The aim was to describe the characteristics and outcome of HBV-related HCC according to fibrosis stage. METHOD: All patients with chronic HBV infection and HCC discussed in a multidisciplinary tumor board between 2007 and 2017 were retrospectively included. RESULTS: A total of 152 out of 2,038 HCC patients had underlying HBV infection. HBV viral load>2000IU/ml, positive HBeAg and Hepatitis D coinfection were observed in 41%, 13% and 13% of cases, respectively. HCC was uninodular in 53%, associated with portal thrombosis in 16% and/or metastasis in 9% of cases. 130 patients (86%) had cirrhosis. No difference regarding HCC risk factors and viral characteristics was

observed according to fibrosis stage. 5-year survival was 48%(47% on cirrhosis versus 57% without cirrhosis, P=0.26). At HCC diagnosis, 47% and 32% of cirrhotic and non-cirrhotic patients received an antiviral treatment (AVT), which was associated with less aggressive tumor and better survival (P=0.005). In cirrhosis, screening was associated with a lower tumor burden and patients were more amenable to curative treatment with better outcome (P<0.001). CONCLUSION: HBV represents 8% of HCC etiologies without differences of viral characteristics according to fibrosis stage. AVT and surveillance were associated with less aggressive tumors, better access to curative treatment and outcome.

Campbell, C, T Wang, AL McNaughton, E Barnes and PC Matthews (2021). "**Risk factors for the development of hepatocellular carcinoma (HCC) in chronic hepatitis B virus (HBV) infection: a systematic review and meta-analysis**." J Viral Hepat **28**(3): 493-507.

Hepatocellular carcinoma (HCC) is one of the leading contributors to cancer mortality worldwide and is a leading cause of death in individuals with chronic hepatitis B virus (HBV) infection. It is uncertain how the presence of other metabolic factors and comorbidities influences HCC risk in HBV. Therefore, we performed a systematic literature review and meta-analysis to seek evidence for significant associations. MEDLINE, EMBASE and Web of Science databases were searched from 1 January 2000 to 24 June 2020 for studies investigating associations of metabolic factors and comorbidities with HCC risk in individuals with chronic HBV infection, written in English. We extracted data for meta-analysis and generated pooled effect estimates from a fixed-effects model. Pooled estimates from a random-effects model were also generated if significant heterogeneity was present. We identified 40 observational studies reporting on associations of diabetes mellitus (DM), hypertension, dyslipidaemia and obesity with HCC risk. Only DM had a sufficient number of studies for meta-analysis. DM was associated with >25% increase in hazards of HCC (fixed-effects hazards ratio [HR] 1.26, 95% confidence interval (CI) 1.20-1.32, random-effects HR 1.36, 95% CI 1.23-1.49). This association was attenuated towards the null in a sensitivity analysis restricted to studies adjusted for metformin use. In conclusion, in adults with chronic HBV infection, DM is a significant risk factor for HCC, but further investigation of the influence of antidiabetic drug use and glycaemic control on this association is needed. Enhanced screening of individuals with HBV and diabetes may be warranted.

Datfar, T, M Doulberis, A Papaefthymiou, IN Hines and G Manzini (2021). "**Viral Hepatitis and Hepatocellular Carcinoma: State of the Art**." Pathogens **10**(11).

Viral hepatitis is one of the main causes leading to hepatocellular carcinoma (HCC). The continued rise in incidence of HCC suggests additional factors following infection may be involved. This review examines recent studies investigating the molecular mechanisms of chronic hepatitis and its association with hepatocarcinogenesis. Hepatitis B virus patients with genotype C display an aggressive disease course leading to HCC more than other genotypes. Furthermore, hepatitis B excretory antigen (HBeAg) seems to be a more sensitive predictive tumor marker exhibiting a six-fold higher relative risk in patients with positive HBsAg and HBeAg than those with HBsAg only. Single or combined mutations of viral genome can predict HCC development in up to 80% of patients. Several mutations in HBx-gene are related with higher HCC incidence. Overexpression of the core protein in HCV leads to hepatocellular lipid accumulation associated with oncogenesis. Reduced number and decreased functionality of natural killer cells in chronic HCV individuals dysregulate their surveillance function in tumor and viral cells resulting in HCC. Furthermore, high T-cell immunoglobulin and mucin 3 levels supress CD8+ T-cells, which lead to immunological dysregulation. Hepatitis D promotes HCC development indirectly via modifications to innate immunity, epigenetic alterations and production of reactive oxygen species with the LHDAg being the most highly associated with HCC development. Summarizing the results, HBV and HCV infection represent the most associated forms of viral hepatitis causing HCC. Further studies are warranted to further

improve the prediction of high-risk patients and development of targeted therapeutics preventing the transition from hepatic inflammation-fibrosis to cancer.

Del Poggio, P, M Mazzoleni, S Lazzaroni and A D'Alessio (2021). "**Surveillance for hepatocellular carcinoma at the community level: Easier said than done**." World Journal of Gastroenterology **27**(37): 6180-6190. (<Go to ISI>://WOS:000710560200002)

Surveillance for hepatocellular carcinoma (HCC) in high-risk patients with semiannual ultrasound examinations is advocated by all international guidelines. However, as long as the identification of the population to be screened and the surveillance programs are not well implemented, the real-life impact of HCC surveillance in reducing mortality for HCC cannot be known. We propose a new approach that promotes the identification of cirrhotic patients by primary care physicians (PCPs) and referral of patients to the hepatologist for surveillance. Surveillance should be incorporated, when feasible, in a hub and spoke model of comprehensive hepatology care. Training PCPs to identify cirrhotic patients and performing surveillance in a subspecialist setting are equally important to improve the effectiveness of real-life surveillance and to decrease HCC mortality over time.

de Mattos Â, Z, JD Debes, A Boonstra, JD Yang, DC Balderramo, GDP Sartori and AA de Mattos (2021). "**Current impact of viral hepatitis on liver cancer development: The challenge remains**." World J Gastroenterol **27**(24): 3556-3567.

Chronic infections due to hepatitis B and hepatitis C viruses are responsible for most cases of hepatocellular carcinoma (HCC) worldwide, and this association is likely to remain during the next decade. Moreover, viral hepatitis-related HCC imposes an important burden on public health in terms of disability-adjusted life years. In order to reduce such a burden, some major challenges must be faced. Universal vaccination against hepatitis B virus, especially in the neonatal period, is probably the most relevant primary preventive measure against the development of HCC. Moreover, considering the large adult population already infected with hepatitis B and C viruses, it is also imperative to identify these individuals to ensure their access to treatment. Both hepatitis B and C currently have highly effective therapies, which are able to diminish the risk of development of liver cancer. Finally, it is essential for individuals at high-risk of HCC to be included in surveillance programs, so that tumors are detected at an early stage. Patients with hepatitis B or C and advanced liver fibrosis or cirrhosis benefit from being followed in a surveillance program. As hepatitis B virus is oncogenic and capable of leading to liver cancer even in individuals with early stages of liver fibrosis, other high-risk groups of patients with hepatitis B are also candidates for surveillance. Considerable effort is required concerning these strategies in order to decrease the incidence and the mortality of viral hepatitis-related HCC.

Güzelbulut, F, P Gökçen, G Can, G Adalı, AG Değirmenci Saltürk, E Aslan, K Özdil and HL Doğanay (2021). "**Comparison of the Efficacy of Entecavir and Tenofovir in Reducing Hepatocellular Carcinoma Risk in Chronic Hepatitis B Patients: A Real-Life Study in Turkey**." Turk J Gastroenterol **32**(4): 412-421.

BACKGROUND: It is controversial whether entecavir or tenofovir differs in reducing hepatocellular carcinoma (HCC) risk. We aimed to compare the efficacy of entecavir and tenofovir in reducing HCC risk in chronic hepatitis B (CHB) patients. METHODS: This retrospective study included 607 nucleos(t)ide naive CHB patients who had received entecavir or tenofovir. Patients who developed HCC during the first 12 months of therapy were excluded. Cumulative HCC incidences at years 2, 3, 4, 5 and 10 were compared between entecavir and tenofovir groups. Factors associated with HCC were determined by univariate and multivariate analyses. RESULTS: Nineteen (3.1%) patients developed HCC, 12 (4.8%) in entecavir group and 7 (1.9%) in tenofovir group (P = .045). In the entire cohort, cumulative HCC incidences at years 2, 3, 4, 5 and 10 were 1.8%, 2.9%, 4.4%, 5.2% and 9.9% in entecavir group, and 0.6%, 2.4%, 2.4%, 2.4% and 3.7% in tenofovir group, respectively (log-rank P = .130). In multivariate

analysis, age ≥50 years, cirrhosis, decompensated cirrhosis, high GGT and low platelet levels were associated with HCC in the entire cohort. In advanced fibrosis/cirrhosis cohort, cumulative HCC incidences at years 2, 3, 4, 5 and 10 were 4.6%, 7.1%, 8.6%, 12.1% and 15.5% in entecavir group, and 1.8%, 5.6%, 5.6%, 5.6% and 8.5% in tenofovir group, respectively (log-rank P = .267). In multivariate analysis, age ≥50 years, decompensated cirrhosis, high GGT and low platelet levels were associated with HCC in the advanced fibrosis/cirrhosis cohort. CONCLUSION: Entecavir and tenofovir are similarly effective in reducing HCC risk in CHB patients.

Huang, DQ and MH Nguyen (2021). "**Cost-effectiveness of HCC surveillance among HCV patients after sustained virological response with direct-acting antivirals**." Liver Int **41**(12): 3036-3037.

Ji, F, T Li and MH Nguyen (2021). "**Improved survival and high sustained virologic response with DAA therapy in patients with HCV-related HCC: A call for expanded use**." J Gastroenterol Hepatol **36**(6): 1721-1722.

Kamal, H, R Fornes, J Simin, P Stal, AS Duberg, N Brusselaers and S Aleman (2021). "**Risk of hepatocellular carcinoma in hepatitis B and D virus co-infected patients: A systematic review and meta-analysis of longitudinal studies.**" J Viral Hepat **28**(10): 1431-1442. (https://www.ncbi.nlm.nih.gov/pubmed/34291520)

Hepatitis D virus (HDV) infection causes a severe chronic viral hepatitis with accelerated development of liver cirrhosis and decompensation, but whether it further increases the risk of hepatocellular carcinoma (HCC) is unclear. We performed a comprehensive systematic review of the published literature and meta-analysis to assess the risk of HCC in HDV and hepatitis B virus (HBV) co-infected, compared to HBV mono-infected patients. The study was conducted per a priori defined protocol, including only longitudinal studies, thus excluding cross-sectional studies. Random-effects models were used to determine aggregate effect sizes (ES) with 95% confidence intervals (CI). Meta-regression was used to examine the associations among study level characteristics. Twelve cohort studies comprising a total of 6099 HBV/HDV co-infected and 57,620 chronic HBV mono-infected patients were analysed. The overall pooled ES showed that HBV/HDV co-infected patients were at 2-fold increased risk of HCC compared to HBV mono-infected patients (ES = 2.12, 95% CI 1.14-3.95, I(2) = 72%, N = 12). A six-fold significant increased risk of HCC was noted among HIV/HBV/HDV triple-infected, compared to HIV/HBV co-infected patients. The magnitude of ES did not differ significantly after adjustment for study design and quality, publication year and follow-up duration in univariable meta-regression analysis. This systematic review and meta-analysis shows that infection with HDV is associated with a 2-fold higher risk of HCC development compared to HBV mono-infection. HCC surveillance strategies taking this increased risk into account, and new treatment options against HDV, are warranted.

Kim, HN, CW Newcomb, DM Carbonari, JA Roy, J Torgersen, KN Althoff, MM Kitahata, KR Reddy, JK Lim, MJ Silverberg, AM Mayor, MA Horberg, ER Cachay, GD Kirk, J Sun, M Hull, MJ Gill, TR Sterling, JR Kostman, MG Peters, RD Moore, MB Klein and V Lo Re, 3rd (2021). "**Risk of HCC With Hepatitis B Viremia Among HIV/HBV-Coinfected Persons in North America.**" Hepatology **74**(3): 1190-1202.

BACKGROUND AND AIMS: Chronic HBV is the predominant cause of HCC worldwide. Although HBV coinfection is common in HIV, the determinants of HCC in HIV/HBV coinfection are poorly characterized. We examined the predictors of HCC in a multicohort study of individuals coinfected with HIV/HBV. APPROACH AND RESULTS: We included persons coinfected with HIV/HBV within 22 cohorts of the North American AIDS Cohort Collaboration on Research and Design (1995-2016). First occurrence of HCC was verified by medical record review and/or cancer registry. We used multivariable Cox regression to determine adjusted HRs (aHRs [95% CIs]) of factors assessed at cohort entry (age, sex, race, body mass index), ever during

observation (heavy alcohol use, HCV), or time-updated (HIV RNA, CD4+ percentage, diabetes mellitus, HBV DNA). Among 8,354 individuals coinfected with HIV/HBV (median age, 43 years; 93% male; 52.4% non-White), 115 HCC cases were diagnosed over 65,392 person-years (incidence rate, 1.8 [95% CI, 1.5-2.1] events/1,000 person-years). Risk factors for HCC included age 40-49 years (aHR, 1.97 [1.22-3.17]), age ≥50 years (aHR, 2.55 [1.49-4.35]), HCV coinfection (aHR, 1.61 [1.07-2.40]), and heavy alcohol use (aHR, 1.52 [1.04-2.23]), while time-updated HIV RNA >500 copies/mL (aHR, 0.90 [0.56-1.43]) and time-updated CD4+ percentage <14% (aHR, 1.03 [0.56-1.90]) were not. The risk of HCC was increased with time-updated HBV DNA >200 IU/mL (aHR, 2.22 [1.42-3.47]) and was higher with each 1.0 log(10) IU/mL increase in time-updated HBV DNA (aHR, 1.18 [1.05-1.34]). HBV suppression with HBV-active antiretroviral therapy (ART) for ≥1 year significantly reduced HCC risk (aHR, 0.42 [0.24-0.73]). CONCLUSION: Individuals coinfected with HIV/HBV on ART with detectable HBV viremia remain at risk for HCC. To gain maximal benefit from ART for HCC prevention, sustained HBV suppression is necessary.

Lebossé, F and F Zoulim (2021). "**[Hepatitis B vaccine and liver cancer]**." Bull Cancer **108**(1): 90-101.

Hepatitis B Virus (HBV) chronic infection contributes to a high risk of hepatocellular cancer (HCC) development. HBV is a strong cancer inducer, due to natural history of infection, virological characteristics and viral DNA integrations events in host genome. Prolonged infection and high viral loads, particularly frequent in patients infected in childhood, are risk factors of HCC development for patients with HBV chronic infection. A HBV vaccine, based on immunization against the surface protein HBs, showed a strong efficacy to prevent chronic HBV infection. The development of universal neonatal vaccination programmes contributed to the decrease of HBV chronic infection incidence in children of high endemic areas. Although HBs antibodies levels diminished years after vaccination, HBV neonatal vaccination programmes led to a lower incidence of chronic HBV infection among young adults. The decrease of HBV chronic infection incidence was associated to a reduction of HCC incidence in children and young adults from areas with a high prevalence of HBV infection.

Manne, V, J Ryan, J Wong, G Vengayil, SA Basit and RG Gish (2021). "**Hepatitis C Vaccination: Where We Are and Where We Need to Be**." Pathogens **10**(12).

The hepatitis C virus (HCV) is a common cause of chronic liver disease and liver cancer worldwide. Despite advances in curative therapies for HCV, the incidence of new infections is not decreasing at the expected rate to hit the World Health Organization (WHO) target for the elimination of HCV by 2030. In fact, there are still more new cases of infection in the United States and worldwide than are being cured. The reasons for the rise in new cases include poor access to care and the opioid epidemic. The clinical burden of HCV requires a multimodal approach to eradicating the infection. Vaccination would be an excellent tool to prevent incidence of new infections; however, the genetic diversity of HCV and its ability to generate quasispecies within an infected host make creating a broadly reactive vaccine difficult. Multiple vaccine candidates have been identified, but to date, there has not been a target that has led to a broadly reactive vaccine, though several of the candidates are promising. Additionally, the virus is very difficult to culture and testing candidates in humans or chimpanzees is ethically challenging. Despite the multiple barriers to creating a vaccine, vaccination still represents an important tool in the fight against HCV.

McMahon, BJ, LD Nolen, M Snowball, C Homan, S Negus, E Roik, PR Spradling and D Bruden (2021). "**HBV Genotype: A Significant Risk Factor in Determining Which Patients With Chronic HBV Infection Should Undergo Surveillance for HCC: The Hepatitis B Alaska Study**." Hepatology **74**(6): 2965-2973.

BACKGROUND AND AIMS: Information is limited regarding HBV genotype and the outcome of chronic HBV (CHB) infection. We examined the effect of HBV genotype on HCC occurrence in Alaska Native (AN) persons with CHB, where five HBV genotypes are found: A2, B6, C2, D, and

F1. APPROACH AND RESULTS: We calculated HCC incidence per 1,000 person-years of follow-up to determine which groups by age, sex, and genotype met current American Association for the Study of Liver Diseases (AASLD) HCC surveillance criteria. We used Poisson regression to compare HCC risk by genotype, age, sex, and Alaska region. Incidence of HCC was calculated using the sex-specific AASLD cutoff recommended for the Asian population of 50 years for women and 40 years for men. HCC screening was conducted semiannually using alpha-fetoprotein levels and abdominal ultrasound. Among 1,185 AN persons, median follow-up was 35.1 years; 667 (63%) were male. The HBV genotype distribution was 49% D, 18% F, 13% A, 6% C, 3% B, 0.1% H, and 12% undetermined. Sixty-three cases of HCC occurred. HCC incidence for genotype F was 5.73 per 1,000 person-years of follow-up, followed by 4.77 for C, 1.28 for A, 0.47 for D, and 0.00 for B. The HCC risk was higher for genotypes F (relative rate [RR], 12.7; 95% CI, 6.1-26.4), C (RR, 10.6; 95% CI, 4.3-26.0), and A (RR, 2.9; 95% CI, 1.0-8.0) compared to genotypes B and D. Among men < 40 years of age and women < 50 years of age, genotype F had the highest incidence (4.79/1,000 person-years). CONCLUSIONS: HBV genotype was strongly associated with HCC. HBV genotype should be considered in risk factor stratification.

Nahon, P, R Layese, C Cagnot, T Asselah, D Guyader, S Pol, GP Pageaux, V De Lédinghen, D Ouzan, F Zoulim and E Audureau (2021). "**HCV Eradication in Primary or Secondary Prevention Optimizes Hepatocellular Carcinoma Curative Management**." Cancer Prev Res (Phila) **14**(5): 581-592.

To assess the impact of HCV eradication on the outcomes of cirrhotic patients treated curatively for incidental hepatocellular carcinoma (HCC) detected during surveillance program. Data were collected on 1,323 French patients with compensated biopsy-proven HCV cirrhosis recruited in 35 centers (ANRS CO12 CirVir cohort). Sustained virologic responses (SVR) and the occurrence of HCC were recorded prospectively. During a median follow-up of 68.3 months, 218 patients developed HCC, 126 of whom underwent a curative procedure as first-line therapy (ablation = 95, resection = 31). The HCC BCLC stage was 0/A in 97.5% of patients; 74 (58.7%) never achieved SVR. During a median follow-up of 26.0 months after HCC treatment, 59 (46.8%) experienced HCC recurrence. SVR was not associated with a recurrence, whether considering final SVR status [HR = 0.77; 95% confidence interval (95% CI), 0.43-1.39; P = 0.39] or its time to achievement (prior to/after HCC occurrence; global P = 0.28). During the same timeframe, 46 patients with HCC (36.5%) died (liver failure: 41.9%, HCC progression: 37.2%, extrahepatic causes: 20.9%). Under multivariate analysis, SVR was associated with improved survival [HR = 0.21; 95% CI, 0.08-0.52; P = 0.001]. Survival benefit was explained by a lower incidence of liver decompensation and higher rates of sequential HCC re-treatment. Direct antiviral intake was not associated with a higher risk of HCC recurrence, but with improved survival (HR = 0.23; 95% CI, 0.06-0.83; P = 0.024). HCV eradication in primary or secondary prevention optimizes HCC management through preservation of liver function and improves survival, whatever the regimen. PREVENTION RELEVANCE: Liver failure is a competing risk of death in patients with HCC eligible for curative procedures. HCV eradication does not decrease risk of HCC recurrence in the first two years, but enables sequential curative HCC treatments through preservation of liver function. Direct-acting antiviral agent intake is not associated with HCC recurrence and improves survival.

Pham, C and MK Sin (2021). "**Use of Electronic Health Records at Federally Qualified Health Centers: a Potent Tool to Increase Viral Hepatitis Screening and Address the Climbing Incidence of Liver Cancer**." J Cancer Educ **36**(5): 1093-1097.

Viral hepatitis B and C are among the leading causes of acute and chronic liver disease in the USA. The nature of chronic liver disease is often asymptomatic. This is problematic because the majority of individuals living with chronic hepatitis B and chronic hepatitis C do not know that they are infected and can communicate the disease to others. Furthermore, early disease recognition and treatment have been shown to improve long-term outcomes and decrease healthcare cost. These diseases affect vulnerable populations disproportionately. Asian

Americans and Pacific Islanders are more likely than the general US population to have CHB, and the baby boomer generation is more likely than any other age group to have CHC. Federally Qualified Health Centers play a vital role in providing comprehensive primary care to medically underserved populations. Utilization of electronic health records reminders in Federally Qualified Health Centers results in increased screening, reduced provider screening bias and improved opportunity for management of patients living with chronic viral hepatitis. Electronic health records technology is a potent tool kit to aggressively screen, treat, and prevent viral hepatitis, ultimately, leading to decreased incidence of liver cancer.

Pol, S (2021). "**Similar 5-year HCC occurrence in Tenofovir- and Entecavir-treated HBV chronic infection in the French AFEF/ANRS CO22 Hepather cohort**." Aliment Pharmacol Ther **53**(5): 616-629.

BACKGROUND: Chronic hepatitis B virus (HBV) infection results in a high risk of cirrhosis and its complications, cirrhosis decompensation (DC), hepatocellular carcinoma (HCC), liver transplantation (LT), death or any of these outcomes (composite endpoint [CE]). Nucleos(t)ide analogues (NUCs) such as tenofovir or entecavir are associated with a reduction in these complications. AIM: To compare the impact of tenofovir and entecavir on these outcomes in patients treated for HBV infection and included in the prospective Hepather cohort. METHODS: All patients with HBV infection who had received tenofovir or entecavir for more than 6 months at or after entry in the ANRS CO22 cohort were selected. Patients with HDV and HCV co-infection or prior liver event were excluded. Incidence rates of events were compared using inverse probability of treatment weighting (IPW). RESULTS: The cohort included 1800 patients (986 tenofovir and 814 entecavir). Median follow-up was 4.2 years. The incidences of HCC, DC, LT, ACD, LRD and CE were not different between tenofovir- (1.8 (0.9; 3.2), 0.6 (0.2; 1.6), 0.2 (0.0; 0.8), 1.7 (0.8; 3.0), 0.8 (0.2, 1.8) and 4.1 (3.0; 5.4) per 1000 person-years) and entecavir-treated patients (1.6 (0.7; 3.0), 0.7 (0.2; 1.8), 0.2 (0.0; 1.0), 3.0 (1.7, 4.8), 0.5 (0.1; 1.5) and 5.0 (3.3; 7.2)) per 1000 person-years, respectively. CONCLUSION: The risk of liver-related events or death was not different between tenofovir- and entecavir-treated patients in this large prospective cohort of predominantly non-cirrhotic French patients. TRIAL REGISTRATION NUMBER: NCT019553458.

Qi, WQ, Q Zhang, X Wang, Y Xu, P Zhao, HH Guo, CY Zhou, Y Sun, L Liu and JB Wang (2021). "**Long-term clinical benefit of Peg-IFNα and NAs sequential anti-viral therapy on HBV related HCC**." Neoplasma **68**(1): 200-207.

Analysis of the value of long-term antiviral therapy using sequential Peg-IFN therapy and nucleos(t)ide analogues (NAs) improves the prognosis of HBV-related HCC. HBV-related HCC patients were classified into sequential therapy with Peg-IFNα-2a and NAs, and NAs therapy alone. All patients were followed up for 5 years. The survival rate, HCC recurrence rate, Child-Pugh score, and side effects of drugs were evaluated. Firstly, the early and late cumulative survival rate was higher in patients receiving antiviral therapy compared with the control patients ($p<0.05$). Patients receiving sequential therapy with Peg-IFNα-2a and NAs showed a higher late cumulative survival rate and significantly reduced early and late recurrence rate, compared to those in the NA-alone group ($p<0.05$). Single NAs therapy only reduced the late recurrence rate in HCC-patients. Secondly, NAs therapy significantly increased the Child-Pugh score after five years of therapy (five-year therapy 7.03±1.50 vs. initial score 6.63±0.85; $p<0.05$), whereas the sequential therapy with Peg-IFNα-2a and NAs did not greatly alter the Child-Pugh score (6.88±1.26; $p>0.05$). Compared to the control patients, patients receiving antiviral therapy (NAs alone or sequential therapy with Peg-IFNα-2a and NAs) exhibited a significantly decreased Child-Pugh score ($p<0.05$). Compared to NAs alone, sequential therapy with Peg-IFNα-2a and NAs provided a more efficient strategy for improving both the five-year survival rate and the two-year or five-year recurrence rate in patients.

Rinaldi, B, V Rosato, R Galiero, E Vetrano, M Fasano and L Rinaldi (2021). "**Editorial - Direct-acting antivirals therapy in HCV patients with HCC: lights and shadow**." Eur Rev Med Pharmacol Sci **25**(24): 7622-7625.

Vo Quang, E, Y Shimakawa and P Nahon (2021). "**Epidemiological projections of viral-induced hepatocellular carcinoma in the perspective of WHO global hepatitis elimination**." Liver Int **41**(5): 915-927.

> Hepatitis B is an eminent risk factor for hepatocellular carcinoma (HCC) in Southeast Asia and sub-Saharan Africa, whereas hepatitis C is a key risk factor for HCC in Western Europe and North America. Increased awareness of the global burden of viral hepatitis resulted, in May 2016, in the adoption of the first global health sector strategy on viral hepatitis by the World Health Assembly, which calls for the elimination of viral hepatitis as a public health threat by 2030. Although the incidence of liver cancer resulting from viral infections has increased since the 1990s, the implementation of public health interventions, such as hepatitis B vaccination and antiviral therapies might have reduced the global burdens of HCC. Hepatitis B immunization in infancy has been associated with a reduction in the risk of infant fulminant hepatitis, chronic liver disease, and HCC in Taiwan. Achieving viral hepatitis elimination by 2030 can be accelerated by improving the access to HCC screening programs. HCC surveillance programs in developed countries must be refined to increase an access to personalized surveillance program, whereas the limited access to surveillance and treatment of HCC in developing countries remains a significant public health issue.

*2022*

D'Ambrosio, R and P Lampertico (2022). "**Is it time to refine HCC surveillance strategies in HCV cured patients?**" Hepatology **76**(1): 9-11.

Boccalini, S, B Bonito, B Zanella, D Liedl, P Bonanni and A Bechini (2022). "**The First 30 Years of the Universal Hepatitis-B Vaccination-Program in Italy: A Health Strategy with a Relevant and Favorable Economic-Profile**." Int J Environ Res Public Health **19**(23).

> In 1991, Italy was one of the first countries worldwide to introduce a universal hepatitis-B vaccination for children. Since then, epidemiological data have clearly demonstrated the huge clinical benefits of the vaccination. The aim of this study was to update the favorable economic impact of the hepatitis B virus (HBV) vaccination, 30 years after its implementation. A mathematical model was developed to simulate the clinical/economic impact of the universal HBV-vaccination program versus a hypothetical no-vaccination scenario as a posteriori analysis. We assessed the vaccination benefits over a 30-year-immunization-period (1991−2020), and the following period, 2021−2070. Our data showed a big drop in HBV-related diseases (−82% in infections, chronic disease, and hepatocellular-carcinoma cases), and related costs (−67% in the immunization period and −85% in 2021−2070), attributable to vaccination. The return on investment (ROI) and the benefit-to-cost (BCR) ratios are >1 for the first thirty-year-immunization-period, and are predicted to almost triplicate the economic savings in the period 2021−2070, both for the National Health Service (NHS) and from societal perspectives. Our model confirmed that the implementation of universal HBV-vaccination in Italy during the first 30 years continues to be a cost-saving strategy, and more advantageous effects will be further achieved in the future. The HBV-vaccination strategy greatly expresses a huge impact in both the short- and long-term, and from the clinical and economic point-of-views.

Cao, M, J Fan, L Lu, C Fan, Y Wang, T Chen, S Zhang, Y Yu, C Xia, J Lu, K Chen, H Yao, W Chen and C Qu (2022). "**Long term outcome of prevention of liver cancer by hepatitis B vaccine: Results from an RCT with 37 years.**" Cancer Lett **536**: 215652. (https://www.ncbi.nlm.nih.gov/pubmed/35318115)

We aimed to evaluate the long-term efficacy of the hepatitis B vaccine in China. In an initial efficacy study, participants were collected from a cluster-randomized clinical trial conducted in 1983-90 in Qidong. All the participants in the vaccination group were vaccinated at birth, 1 and 6 months of age, and no intervention was implemented to the control group. In this 37-year extended follow-up study, the Poisson regression method was employed to derive rates per 10(5) person-years. The frailty Cox proportional hazard regression models obtained the hazard ratio (HR). Cumulative incidence/mortality rates were calculated and compared with log-rank tests. 41,136 in the vaccination and 41,730 in the control group were recorded. The incidence rate of liver cancer was significantly lower in the vaccinated group than in the control group [HR, 0.28; 95% confidence interval (CI) 0.11-0.70, P = 0.007]. The vaccine offers 72% (95% CI, 30-89) protection to prevent the occurrence of liver cancer. There is 70% (95% CI, 23-88) protective efficacy against liver cancer deaths and 64% (95% CI, 27-82) benefits in the prevention of deaths associated with liver diseases. Hepatitis B vaccine given at birth shows excellent protective effects in preventing the development of liver cancer and reducing mortality from liver cancer and liver diseases.

Dietz, CA and H Wedemeyer (2022). "**[Vaccination against hepatitis B as prevention for hepatocellular carcinoma]**." Onkologe (Berl) **28**(1): 15-22.

BACKGROUND: Chronic infection with the hepatitis B virus (HBV) is an important risk factor for the development of hepatocellular carcinoma (HCC). Even though treatment options for HCC are constantly improving, preventive measures must not be neglected. CONCLUSION: The vaccination against hepatitis B has proven effective in preventing infection with HBV. As shown more than 20 years ago in Taiwan, vaccination programs lower not only the prevalence of HBsAg carriers but also decrease the incidence of HCC. By achieving immunity against HBV, the infection with hepatitis D virus can also be prevented. This is important in the light of HCC prevention as HBV/HDV coinfection is known to drastically increase the risk of HCC. New approaches aim for the development of therapeutic HBV vaccines ideally curing chronic infections. Beside the prevention of infections, it is pivotal to detect existing infections. This helps to minimize the HCC risk by initiating treatment in those who need it.

Duberg, AS, C Lybeck, A Fält, S Montgomery and S Aleman (2022). "**Chronic hepatitis B virus infection and the risk of hepatocellular carcinoma by age and country of origin in people living in Sweden: A national register study.**" Hepatol Commun **6**(9): 2418-2430.

Chronic hepatitis B virus (HBV) infection is a major risk factor for hepatocellular carcinoma (HCC), and surveillance is recommended for patients without cirrhosis when risk exceeds an incidence rate (IR) of 0.2%. Populations in Asia and sub-Saharan Africa have been associated with HCC at younger ages, but the risk after immigration to Western countries should be investigated. The aim of this study was to study HCC by age and country of origin in people with chronic HBV infection in Sweden. Through national registers, residents with chronic HBV diagnosis (1990-2015) were identified with information on country of origin, immigration/emigration, death, coinfections, antiviral therapy, and HCC. Observation time started at HBV diagnosis, and IR and hazard ratios for HCC were calculated by sex, age, and region of origin. Among 16,410 individuals (47% women), the origin and observation time (person years) were as follows: Western Europe, 2316 (25,415); Eastern Europe, 2349 (26,237); Middle East/North Africa, 4402 (47,320); sub-Saharan Africa, 3677 (30,565); Asia, 3537 (35,358); and other, 129 (1277). There were 232 individuals with HCC (82% in men). The IR increased with age and exceeded 0.2% for Asian men from age group 40-49 years (IR, 0.63; 95% confidence interval, 0.39-1.00), for men of other origins from age group 50-59 years, and for women aged ≥60 years originating from Eastern Europe, Asia, and Middle East/North

Africa. After exclusion of patients with cirrhosis or HBV treatment, the IR still exceeded 0.2% in Asian men aged 40-49 years. This study demonstrates that HBV-infected men of Asian origin should be recommended HCC surveillance at younger ages, but there is a need for further studies of HCC incidence in African-born men without cirrhosis living in the Western world.

Flores, JE, AJ Thompson, M Ryan and J Howell (2022). "**The Global Impact of Hepatitis B Vaccination on Hepatocellular Carcinoma**." Vaccines (Basel) **10**(5).

Over 1.5 million preventable new hepatitis B infections continue to occur each year and there are an estimated 296 million people living with chronic hepatitis B infection worldwide, resulting in more than 820,000 deaths annually due to liver cirrhosis and hepatocellular carcinoma (HCC). Hepatitis B vaccination remains the cornerstone of public health policy to prevent HCC and a vital component of the global hepatitis B elimination response. The WHO has set a 90% vaccination target to achieve hepatitis B elimination by 2030; however, there is wide variability in reported birth dose coverage, with global coverage at only 42%. In this review, we outline the global trends in hepatitis B vaccination coverage and the impact of hepatitis B vaccination on HCC incidence and discuss the challenges and enabling factors for achieving WHO 2030 hepatitis B vaccination coverage targets.

Giri, S, H Darak and S Kasturi (2022). "**Benefit of Antiviral Therapy for HBV-Related HCC with Undetectable HBV DNA Is Still Dubious**." Dig Dis Sci **67**(10): 4962-4964.

Huang, R, J Liu, J Wang, J Li and C Wu (2022). "**Letter to the Editor: Is HBV genotype strongly associated with HCC risk in patients with chronic hepatitis B?**" Hepatology **75**(1): 233-234.

Jin, B, S Du and H Yang (2022). "**HBsAg seroclearance reduces the risk of late recurrence in HBV-related HCC**." J Hepatol **77**(5): 1469-1470.

Mueller, PP, Q Chen, T Ayer, GS Nemutlu, A Hajjar, ED Bethea, MLB Peters, BP Lee, NZ Janjua, F Kanwal and J Chhatwal (2022). "**Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication**." J Hepatol 77(1): 55-62. (https://www.ncbi.nlm.nih.gov/pubmed/35157959)

BACKGROUND & AIMS: Successful treatment of chronic hepatitis C with oral direct-acting antivirals (DAAs) leads to virological cure, however, the subsequent risk of hepatocellular carcinoma (HCC) persists. Our objective was to evaluate the cost-effectiveness of biannual surveillance for HCC in patients cured of hepatitis C and the optimal age to stop surveillance. METHODS: We developed a microsimulation model of the natural history of HCC in individuals with hepatitis C and advanced fibrosis or cirrhosis who achieved virological cure with oral DAAs. We used published data on HCC incidence, tumor progression, real-world HCC surveillance adherence, and costs and utilities of different health states. We compared biannual HCC surveillance using ultrasound and alpha-fetoprotein for varying durations of surveillance (from 5 years to lifetime) vs. no surveillance. RESULTS: In virologically cured patients with cirrhosis, the incremental cost-effectiveness ratio (ICER) of biannual surveillance remained below $150,000 per additional quality-adjusted life year (QALY) (range: $79,500-$94,800) when surveillance was stopped at age 70, irrespective of the starting age (40-65). Compared with no surveillance, surveillance detected 130 additional HCCs in 'very early'/early stage and yielded 51 additional QALYs per 1,000 patients with cirrhosis. In virologically cured patients with advanced fibrosis, the ICER of biannual surveillance remained below $150,000/QALY (range: $124,600-$129,800) when surveillance was stopped at age 60, irrespective of the starting age (40-50). Compared with no surveillance, surveillance detected 24 additional HCCs in 'very early'/early stage and yielded 12 additional QALYs per 1,000 patients with advanced fibrosis. CONCLUSION: Biannual surveillance for HCC in patients cured of hepatitis C is cost-effective until the age of 70 for patients with cirrhosis, and until the age

of 60 for patients with stable advanced fibrosis. LAY SUMMARY: Individuals who are cured of hepatitis C using oral antiviral drugs remain at risk of developing liver cancer. The value of lifelong screening for liver cancer in these individuals is not known. By simulating the life course of hepatitis C cured individuals, we found that ultrasound-based biannual screening for liver cancer is cost-effective up to age 70 in those with cirrhosis and up to age 60 in those with stable advanced fibrosis.

Pageaux, GP, CL Nzinga, N Ganne, D Samuel, C Dorival, F Zoulim, C Cagnot, T Decaens, D Thabut, T Asselah, P Mathurin, F Habersetzer, JP Bronowicki, D Guyader, I Rosa, V Leroy, O Chazouilleres, V de Ledinghen, M Bourliere, X Causse, P Cales, S Metivier, V Loustaud-Ratti, G Riachi, L Alric, M Gelu-Simeon, A Minello, J Gournay, C Geist, A Tran, A Abergel, I Portal, L d'Alteroche, F Raffi, H Fontaine, F Carrat and S Pol (2022). "**Clinical outcomes after treatment with direct antiviral agents: beyond the virological response in patients with previous HCV-related decompensated cirrhosis.**" BMC Infect Dis **22**(1): 94.

BACKGROUND: In HCV-infected patients with advanced liver disease, the direct antiviral agents-associated clinical benefits remain debated. We compared the clinical outcome of patients with a previous history of decompensated cirrhosis following treatment or not with direct antiviral agents from the French ANRS CO22 HEPATHER cohort. METHODS: We identified HCV patients who had experienced an episode of decompensated cirrhosis. Study outcomes were all-cause mortality, liver-related or non-liver-related deaths, hepatocellular carcinoma, liver transplantation. Secondary study outcomes were sustained virological response and its clinical benefits. RESULTS: 559 patients met the identification criteria, of which 483 received direct antiviral agents and 76 remained untreated after inclusion in the cohort. The median follow-up time was 39.7 (IQR: 22.7-51) months. After adjustment for multivariate analysis, exposure to direct antiviral agents was associated with a decrease in all-cause mortality (HR 0.45, 95% CI 0.24-0.84, p = 0.01) and non-liver-related death (HR 0.26, 95% CI 0.08-0.82, p = 0.02), and was not associated with liver-related death, decrease in hepatocellular carcinoma and need for liver transplantation. The sustained virological response was 88%. According to adjusted multivariable analysis, sustained virological response achievement was associated with a decrease in all-cause mortality (HR 0.29, 95% CI 0.15-0.54, p < 0.0001), liver-related mortality (HR 0.40, 95% CI 0.17-0.96, p = 0.04), non-liver-related mortality (HR 0.17, 95% CI 0.06-0.49, p = 0.001), liver transplantation (HR 0.17, 95% CI 0.05-0.54, p = 0.003), and hepatocellular carcinoma (HR 0.52, 95% CI 0.29-0.93, p = 0.03). CONCLUSION: Treatment with direct antiviral agents is associated with reduced risk for mortality. The sustained virological response was 88%. Thus, direct antiviral agents treatment should be considered for any patient with HCV-related decompensated cirrhosis. TRIAL REGISTRATION: ClinicalTrials.gov registry number: NCT01953458.

Papatheodoridi, M, TH Su, E Hadziyannis, CH Liao, A Orfanidou, HC Yang, K Zachou, CJ Liu, A Kourikou, N Gatselis, S Manolakopoulos, G Dalekos, JH Kao, S Hadziyannis and GV Papatheodoridis (2022). "**Hepatocellular carcinoma after treatment cessation in non-cirrhotic HBeAg-negative chronic hepatitis B: A multicentre cohort study.**" Liver Int **42**(3): 541-550. (https://www.ncbi.nlm.nih.gov/pubmed/34890120)

BACKGROUND AND AIMS: Scarce data exist on the effect of nucleos(t)ide analogue (NA) discontinuation on hepatocellular carcinoma (HCC) risk in HBeAg-negative chronic hepatitis B (CHBe-). Therefore, we assessed whether HCC risk is increased in non-cirrhotic CHBe- patients who discontinue compared to those remaining on NAs. METHODS: This cohort study included 650 consecutive non-cirrhotic Caucasian or Asian patients with CHBe- without a history of HCC who discontinued NAs after a median of 5 or 3 years (cases, n = 325; Caucasians: 143, Asians: 182) or remained on NA therapy beyond 5 or 3 years respectively (controls, n = 325; Caucasians: 223, Asians: 102). Propensity score (PS) 1:1 matching was applied to adjust for patients' origin, age and sex. RESULTS: During a median follow-up of 44 months, HCC

developed in 7/325 cases and 9/325 controls or 7/245 PS-matched cases and 7/245 PS-matched controls with 5-year cumulative HCC incidence of 5.1% and 4.9% respectively (log-rank, P = .836). No difference in 5-year HCC risk was observed between cases and controls of Caucasian (3.0% vs 4.8%; log-rank, P = .510) or Asian origin (1.3% vs 2.2%; log-rank, P = .873). In both cases and controls, HCC incidence was independently associated with age and PAGE-B score. In cases alone, HCC development after NA discontinuation was associated only with pretreatment platelet counts and PAGE-B score, but not with any type of relapse or HBsAg loss. CONCLUSIONS: Our findings suggest that discontinuation of effective long-term NA therapy in non-cirrhotic CHBe- patients are not associated with increased HCC risk, which is not affected by post-NA relapses and/or HBsAg loss.

Papatheodoridi, M, M Tampaki, AS Lok and GV Papatheodoridis (2022). "**Risk of HBV reactivation during therapies for HCC: A systematic review**." Hepatology **75**(5): 1257-1274.

BACKGROUND AND AIMS: Treatment for HCC has evolved rapidly, but the risk of HBV reactivation to new therapies is unclear. We systematically reviewed data on HBV reactivation in patients receiving HCC therapy in relation to use of HBV antiviral prophylaxis. APPROACH AND RESULTS: A literature search was performed to identify all published studies including HBsAg-positive patients with HCC providing data on HBV reactivation. Forty-one studies with 10,223 patients, all from Asia, were included. The pooled HBV reactivation rate was 5% in patients receiving no specific HCC therapy and was higher in patients undergoing surgical resection (16%), transarterial chemoembolization (19%), or radiotherapy (14%) and intermediate in patients treated with local ablation therapy (7%) or systemic agents (7%). HBV reactivation rates were higher in those without compared to those with HBV prophylaxis (ablation, 9% versus 0%; resection, 20% versus 3%; chemoembolization, 23% versus 1%; external radiotherapy alone, 18% versus 0%; systemic therapy, 9% versus 3%). HBV-related biochemical reactivation rates varied between 6%-11% and 2% in patients receiving HCC therapies with high and intermediate HBV reactivation risk, respectively. Liver decompensation and death were rarely reported (0%-3%) and only in patients receiving HCC treatment with high HBV reactivation risk. CONCLUSIONS: HBsAg-positive patients with HCC are at high or intermediate risk of HBV reactivation depending on the type of HCC therapy. Nucleos(t)ide analogue prophylaxis reduces the risk of HBV reactivation, practically eliminates the risk of hepatitis flare, and should be administered regardless of HCC treatment.

Ramos-Rincon, JM, H Pinargote-Celorio, C de Mendoza, C Ramos-Belinchón, P Barreiro, A Treviño, O Corral and V Soriano (2022). "**Liver cancer and hepatic decompensation events in patients hospitalized with viral hepatitis in Spain**." Hepatol Int **16**(5): 1161-1169.

BACKGROUND: Chronic viral hepatitis B, C, and D are the main causes of decompensated cirrhosis and liver cancer worldwide. Newborn HBV vaccination was implemented more than 2 decades ago in most EU countries. Furthermore, potent oral antivirals have been available to treat HBV for 15 years and to cure HCV since 2014. The real-life clinical benefits of these interventions at country level have not been assessed, especially regarding major hepatic outcomes such as cirrhotic decompensation events and hepatocellular carcinoma (HCC). METHODS: Retrospective study of all hospitalizations in Spain having HBV, HCV, and HDV as diagnosis using the Spanish National Registry of Hospital Discharges. Information was retrieved from 1997 up to 2017. RESULTS: From a total of 73,939,642 hospital admissions during the study period, a diagnosis of HBV, HCV, and HDV was made in 124,915 (1.7‰), 981,985 (13.3‰), and 4850 (0.07‰) patients, respectively. The median age of patients hospitalized within each group was 53.2, 55.9, and 47.0 years, respectively. Significant increases in mean age at hospitalization occurred in all groups (0.6 years older per calendar year on average). The overall rate of hepatic decompensation events for HBV, HCV, and HDV was 12.1%, 14.1%, and 18.8%, respectively. For HCC hospitalizations, these figures were 6.7%, 8.0%, and 7.8%, respectively. Whereas, the rate of decompensation events declined in recent years for HBV,

and more recently for HCV, it continued rising up for HDV. Likewise, liver cancer rates recently plateaued for HBV and HCV, but kept growing for HDV. CONCLUSION: The rate of hepatic decompensation events and liver cancer has declined and/or plateaued in recent years for patients hospitalized with HBV and HCV infections, following the widespread use of oral antiviral therapies for these viruses. In contrast, the rate of decompensated cirrhotic events and HCC has kept rising up for patients with hepatitis delta, for which effective antiviral treatment does not exist yet.

Russo, FP, A Zanetto, E Pinto, S Battistella, B Penzo, P Burra and F Farinati (2022). "**Hepatocellular Carcinoma in Chronic Viral Hepatitis: Where Do We Stand?**" Int J Mol Sci **23**(1).

Hepatocellular carcinoma (HCC) is one of the major causes of cancer-related death. Although the burden of alcohol- and NASH-related HCC is growing, chronic viral hepatitis (HBV and HCV) remains a major cause of HCC development worldwide. The pathophysiology of viral-related HCC includes liver inflammation, oxidative stress, and deregulation of cell signaling pathways. HBV is particularly oncogenic because, contrary to HCV, integrates in the cell DNA and persists despite virological suppression by nucleotide analogues. Surveillance by six-month ultrasound is recommended in patients with cirrhosis and in "high-risk" patients with chronic HBV infection. Antiviral therapy reduces the risks of development and recurrence of HCC; however, patients with advanced chronic liver disease remain at risk of HCC despite virological suppression/cure and should therefore continue surveillance. Multiple scores have been developed in patients with chronic hepatitis B to predict the risk of HCC development and may be used to stratify individual patient's risk. In patients with HCV-related liver disease who achieve sustained virological response by direct acting antivirals, there is a strong need for markers/scores to predict long-term risk of HCC. In this review, we discuss the most recent advances regarding viral-related HCC.

Sandmann, L and M Cornberg (2022). "**HCC and HBV reactivation-A preventable condition not to be missed**." Hepatology **75**(5): 1075-1077.

Sanduzzi-Zamparelli, M, Z Mariño, S Lens, V Sapena, G Iserte, A Pla, N Granel, C Bartres, N Llarch, R Vilana, I Nuñez, A Darnell, E Belmonte, A García-Criado, A Díaz, S Muñoz-Martinez, C Ayuso, L Bianchi, C Fuster-Anglada, J Rimola, A Forner, F Torres, J Bruix, X Forns and M Reig (2022). "**Liver cancer risk after HCV cure in patients with advanced liver disease without non-characterized nodules**." J Hepatol **76**(4): 874-882.

BACKGROUND & AIMS: Recognition of non-characterized liver nodules (NCLN) prior to direct-acting antivirals (DAAs) is associated with increased hepatocellular carcinoma (HCC) risk in patients with HCV. The risk of HCC has not been defined in F3/F4 patients in whom NCLN have been ruled-out before starting DAAs and at sustained virological response (SVR). This study aimed to estimate HCC incidence in this population. METHODS: We performed a prospective study including HCV-infected patients with F3/F4 fibrosis, without a history of HCC, and who achieved SVR after DAAs. Patients were only included if they had undergone ultrasound imaging that excluded the presence of HCC/NCLN within 30 days after SVR. All patients were evaluated every 6 months until developing primary liver cancer, death or withdrawal of informed consent. HCC incidence was expressed per 100 patient-years (/100PY). Adherence to screening program was calculated every 6 months for the first 48 months. RESULTS: A total of 185 patients (63/122, F3/F4) were included. Among those with cirrhosis, 92% were Child-Pugh A and 42.7% had clinically significant portal hypertension (CSPH). Albumin-bilirubin score was 1 in 84.9% and 2 in 15.1% of patients, respectively. The median clinical and radiologic follow-up was 52.4 months and 48 months, respectively. Ten patients developed HCC: HCC incidence was 1.46/100PY (95% CI 0.79-2.71) in the whole cohort, 2.24/100PY (95% CI 1.21-4.17) in F4 only and 3.63/100PY (95% CI 1.95-6.74) in patients with CSPH. No HCC was registered in patients with F3. Median time between SVR and HCC occurrence was 28.1 months; 12 non-

primary liver cancers were also identified. CONCLUSIONS: Patients with cirrhosis without NCLN at SVR remain at risk of HCC development. The absence of HCC in patients with F3 reinforces their marginal cancer risk, but prospective studies are needed to exclude them from screening programs. LAY SUMMARY: Patients with HCV-related cirrhosis, without non-characterized liver nodules at sustained virologic response, remain at risk of hepatocellular carcinoma despite viral cure. However, the cancer risk after successful direct-acting antiviral treatment is marginal in patients with F3 fibrosis without non-characterized liver nodules. If confirmed in larger prospective studies, current screening recommendations may need to be revisited in this group of patients.

Semmler, G, EL Meyer and M Mandorfer (2022). "**Reply to: "HCC prediction post SVR: many tools yet limited generalizability!": De novo HCC risk stratification after HCV cure: All roads lead to Rome?**" J Hepatol **77**(4): 1228-1230.

Sharrock, KC, T Noori, M Axelsson, M Buti, A Diaz, O Fursa, G Hendrickx, C James, I Klavs, M Korenjak, M Maticic, A Mozalevskis, L Peters, R Rigoni, M Rosinska, K Ruutel, E Schatz, T Seyler, I Veldhuijzen and E Duffell (2022). "**Monitoring progress towards elimination of hepatitis B and C in the EU/EEA**." PLOS Glob Public Health **2**(8): e0000841.

This paper presents data on selected indicators to show progress towards elimination goals and targets for hepatitis B and hepatitis C in the 31 countries of the European Union (EU) and European Economic Area (EEA). A monitoring system was developed by the European Centre for Disease Prevention and Control, which combined newly collected data from EU/EEA countries along with relevant data from existing sources. Data for 2017 were collected from the EU/EEA countries via an online survey. All countries provided responses. In 2017, most countries reporting data had not reached prevention targets for childhood hepatitis B vaccination and for harm reduction services targeting people who inject drugs (PWID). Four of 12 countries had met the target for proportion of people living with chronic HBV diagnosed and seven of 16 met this target for hepatitis C. Data on diagnosed cases treated were lacking for hepatitis B. Of 12 countries reporting treatment data for hepatitis B, only Iceland met the target. This first collection of data across the EU/EEA highlighted major issues with data completeness and quality and in the indicators that were used, which impairs a clear overview of progress towards the elimination of hepatitis. The available data, whilst incomplete, suggest that as of 2017, the majority of the EU/EEA countries were far from meeting most of the 2020 targets, in particular those relating to harm reduction and diagnosis. It is critical to improve the data collected in order to develop more effective services for hepatitis prevention, diagnosis, and treatment that are needed in order to meet the 2030 elimination targets.

Tabrizian, P, B Saberi, ML Holzner, C Rocha, Y Kyung Jung, B Myers, SS Florman and ME Schwartz (2022). "**Outcomes of transplantation for HBV- vs. HCV-related HCC: impact of DAA HCV therapy in a national analysis of >20,000 patients**." HPB (Oxford) **24**(7): 1082-1090.

BACKGROUND: The development of direct-acting antiviral (DAA) therapy has revolutionized HCV management. We present a large national study comparing post-LT outcomes for HBV-HCC vs. HCV-HCC according to DAA era. METHODS: Data were collected from OPTN/UNOS Registry. Groups included pre-DAA (January 2003-October 2013) and post-DAA (November2013-January2019) eras. Outcomes for patients with HBV(n = 2000) vs. HCV(n = 18,964) were compared in each era. RESULTS: In the pre-DAA era, there were significant differences between HBV-versus HCV, including the percentage of Caucasian race, pre-LT and maximum AFP levels <20 ng/mL, MELD-score, complete tumor necrosis, and vascular invasion. In the post-DAA-era, differences were noted in wait time>9 months, the percentage of Caucasian race, pre-LT and AFP(max) levels<20 ng/mL, and MELD-score. In the pre-DAA-era, the 5-and-10 year survival rates were 80.5% and 71% for HBV-HCC, and 69% and

54.4% for HCV-HCC ($p < 0.001$); in the post-DAA-era, 5-year survival was 83.4% for HBV-HCC and 78.5% for HCV-HCC($p = 0.08$). Independent pre-LT predictors of lower survival included recipient and donor age>50yrs, wait-time>9months, higher MELD-score ($p < 0.001$), AFP level>20 ng/mL, and MC at diagnosis. HCV status did not predict outcome in the post-DAA-era after adjusting for tumor characteristics. CONCLUSION: After the introduction of effective DAA-HCV therapy, results of LT for HCV-HCC are significantly improved and are no longer statistically different from results in patients with HBV-HCC.

Tacke, F, H Klinker, KHW Boeker, U Merle, R Link, P Buggisch, D Hüppe, M Cornberg, C Sarrazin, H Wedemeyer, T Berg and S Mauss (2022). "**Elevated liver enzymes predict morbidity and mortality despite antiviral cure in patients with chronic hepatitis C: Data from the German Hepatitis C-Registry**." Hepatol Commun **6**(9): 2488-2495.

While direct-acting antivirals (DAAs) cure chronic hepatitis C virus (HCV) infection in almost all patients, some patients remain at risk of liver disease despite HCV cure. In order to identify risk factors indicating liver-related morbidity and death after viral cure, we included 6982 patients from the national multicenter real-world German Hepatitis C Registry with regular follow-up visits for up to 7 years after DAA therapy. Definitions for normal liver function tests (in women/men) were alanine aminotransferase (ALT; ≤35/≤50 U/L), ALT according to American Association for the Study of Liver Diseases (AASLD; ≤19/≤30 U/L), and gamma-glutamyltransferase (GGT; ≤40/≤60 U/L). In our cohort, 97.4% of patients achieved sustained virologic response (SVR). At 24 weeks after SVR (SVR24), elevated ALT occurred in 657/6982 (9.4%), elevated ALT (AASLD) in 2609/6982 (37.4%), and elevated GGT in 1777/6982 (25.5%) patients. Risk factors for increased ALT at SVR24 were obesity, alcohol, cirrhosis, elevated baseline ALT, and non-SVR. Increased GGT at SVR24 was significantly ($p < 0.05$) and independently associated with male sex (odds ratio [OR], 2.12), higher body mass index (OR, 1.04), age >50 years (OR, 1.60), liver cirrhosis (OR, 3.97), alcohol consumption (OR, 2.99), diabetes (OR, 1.63), non-SVR (OR, 8.00), and elevated GGT at baseline (OR, 17.12). In multivariate regression analysis, elevated GGT at SVR24, particularly in combination with cirrhosis, was the best predictor for hepatic decompensation, hepatocellular carcinoma development, and death, followed by elevated ALT (AASLD) and standard ALT, which predicted hepatic decompensation. Despite successful HCV therapy, elevated GGT at SVR24 and to a lesser extent ALT are predictive of the future clinical outcome and linked with liver-associated comorbidities. This may highlight the relevance of nonalcoholic fatty liver disease, diabetes mellitus, alcohol, and cirrhosis for the clinical outcome in a vulnerable population, even after HCV cure.

Wong, GL, VW Hui, TC Yip, LY Liang, X Zhang, YK Tse, JC Lai, HL Chan and VW Wong (2022). "**Universal HBV vaccination dramatically reduces the prevalence of HBV infection and incidence of hepatocellular carcinoma**." Aliment Pharmacol Ther **56**(5): 869-877.

BACKGROUND: Universal vaccination of newborns with hepatitis B virus (HBV) vaccine is the most important strategy to prevent chronic HBV infection and its complications of which hepatocellular carcinoma (HCC) as the deadliest. AIMS: To evaluate the impact of universal HBV vaccination on the prevalence of chronic HBV infection, and the incidences of HCC and hepatic events in young adults born before and after the introduction of the universal HBV vaccination programme in 1988 in Hong Kong METHODS: This was a territory-wide retrospective observational cohort study of consecutive adult subjects born in 1970-2002 with hepatitis B surface antigen (HBsAg) checked. Subjects born during the vaccination era (1988-2002) were included in the vaccinated cohort; subjects born between 1970 and 1987 were included in the unvaccinated cohort. RESULTS: We included 695,925 subjects for HBV prevalence analysis. Chronic HBV infection dropped from 14.3% in subjects born in 1970, to 6.7% in subjects born in 1988. In total, 53,960 vaccinated and 318,290 unvaccinated subjects who had available clinical data were included for event analysis. HCC and hepatic events

occurred in 44 (0.1%) and 75 (0.1%) of the vaccinated subjects and in 1305 (0.4%) and 1806 (0.6%) of the unvaccinated subjects, respectively. All incidence rates remained numerically lower in vaccinated subjects after adjustment for age, gender and antiviral treatment, but failed to reach statistical significance due to very low incidence rates. CONCLUSIONS: Universal HBV vaccination markedly reduces the prevalence of chronic HBV infection and may contribute to the decreased incidences of HCC and hepatic events.

Yu, S, X Zi, Q Zhu, Y Zheng, C Wu, H Ren, X Liu, Z Liu, Y Li, Q Pan and YJ Zheng (2022). "**Accelerating Decreases in the Incidences of Hepatocellular Carcinoma at a Younger Age in Shanghai Are Associated With Hepatitis B Virus Vaccination**." Front Oncol **12**: 855945.

BACKGROUND: Routine vaccination of infants for protecting against hepatitis B virus (HBV) infection and its serious consequences, including hepatocellular cancer (HCC), has been carried out in Shanghai, China, since 1986. We therefore have examined the trend of HBV infection and HCC incidences before and after HBV vaccination over decades to assess the potential influences of the Shanghai HBV vaccination program. METHODS: Data on incidences of HBV infection and HCC were collected from the Shanghai Cancer Registry and the Shanghai HBV vaccination follow-up study. Joint-point regression and the Bayesian age-period-cohort statistical analysis methods were used. RESULTS: The incidences of HBV infection dramatically declined from 23.09 and 1.13 per 100,000 for males and females in 2000 to 3.24 (-85.97%) and 0.22 (-80.53%) per 100,000 in 2014, respectively. Sero-epidemiological data from the sampling surveys during 20 years of follow-up showed that less than 1% of people undergoing HBV vaccination have a positive serum HBsAg. Consistently, the annual adjusted standardization rates (ASR) of HCC steadily fell from 33.38 and 11.65 per 100,000 for males and females in 1973 to 17.34 (-49.2%) and 5.60 (-51.9%) per 100,000 in 2014, respectively. The annual percentage change in overall HCC incidences is about -2%. HCC incidences in males at younger age groups (age <50 years old), particularly in those with age <34 groups, showed an accelerating decrease over time, whereas HCC incidences significantly declined in the female population across all age groups except for those under 19 years of age. The results supported that the universal HBV vaccination in newborns is easy to implement with high coverages and is effective for preventing both HBV infection and HCC in populations.

Corrigendum: Accelerating Decreases in the Incidences of Hepatocellular Carcinoma at a Younger Age in Shanghai Are Associated With Hepatitis B Virus Vaccination - PubMed

*2023*

Akuta, N, H Sezaki, S Fujiyama, Y Kawamura, T Hosaka, M Kobayashi, S Saitoh, Y Arase, K Ikeda, Y Suzuki, F Suzuki and H Kumada (2023). "**Simple Predictive Markers and Clinicopathological Features of Primary Liver Cancer following HCV Clearance with Direct-Acting Antivirals**." Oncology **101**(2): 79-88.

INTRODUCTION: Simple predictive markers enabling even nonspecialized medical doctors and clinicopathological features of primary liver cancer (PLC) following HCV clearance with direct-acting antivirals (DAAs) are unclear. METHODS: The subjects of this retrospective study were 2,476 patients following HCV clearance with DAAs. All patients were confirmed to be PLC-free before and during DAAs. RESULTS: PLC was diagnosed in 73 patients during the follow-up, with an incidence rate per 1 000 person-years of 5.9. The annual rate of PLC during the first 6 years was 0.6%. Multivariate analysis identified gender, GGT, and FIB-4 index as the significant determinants of PLC. According to a combination of these risk factors, the cumulative PLC incidence rates were significantly different among the five subgroups based on the number of PLC risk scores. In 73 patients with PLC, the rates of abnormal AFP, PIVKAII, and serum TERT C228T positive were 37.0, 32.4, and 22.2%. PIVKAII levels in BCLC stage A and B were significantly higher than those in stage 0. In 41 patients, who underwent surgical resection for PLC, maximum tumor diameters of abnormal PIVKAII were significantly larger than those of

normal PIVKAII. PLC of abnormal PIVKAII significantly indicated presence of vp more than that of normal PIVKAII, and did not contain well-differentiated HCC. CONCLUSIONS: Combination of simple markers, enabling even nonspecialized medical doctors, is useful for the evaluation of PLC risk following HCV clearance with DAAs. However, imaging studies are regularly recommended for the early detection of PLC.

B, GBDEH and C Collaborators (2023). "**Hepatitis B and C in Europe: an update from the Global Burden of Disease Study 2019**." Lancet Public Health **8**(9): e701-e716. (https://www.ncbi.nlm.nih.gov/pubmed/37633679)

BACKGROUND: In 2016, the World Health Assembly adopted the resolution to eliminate viral hepatitis by 2030. This study aims to provide an overview of the burdens of hepatitis B virus (HBV) and hepatitis C virus (HCV) in Europe and their changes from 2010 to 2019 using estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019. METHODS: We used GBD 2019 estimates of the burden associated with HBV-related and HCV-related diseases: acute hepatitis, cirrhosis and other chronic liver diseases, and liver cancer. We report total numbers and age-standardised rates per 100 000 for mortality, prevalence, incidence, and disability-adjusted life-years (DALYs) from 2010 to 2019. For each HBV-related and HCV-related disease and each measure, we analysed temporal changes and percentage changes for the 2010-19 period. FINDINGS: In 2019, across all age groups, there were an estimated 2.08 million (95% uncertainty interval [UI] 1.66 to 2.54) incident cases of acute hepatitis B and 0.49 million (0.42 to 0.57) of hepatitis C in Europe. There were an estimated 8.24 million (7.56 to 8.88) prevalent cases of HBV-related cirrhosis and 11.87 million (9.77 to 14.41) of HCV-related cirrhosis, with 24.92 thousand (19.86 to 31.03) deaths due to HBV-related cirrhosis and 36.89 thousand (29.94 to 45.56) deaths due to HCV-related cirrhosis. Deaths were estimated at 9.00 thousand (6.88 to 11.62) due to HBV-related liver cancer and 23.07 thousand (18.95 to 27.31) due to HCV-related liver cancer. Between 2010 and 2019, the age-standardised incidence rate of acute hepatitis B decreased (-22.14% [95% UI -35.44 to -5.98]) as did its age-standardised mortality rate (-33.27% [-43.03 to -25.49]); the age-standardised prevalence rate (-20.60% [-22.09 to -19.10]) and mortality rate (-33.19% [-37.82 to -28.13]) of HBV-related cirrhosis also decreased in this time period. The age-standardised incidence rate of acute hepatitis C decreased by 3.24% (1.17 to 5.02) and its age-standardised mortality rate decreased by 35.73% (23.48 to 47.75) between 2010 and 2019; the age-standardised prevalence rate (-6.37% [-8.11 to -4.32]), incidence rate (-5.87% [-11.24 to -1.01]), and mortality rate (-11.11% [-16.54 to -5.53]) of HCV-related cirrhosis also decreased. No significant changes were observed in age-standardised rates of HBV-related and HCV-related liver cancer, although we observed a significant increase in numbers of cases of HCV-related liver cancer across all ages between 2010 and 2019 (16.41% [2.81 to 30.91] increase in prevalent cases). Substantial reductions in DALYs since 2010 were estimated for acute hepatitis B (-27.82% [-36.92 to -20.24]), acute hepatitis C (-27.07% [-15.97 to -39.34]), and HBV-related cirrhosis (-30.70% [-35.75 to -25.03]). A moderate reduction in DALYs was estimated for HCV-related cirrhosis (-6.19% [-0.19 to -12.57]). Only HCV-related liver cancer showed a significant increase in DALYs (10.37% [4.81-16.63]). Changes in age-standardised DALY rates closely resembled those observed for overall DALY counts, except for HCV-liver related cancer (-2.84% [-7.75 to 2.63]). INTERPRETATION: Although decreases in some HBV-related and HCV-related diseases were estimated between 2010 and 2019, HBV-related and HCV-related diseases are still associated with a high burden, highlighting the need for more intensive and coordinated interventions within European countries to reach the goal of elimination by 2030. FUNDING: Bill & Melinda Gates Foundation.

Lazarus, JV, CA Picchio and M Colombo (2023). "**Hepatocellular Carcinoma Prevention in the Era of Hepatitis C Elimination**." International Journal of Molecular Sciences **24**(18). (<Go to ISI>://WOS:001071911400001)

The hepatitis C virus (HCV), a single-stranded RNA virus belonging to the Flaviviridae family, is a major cause of hepatocellular carcinoma (HCC) worldwide. Tumors caused by HCC have an increased mortality rate globally, which is more accentuated in Western countries. The carcinogenic potential of this virus is mediated through a wide range of mechanisms, spanning from the induction of chronic inflammation to oxidative stress and deregulation of cellular pathways by viral proteins. As the number of new infections continues unabated, HCC-related mortality should be prioritized through early detection, continued prevention of HCV transmission, and treatment of HCV with safe and efficacious direct antiviral agents (DAAs). People who inject drugs (PWID) are a significant reservoir of new HCV infections globally, and in order to eliminate hepatitis C as a global health threat, as set out by the World Health Organization, an integrated approach based on the optimization of care delivery and increased access to harm reduction and treatment for PWID is needed. Thanks to the development of safe and effective antiviral agents, eradication of the infection is now possible in almost all treated patients, leading to a significant reduction but not the elimination of the risk for HCC in cured patients. This is particularly relevant among aged populations who have cofactors of morbidity known to accelerate HCC progression, such as diabetes, obesity, and excessive alcohol consumption. Given the restless accumulation of individuals with cured HCV infection, the implementation of risk-stratified surveillance programs becomes impellent from a cost-effectiveness perspective, whereas the availability of a performant biomarker to predict HCC in cured patients remains an unmet clinical need.

Lim, YS, WR Kim, D Dieterich, JH Kao, JF Flaherty, LJ Yee, LR Roberts, H Razavi and PTF Kennedy (2023). "**Evidence for Benefits of Early Treatment Initiation for Chronic Hepatitis B.**" Viruses **15**(4).

Chronic hepatitis B (CHB) is the most common cause of hepatocellular carcinoma (HCC) worldwide. Antiviral treatment reduces the risk of HCC and mortality; nonetheless, globally in 2019, only 2.2% of CHB patients received treatment. Current international CHB guidelines recommend antiviral treatment only in subsets of patients with clear evidence of liver damage. This contrasts with hepatitis C or HIV where early treatment is recommended in all infected patients, regardless of end-organ damage. This narrative review aims to provide an overview of data on the early initiation of antiviral treatment and its related potential economic impact. Literature searches were performed using PubMed and abstracts from international liver congresses (2019-2021). Data on risk of disease progression and HCC and the impact of antiviral treatment in currently ineligible patients were summarized. Cost-effectiveness data on early antiviral treatment initiation were also collated. Accumulating molecular, clinical, and economic data suggest that early initiation of antiviral treatment could save many lives through HCC prevention in a highly cost-effective manner. In light of these data, we consider several alternative expanded treatment strategies that might further a simplified 'treatment as prevention' approach.

Momin, B, J Mezzo, D Nielsen, A Richardson and EE Conners (2023). "**Implementing Promising Strategies to Reduce the Risk for Viral Hepatitis and Liver Cancer Among People Who Inject Drugs.**" Am J Health Promot **37**(7): 982-987.

PURPOSE: To describe a 3-year demonstration project with selected Centers for Disease Control and Prevention National Comprehensive Cancer Control Program (NCCCP) award recipients to build partnerships with local organizations to improve knowledge and awareness of the association between injecting drugs and the risk for viral hepatitis and liver cancer, improve delivery of viral hepatitis services, and implement comprehensive syringe services programs. DESIGN: A mixed-methods descriptive evaluation of selected evidence-based interventions or promising strategies that each award recipient implemented based on the needs of their population. SETTING: Selected provider and patient populations served by NCCCP award recipients in Iowa, Minnesota (American Indian Cancer Foundation), Mississippi, and West Virginia. SUBJECTS: Four award recipients that implemented individually-tailored

strategies and activities. MEASURES: Processes were assessed through monitoring and tracking tools. Challenges, lessons learned, and recommendations were collected via qualitative interviews. ANALYSIS: We used descriptive statistics to analyze quantitative data. We analyzed award recipient interviews using thematic analysis. RESULTS: Activities were implemented across four strategies. Strong public-private partnerships, ongoing technical assistance, a deep understanding of individual populations, and a shared commitment to remaining flexible were main factors. CONCLUSION: While challenges existed, award recipients implemented key strategies and activities in their populations. Findings contribute to the scaling of best practices to the larger cancer control community especially those whose populations are at higher risk for viral hepatitis.

Moreau, C, M Roux, J Riou, CM Canivet, E Audureau, C Lusivika-Nzinga, P Nahon, F Carrat and J Boursier (2023). "**Dynamic personalized prediction of the individual liver-related risk after sustained viral response in HCV patients**." J Viral Hepat **30**(6): 567-577.
Sustained viral response (SVR) significantly improves the prognosis in patients with hepatitis C virus (HCV) chronic infection but does not totally alleviate the risk of liver-related complications (LRC). We aimed to evaluate whether the dynamics of multiple measurements of simple parameters after SVR enable the development of a personalized prediction of prognosis in HCV patients. HCV mono-infected patients who experienced SVR in two prospective cohorts (ANRS CO12 CirVir cohort: derivation set; ANRS CO22 HEPATHER cohort: validation set) were included. The study outcome was LRC, a composite criterion including decompensation of cirrhosis and/or hepatocellular carcinoma. Joint latent class modelling accounting for both biomarker trajectory and event occurrence during follow-up was developed in the derivation set to compute individual dynamic predictions, with further evaluation in the validation set. In the derivation set (n = 695; 50 LRC during the median 3.8 [1.6-7.5] years follow-up), FIB4 was identified as a biomarker associated with LRC occurrence after SVR. Joint modelling used sex and the dynamics of FIB4 and diabetes status to develop a personalized prediction of LRC. In the validation set (n = 7064; 273 LRC during the median 3.6 [2.5-4.9] years follow-up), individual dynamic predictions from the model accurately stratified the risk of LRC. Time-dependent Brier Score showed good calibration that improved with the accumulation of visits, justifying our modelling approach considering both baseline and follow-up measurements. Dynamic modelling using repeated measurements of simple parameters predicts the individual residual risk of LRC and improves personalized medicine after SVR in HCV patients.

So, SM, N Terrault and EE Conners (2023). "**Universal Adult Hepatitis B Screening and Vaccination as the Path to Elimination**." Jama-Journal of the American Medical Association **329**(19): 1639-1640. (<Go to ISI>://WOS:000947139200002)
This Viewpoint describes new recommendations from the CDC regarding universal screening of adults for hepatitis B virus infection.

Stroffolini, T and G Stroffolini (2023). "**A Historical Overview on the Role of Hepatitis B and C Viruses as Aetiological Factors for Hepatocellular Carcinoma**." Cancers (Basel) **15**(8).
Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the leading cause of hepatocellular carcinoma (HCC) worldwide. Currently, HBV-related HCC predominates in Sub-Saharan Africa and South-East-Asia, while HCV-related HCC predominates in northern Africa and in the western world. Liver cirrhosis is the underlying condition in most HBV cases and in nearly all HCV cases. Several cofactors, viral and non-viral, play a role in the progression toward HCC: dual HBV/HCV infection, HDV, HIV, alcohol intake, smoking, diabetes mellitus, obesity, and NAFLD/NASH. HBV vaccine is effective in preventing both infection and HCC; antiviral drugs may suppress HBV replication and eradicate HCV infection, halting progression to HCC. Inequalities exist between high- and low-income countries with respect to vaccine availability

and access to antivirals. These factors represent barriers to the control of HCC incidence. Lack of an effective vaccine against HCV is also a serious barrier to HCV elimination and HCC prevention. The most crucial steps and knowledge that have arisen over time on the association between the two major hepatotropic viruses and HCC are discussed in this historical review.

*2024*

Bencina, G, E Oliver, A Meiwald, R Hughes, E Morais, G Weston and K Sundström (2024). "**Global burden and economic impact of vaccine-preventable cancer mortality**." J Med Econ **27**(sup2): 9-19.

BACKGROUND: Infections are responsible for approximately 13% of cancer cases worldwide and many of these infections can be prevented by vaccination. Human papillomavirus (HPV) and hepatitis B virus (HBV) are among the most common infections that cause cancer deaths globally, despite effective prophylactic vaccines being available. This analysis aims to estimate the global burden and economic impact of vaccine-preventable cancer mortality across World Health Organization (WHO) regions. METHODS: The number of deaths and years of life lost (YLL) due to five different vaccine-preventable cancer forms (oral cavity, liver, laryngeal, cervical, and oropharyngeal cancer) in each of the WHO regions (African, Eastern Mediterranean, European, the Americas, South-East Asia Pacific, and Western Pacific) were obtained from the Institute for Health Metrics Evaluation global burden of disease dataset. Vaccine-preventable mortality was estimated considering the fraction attributable to infection, to estimate the number of deaths and YLL potentially preventable through vaccination. Data from the World Bank on GDP per capita were used to estimate the value of YLL (VYLL). The robustness of these results was explored with sensitivity analysis. Given that several Epstein-Barr virus (EBV) vaccines are in development, but not yet available, the impact of a potential vaccine for EBV was evaluated in a scenario analysis. RESULTS: In 2019, there were 465,740 potentially vaccine-preventable cancer deaths and 14,171,397 YLL across all WHO regions. The estimated economic impact due to this mortality was $106.3 billion globally. The sensitivity analysis calculated a range of 403,025-582,773 deaths and a range in productivity cost of $78.8-129.0 billion. In the scenario analysis EBV-related cancer mortality increased the global burden by 159,723 deaths and $32.4 billion. CONCLUSION: Overall, the findings from this analysis illustrate the high economic impact of premature cancer mortality that could be potentially preventable by vaccination which may assist decision-makers in allocating limited resources among competing priorities. Improved implementation and increased vaccination coverage of HPV and HBV should be prioritized to decrease this burden.

Bencina, G, U Sabale, E Morais, O Ovcinnikova, E Oliver, H Shoel, A Meiwald, R Hughes, G Weston and K Sundstrom (2024). "**Burden and indirect cost of vaccine-preventable cancer mortality in Europe**." J Med Econ **27**(sup2): 30-40.

BACKGROUND: The economic and mortality burden of cancer is high worldwide. In Europe, cancer was responsible for 1.3 million deaths in 2020 and incurred an estimated cost of euro50 billion from premature mortality. Human papillomavirus (HPV) and hepatitis B virus (HBV) are among the leading causes of infection-related cancers despite the availability of effective vaccines against these infections. This analysis estimated the mortality and productivity loss of HBV- and HPV-associated cancers that could be preventable through vaccination across European regions. MATERIALS AND METHODS: Institute for Health Metrics Evaluation (IHME) data were used to estimate mortality, years of life lost (YLL), and the value of years of life lost (VYLL) from five HBV- and HPV-related cancers (oral cavity, oropharynx, larynx, cervical, and liver cancers) across 40 European countries in 2019. Preventable deaths and YLL were estimated based on fractions attributable to infections. Data from the World Bank on GDP per

capita were used to estimate the VYLL. The robustness of these results was explored with sensitivity and scenario analyses. RESULTS: In 2019, 31,906 cancer deaths resulted in an economic burden of euro18,521,614,725 due to productivity losses across Europe. HPV-related cervical cancer had the highest mortality (19,473 deaths) and economic burden (euro10,706,253,185). HBV-related liver cancer and HPV-related larynx, oral cavity, and oropharynx cancers also had a substantial burden, particularly in males. Eastern Europe had the highest YLL (308,179; 39%) and Western Europe was responsible for the greatest VYLL (euro8,281,306,504; 45%), although the highest VYLL per death was in Northern Europe (euro923,638). HPV-related oropharynx cancer had the highest VYLL per death (euro656,607). CONCLUSION: HPV- and HBV-related cancer deaths are associated with substantial mortality and productivity losses in Europe, which could be reduced by the continued prioritization and implementation of prophylactic public health measures including systematic awareness, vaccination, and screening efforts.

Capasso, M, V Cossiga, M Guarino, L Ranieri and F Morisco (2024). "**The Role of Hepatitis Viruses as Drivers of Hepatocancerogenesis.**" Cancers (Basel) **16**(8).

Recently, metabolic associated steatotic liver disease (MASLD) became the leading cause of chronic liver disease worldwide and one of the most frequent causes of hepatocellular carcinoma (HCC). Nonetheless, in this epidemiological trend, viral hepatitis remains the major driver in hepatic carcinogenesis. Globally, hepatitis B virus (HBV) is the leading cause of hepatocellular carcinoma, with an overall attributable risk of approximately 40%, followed by hepatitis C virus (HCV), which accounts for 28-30% of cases, with significant geographic variations between the Eastern and Western world. Considering all the etiologies, HCC risk increases proportionally with the progression of liver disease, but the risk is consistently higher in patients with viral triggers. This evidence indicates that both direct (due to the oncogenic properties of the viruses) and indirect (through the mechanisms of chronic inflammation that lead to cirrhosis) mechanisms are involved, alongside the presence of co-factors contributing to liver damage (smoking, alcohol, and metabolic factors) that synergistically enhance the oncogenic process. The aim of this review is to analyze the oncogenic role of hepatitis viruses in the liver, evaluating epidemiological changes and direct and indirect viral mechanisms that lead to liver cancer.

Chun, HS, GV Papatheodoridis, M Lee, HA Lee, YH Kim, SH Kim, YS Oh, SJ Park, J Kim, HA Lee, HY Kim, TH Kim, EL Yoon, DW Jun, SH Ahn, V Sypsa, C Yurdaydin, P Lampertico, JL Calleja, H Janssen, GN Dalekos, J Goulis, T Berg, M Buti, SU Kim and YJ Kim (2024). "**PAGE-B incorporating moderate HBV DNA levels predicts risk of HCC among patients entering into HBeAg-positive chronic hepatitis B**." J Hepatol **80**(1): 20-30.

BACKGROUND & AIMS: Recent studies reported that moderate HBV DNA levels are significantly associated with hepatocellular carcinoma (HCC) risk in hepatitis B e antigen (HBeAg)-positive, non-cirrhotic patients with chronic hepatitis B (CHB). We aimed to develop and validate a new risk score to predict HCC development using baseline moderate HBV DNA levels in patients entering into HBeAg-positive CHB from chronic infection. METHODS: This multicenter cohort study recruited 3,585 HBeAg-positive, non-cirrhotic patients who started antiviral treatment with entecavir or tenofovir disoproxil fumarate at phase change into CHB from chronic infection in 23 tertiary university-affiliated hospitals of South Korea (2012-2020). A new HCC risk score (PAGED-B) was developed (training cohort, n = 2,367) based on multivariable Cox models. Internal validation using bootstrap sampling and external validation (validation cohort, n = 1,218) were performed. RESULTS: Sixty (1.7%) patients developed HCC (median follow-up, 5.4 years). In the training cohort, age, gender, platelets, diabetes and moderate HBV DNA levels (5.00-7.99 log(10) IU/ml) were independently associated with HCC development; the PAGED-B score (based on these five predictors) showed a time-dependent AUROC of 0.81 for the prediction of HCC development at 5 years. In the validation cohort, the

AUROC of PAGED-B was 0.85, significantly higher than for other risk scores (PAGE-B, mPAGE-B, CAMD, and REAL-B). When stratified by the PAGED-B score, the HCC risk was significantly higher in high-risk patients than in low-risk patients (sub-distribution hazard ratio = 8.43 in the training and 11.59 in the validation cohorts, all p <0.001). CONCLUSIONS: The newly established PAGED-B score may enable risk stratification for HCC at the time of transition into HBeAg-positive CHB. IMPACT AND IMPLICATIONS: In this study, we developed and validated a new risk score to predict hepatocellular carcinoma (HCC) development in patients entering into hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) from chronic infection. The newly established PAGED-B score, which included baseline moderate HBV DNA levels (5-8 log(10) IU/ml), improved on the predictive performance of prior risk scores. Based on a patient's age, gender, diabetic status, platelet count, and moderate DNA levels (5-8 log(10) IU/ml) at the phase change into CHB from chronic infection, the PAGED-B score represents a reliable and easily available risk score to predict HCC development during the first 5 years of antiviral treatment in HBeAg-positive patients entering into CHB. With a scoring range from 0 to 12 points, the PAGED-B score significantly differentiated the 5-year HCC risk: low <7 points and high ≥7 points.

Cocco, N, MP Tramonti Fantozzi, JN Ihuthia, B Moazen, F Meroueh, I Barbîroș, J Mavrou, A Bardelli, E De Vita, E Plugge and L Tavoschi (2024). "**Cancer-preventing vaccination programs in prison: promoting health equity in Europe**." Lancet Reg Health Eur **43**: 100958.

The most important human oncogenic viruses are hepatitis B virus (HBV) and human papillomavirus (HPV). The roll-out of vaccinations against HPV and HBV is a significant public health initiative with robust evidence of impact on the prevention of infection and neoplastic disease sequelae. Incarcerated individuals frequently have suboptimal immunisation levels for a wide variety of vaccine-preventable diseases, including HBV and HPV, and a high burden of disease for HBV/HPV-related cancers. In this Personal View, we analyse evidence regarding HBV and HPV vaccination in prison settings in 20 European countries and integrate it with existing scientific literature to discuss the rationale and possible strategies to expand cancer-preventing vaccination in prison populations. Enhancing HBV/HPV vaccination offer and uptake of HBV/HPV vaccination for this population would not only contribute to reducing the derived burden among the European population, but would also foster health equity and boost efforts towards the attainment of global and regional public health targets.

Craven, CK, R Bobadilla, E Yao, C Castillo, J Cerroblanco, BE Flores, M Jain, A Radunsky, M Plesak, C Gentry, R Das and G Gharibi (2024). "**STOP-HCV-HCC Program: Privacy-Preserving Innovation for Remote Data Access Analytics at Federally Qualified Health Centers in South Texas**." Stud Health Technol Inform **316**: 1716-1717.

STOP-HCV-HCC program to screen and treat hepatitis C, vaccinate for hepatitis B, and prevent hepatocellular carcinoma is implementing a cloud-based privacy-preserving platform to overcome electronic health record barriers to reporting, without data transfer, at four federally qualified health centers in South Texas, USA.

Giusti, F, C Martos, RN Carvalho, V Zadnik, O Visser, M Bettio and L Van Eycken (2024). "**Facing further challenges in cancer data quality and harmonisation**." Frontiers in Oncology **14**.

This article highlights the recent and ongoing activities of European population-based cancer registries (PBCRs) in data quality and harmonisation in the framework of the collaboration between the European Network of Cancer Registries (ENCR) and the Directorate-General Joint Research Centre (JRC), the science and knowledge centre of the European Commission. The article concludes the Frontiers in Oncology's Research Topic "Joining Efforts to Improve Data Quality and Harmonization Among European Population-Based Cancer Registries", which has been an opportunity for several European researchers to share their experience on cancer data quality and harmonisation. Such experience will be helpful for PBCRs in view of future

challenges and opportunities in cancer epidemiology, with a few examples discussed in the present article.

Gu, W, V de Lédinghen, C Aubé, A Krag, C Strassburg, L Castéra, J Dumortier, M Friedrich-Rust, S Pol, I Grgurevic, Y Zeleke, M Praktiknjo, R Schierwagen, S Klein, S Francque, H Gottfriedová, I Sporea, P Schindler, F Rennebaum, MJ Brol, M Schulz, FE Uschner, J Fischer, C Margini, W Wang, A Delamarre, J Best, A Canbay, DJM Bauer, B Simbrunner, G Semmler, T Reiberger, J Boursier, DN Rasmussen, V Vilgrain, A Guibal, S Zeuzem, C Vassord, L Vonghia, R Šenkeříková, A Popescu, A Berzigotti, W Laleman, M Thiele, C Jansen and J Trebicka (2024). "**Hepatocellular Cancer Surveillance in Patients with Advanced Chronic Liver Disease**." NEJM Evid **3**(11): EVIDoa2400062.

BACKGROUND: Patients with advanced chronic liver disease (ACLD) are at high risk of developing hepatocellular carcinoma (HCC). Therefore, biannual surveillance is recommended. This large-scale multicenter study aimed to stratify the risk of HCC development in ACLD. METHODS: From 3016 patients with ACLD screened in 17 European and Chinese centers, 2340 patients with liver stiffness measurement (LSM) determined using different techniques (two-dimensional shear-wave elastography [2D-SWE], transient elastography, and point shear-wave elastography) and with different disease severities were included. Cox regression was used to explore risk factors for HCC. We used these data to create an algorithm, named PLEASE, but referred to in this manuscript as "the algorithm"; the algorithm was validated in internal and two external cohorts across elastography techniques. RESULTS: HCC developed in 127 (5.4%) patients during follow-up. LSM by 2D-SWE (hazard ratio: 2.28) was found to be associated with developing HCC, alongside age, sex, etiology, and platelet count (C-index: 0.8428). We thus established the algorithm with applicable cutoffs, assigning a maximum of six points: platelet count less than 150×10(9)/l, LSM greater than or equal to 15 kPa, age greater than or equal to 50 years, male sex, controlled/uncontrolled viral hepatitis, or presence of steatotic liver diseases. Within 2 years, with a median follow-up of 13.7 months, patients in the high-risk group (≥4 points) had an HCC incidence of 15.6% (95% confidence interval [CI], 12.1% to 18.7%) compared with the low-risk group, at 1.7% (95% CI, 0.9% to 2.5%). CONCLUSIONS: Our algorithm stratified patients into two groups: those at higher risk of developing HCC and those at lower risk. Our data provide equipoise to test the prospective utility of the algorithm with respect to clinical decisions about screening patients with ACLD for incident HCC. (Funded by the German Research Foundation and others; ClinicalTrials.gov number, NCT03389152.).

Haraldsson, HA, S Olafsson, M Gottfredsson, U Benitez Hernandez and ES Bjornsson (2024). "**Incidence of cirrhosis in Iceland-impact of the TraP HepC nationwide HCV elimination program**." Scand J Gastroenterol **59**(7): 835-842.

OBJECTIVE: In 2016, a nationwide elimination program for hepatitis C virus (HCV) was initiated in Iceland, entitled Treatment as Prevention for Hepatitis C (TraP HepC), providing unrestricted access to antiviral treatment. The aims were to describe the changes in etiology and epidemiology of cirrhosis in Iceland and to assess the trends in HCV-related cirrhosis following TraP HepC. METHODS: The study included all patients newly diagnosed with cirrhosis in 2016-2022. Diagnosis was based on liver elastography, histology, or 2 of 4 criteria: cirrhosis on imaging, ascites, varices, or elevated international normalized ratio (INR). RESULTS: Over the study period, 342 new cirrhosis patients were identified, 223 (65%) males, median age 62 years. The crude overall incidence was 13.8 cases per 100,000 inhabitants annually. The most common etiologies were alcohol-related liver disease (ALD) (40%), metabolic dysfunction-associated steatotic liver disease (MASLD) (28%), and HCV with or without alcohol overconsumption (15%). The number of HCV cirrhosis cases was unusually high in 2016 (n = 23) due to intensified case-finding, but decreased significantly over the study period ($p < 0.001$) to n = 1 (2021) and n = 2 (2022). The overall 5-year survival was 55% (95% CI 48.9-62.3%). The most common causes of death were hepatocellular carcinoma (26%) and liver failure (25%). CONCLUSION: During the past two decades, the incidence of cirrhosis has increased

extraordinarily in Iceland, associated with increased alcohol consumption, obesity, and HCV. ALD and MASLD now collectively make up two thirds of cases in Iceland. Following a nationwide elimination program, incidence of HCV cirrhosis has dropped rapidly in Iceland.

Hobart, C, JM Pescarini, L Evans, HS Adil, ST Adil, A Deal, J Carter, PC Matthews, S Hargreaves and N Sanchez Clemente (2024). "**Hepatitis B infection and immunity in migrant children and pregnant persons in Europe: a systematic review and meta-analysis.**" J Travel Med **31**(6).
BACKGROUND: The WHO's global hepatitis strategy aims to achieve viral hepatitis elimination by 2030. Migrant children and pregnant persons represent an important target group for prevention strategies. However, evidence on the burden of chronic hepatitis B (CHB) infection and the factors affecting its incidence is lacking. METHODS: EMBASE, Global Health, Global Index Medicus, Web of Science and Medline were searched for articles in any language from 1 January 2012 to 8 June 2022. Studies reporting CHB prevalence, disease severity, complications and/or prevention strategies, including vaccination, prevention of vertical transmission and access to care/treatment for migrant children and pregnant migrants, were included. Pooled estimates of CHB prevalence and hepatitis B vaccination (HBV) coverage among migrant children were calculated using random effects meta-analysis. FINDINGS: 42 studies were included, 27 relating to migrant children and 15 to pregnant migrants across 12 European countries, involving data from 64 773 migrants. Migrants had a higher incidence of CHB than host populations. Among children, the pooled prevalence of CHB was higher for unaccompanied minors (UAM) (5%, [95% CI: 3-7%]) compared to other child migrants, including internationally adopted children (IAC) and refugees (1%, [95% CI: 1-2%]). Region of origin was identified as a risk factor for CHB, with children from Africa and pregnant migrants from Africa, Eastern Europe and China at the highest risk. Pooled estimates of HBV vaccine coverage were lower among UAM (12%, [95% CI: 3-21%]) compared to other child migrants (50%, [95% CI: 37-63%]). CONCLUSION: A range of modifiable determinants of HBV prevalence in migrant children and pregnant persons were identified, including sub-optimal screening, prevention and continuum of care. There is a need to develop evidence-based approaches in hepatitis care for these groups, thereby contributing towards global viral hepatitis elimination goals.

Kondili, LA, JV Lazarus, P Jepsen, F Murray, JM Schattenberg, M Korenjak, L Craxi and M Buti (2024). "**Inequities in primary liver cancer in Europe: The state of play**." J Hepatol **80**(4): 645-660.
Given the increasing burden of liver cancer in Europe, it is crucial to investigate how social determinants of health (SDoH) affect liver cancer risk factors and access to care in order to improve health outcomes equitably. This paper summarises the available evidence on the differential distribution of liver cancer risk factors, incidence, and health outcomes in the European Economic Area and the United Kingdom from an SDoH perspective. Vulnerable and marginalised populations have low socio-economic and educational levels and are the most affected by liver cancer risk factors. Reasons for this include varied access to hepatitis B virus vaccination and limited access to viral hepatitis B and C screening, harm reduction, and treatment. Additionally, alcohol-related liver disease remains highly prevalent among individuals with low education, insecure employment, economic instability, migrants, and deprived populations. Moreover, significant variation exists across Europe in the proportion of adults with steatotic liver disease, overweight/obesity, and diabetes, based on geographical area, gender, socio-economic and educational background, and density of ultra-processed food outlets. Inequities in cirrhosis mortality rates have been reported, with the highest death rates among individuals living in socio-economically disadvantaged areas and those with lower educational levels. Furthermore, insufficient healthcare access for key populations with primary liver cancer is influenced by complex healthcare systems, stigmatisation, discrimination, low education, language barriers, and fear of disclosure. These challenges

contribute to inequities in liver cancer care pathways. Future studies are needed to explore the different SDoH-interlinked effects on liver cancer incidence and outcomes in European countries. The ultimate goal is to develop evidence-based multilevel public health interventions that reduce the SDoH impact in precipitating and perpetuating the disproportionate burden of liver cancer in specific populations.

Lani, L, B Stefanini and F Trevisani (2024). "**Surveillance for Hepatocellular Carcinoma in Patients with Successfully Treated Viral Disease of the Liver: A Systematic Review**." Liver Cancer **13**(4): 376-388. (https://www.ncbi.nlm.nih.gov/pubmed/39114761)

BACKGROUND: Surveillance for hepatocellular carcinoma (HCC) has been proven to increase the proportion of tumors detected at early stages and the chance of receiving curative therapies, reducing mortality by about 30%. SUMMARY: Current recommendations consist of a semi-annual abdominal ultrasound with or without serum alpha-fetoprotein measurement in patients with cirrhosis and specific subgroups of populations with chronic viral hepatitis. Antiviral therapies, such as nucleot(s)ide analogs that efficiently suppress the replication of hepatitis B virus (HBV) and direct-acting antiviral drugs able to eliminate the hepatitis C virus (HCV) in >90% of patients, have radically changed the outcomes of viral liver disease and decreased, but not eliminated, the risk of HCC in both cirrhotic and non-cirrhotic patients. HCC risk is a key starting point for implementing a cost-effective surveillance and should also guide the decision-making process concerning its modality. As the global number of effectively treated viral patients continues to rise, there is a pressing need to identify those for whom the benefit-to-harm ratio of surveillance is favorable and to determine how to conduct cost-effective screening on such patients. KEY MESSAGES: This article addresses this topic and attempts to determine which patients should continue HCC surveillance after HBV suppression or HCV eradication, based on cost-effectiveness principles and the fact that HCC risk declines over time. We also formulate a proposal for a surveillance algorithm that switches the use of surveillance for HCC from the "one-size-fits-all" approach to individualized programs based on oncologic risk (precision surveillance).

Lombardo, D, MS Franzè, G Caminiti and T Pollicino (2024). "**Hepatitis Delta Virus and Hepatocellular Carcinoma**." Pathogens **13**(5).

The hepatitis D virus (HDV) is a compact, enveloped, circular RNA virus that relies on hepatitis B virus (HBV) envelope proteins to initiate a primary infection in hepatocytes, assemble, and secrete new virions. Globally, HDV infection affects an estimated 12 million to 72 million people, carrying a significantly elevated risk of developing cirrhosis, liver failure, and hepatocellular carcinoma (HCC) compared to an HBV mono-infection. Furthermore, HDV-associated HCC often manifests at a younger age and exhibits more aggressive characteristics. The intricate mechanisms driving the synergistic carcinogenicity of the HDV and HBV are not fully elucidated but are believed to involve chronic inflammation, immune dysregulation, and the direct oncogenic effects of the HDV. Indeed, recent data highlight that the molecular profile of HCC associated with HDV is unique and distinct from that of HBV-induced HCC. However, the question of whether the HDV is an oncogenic virus remains unanswered. In this review, we comprehensively examined several crucial aspects of the HDV, encompassing its epidemiology, molecular biology, immunology, and the associated risks of liver disease progression and HCC development.

Olafsson, S, TJ Love, RH Fridriksdottir, T Tyrfingsson, V Runarsdottir, I Hansdottir, OM Bergmann, ES Björnsson, B Johannsson, B Sigurdardottir, A Löve, GE Baldvinsdottir, M Thordardottir, UB Hernandez, M Heimisdottir, M Hellard and M Gottfredsson (2024). "**Predictors of treatment outcomes for Hepatitis C infection in a nationwide elimination program in Iceland: The treatment as prevention for Hepatitis C (TraP HepC) study**." Int J Drug Policy **133**: 104616.

BACKGROUND: Limited data exists about treatment outcomes in nationwide hepatitis C virus (HCV) elimination programs where injection drug use (IDU) is the main mode of transmission. In 2016 Iceland initiated the HCV elimination program known as Treatment as Prevention for Hepatitis C (TraP HepC). Factors associated with HCV cure in this population are examined. METHODS: Unrestricted access was offered to direct acting antiviral agents (DAAs). Testing and harm reduction was scaled up and re-treatments were offered for those who did not attain cure. Cure rates for the first 36 months were assessed and factors associated with failure to achieve cure analysed using multivariable logistic regression. RESULTS: Treatment was initiated for 718; 705 consented for the study. Median age was 44 years (IQR 35-56), history of IDU reported by 593 (84.1 %), recent IDU by 234 (33.2 %); 48 (6.8 %) were homeless. Of 705 patients, 635 achieved cure (90.1 %) during the first treatment. A total of 70 (9.9 %) patients initiated two or more treatments, resulting in 673 participants cured (95.5 %). By multivariable analysis, homelessness was the only statistically significant independent factor associated with not achieving cure (OR 2.67, 95 % CI 1.32-5.41) after first treatment attempt. CONCLUSION: By reengagement in care and prompt retreatment when needed, a cure rate of 95.5 % was achieved. Unstable housing, a potentially actionable factor is associated with poor outcome.

Ozturk, NB, HN Pham, R Mouhaffel, R Ibrahim, M Alsaqa, A Gurakar and B Saberi (2024). "**A Longitudinal Analysis of Mortality Related to Chronic Viral Hepatitis and Hepatocellular Carcinoma in the United States**." Viruses **16**(5).

(1) Background: Hepatocellular carcinoma (HCC) contributes to the significant burden of cancer mortality in the United States (US). Despite highly efficacious antivirals, chronic viral hepatitis (CVH) remains an important cause of HCC. With advancements in therapeutic modalities, along with the aging of the population, we aimed to assess the contribution of CVH in HCC-related mortality in the US between 1999-2020. (2) Methods: We queried all deaths related to CVH and HCC in the multiple-causes-of-death files from the CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) database between 1999-2020. Using the direct method of standardization, we adjusted all mortality information for age and compared the age-adjusted mortality rates (AAMRs) across demographic populations and by percentile rankings of social vulnerability. Temporal shifts in mortality were quantified using log-linear regression models. (3) Results: A total of 35,030 deaths were identified between 1999-2020. The overall crude mortality increased from 0.27 in 1999 to 8.32 in 2016, followed by a slight reduction to 7.04 in 2020. The cumulative AAMR during the study period was 4.43 (95% CI, 4.39-4.48). Males (AAMR 7.70) had higher mortality rates compared to females (AAMR 1.44). Mortality was higher among Hispanic populations (AAMR 6.72) compared to non-Hispanic populations (AAMR 4.18). Higher mortality was observed in US counties categorized as the most socially vulnerable (AAMR 5.20) compared to counties that are the least socially vulnerable (AAMR 2.53), with social vulnerability accounting for 2.67 excess deaths per 1,000,000 person-years. (4) Conclusions: Our epidemiological analysis revealed an overall increase in CVH-related HCC mortality between 1999-2008, followed by a stagnation period until 2020. CVH-related HCC mortality disproportionately affected males, Hispanic populations, and Black/African American populations, Western US regions, and socially vulnerable counties. These insights can help aid in the development of strategies to target vulnerable patients, focus on preventive efforts, and allocate resources to decrease HCC-related mortality.

Pastras, P, E Zazas, M Kalafateli, I Aggeletopoulou, EP Tsounis, S Kanaloupitis, K Zisimopoulos, EE Kottaridou, A Antonopoulou, D Drakopoulos, G Diamantopoulou, A Tsintoni, K Thomopoulos and C Triantos (2024). "**Predictive Risk Factors and Scoring Systems Associated with the Development of Hepatocellular Carcinoma in Chronic Hepatitis B**." Cancers (Basel) **16**(14).

Chronic hepatitis B (CHB) infection constitutes a leading cause of hepatocellular carcinoma (HCC) development. The identification of HCC risk factors and the development of prognostic

risk scores are essential for early diagnosis and prognosis. The aim of this observational, retrospective study was to evaluate baseline risk factors associated with HCC in CHB. Six hundred thirty-two consecutive adults with CHB (n = 632) [median age: 46 (IQR: 24)], attending the outpatients' Hepatology clinics between 01/1993-09/2020 were evaluated. Core promoter mutations and cirrhosis-HCC (GAG-HCC), Chinese University-HCC (CU-HCC), risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B), Fibrosis-4 (FIB-4), and Platelet Age Gender-HBV (PAGE-B) prognostic scores were calculated, and receiver operating curves were used to assess their prognostic performance. HCC was developed in 34 (5.38%) patients. In the multivariable Cox regression analysis, advanced age (HR: 1.086, 95% CI: 1.037-1.137), male sex (HR: 7.696, 95% CI: 1.971-30.046), alcohol abuse (HR: 2.903, 95% CI: 1.222-6.987) and cirrhosis (HR: 21.239, 95% CI: 6.001-75.167) at baseline were independently associated with the development of HCC. GAG-HCC and PAGE-B showed the highest performance with c-statistics of 0.895 (95% CI: 0.829-0.961) and 0.857 (95% CI: 0.791-0.924), respectively. In the subgroup of patients with cirrhosis, the performance of all scores declined. When treated and untreated patients were studied separately, the discriminatory ability of the scores differed. In conclusion, HCC development was independently associated with advanced age, male sex, alcohol abuse, and baseline cirrhosis among a diverse population with CHB. GAG-HCC and PAGE-B showed high discriminatory performance to assess the risk of HCC development in these patients, but these performances declined in the subgroup of patients with cirrhosis. Further research to develop scores more specific to certain CHB subgroups is needed.

Poorolajal J, Shadi Y, Heshmati B (2024). **Interaction between hepatitis B, hepatitis C and alcohol in the development of hepatocellular carcinoma: A systematic review and meta-analysis**. Journal of Viral Hepatitis 32(1), e14042

The objective of this report is to provide clarification on the interaction among hepatitis B virus (HBV), hepatitis C virus (HCV) and alcohol in the development of hepatocellular carcinoma (HCC). A systematic search was performed in PubMed, Web of Science and Scopus databases up to July 18, 2023. The inclusion criteria involved observational studies that examined the relationship between HBV, HCV, alcohol use and the development of HCC. To assess between-study heterogeneity, the I2 statistics were employed. Publication bias was evaluated using the Begg and Egger tests. The effect sizes were estimated as odds ratios (ORs) with 95% confidence intervals (CIs) utilising a random-effects model. Among the initial pool of 31,021 studies identified, 28 studies involving 42,406 participants met the inclusion criteria. Through our meta-analysis, we found that the combined effect of HBV and alcohol was associated with an OR of 14.56 (95% CI: 9.80, 21.65). The combined impact of HCV and alcohol showed an OR of 42.44 (95% CI: 20.11, 89.56). Coinfection with both HBV and HCV was associated with an OR of 32.58 (95% CI: 20.57, 51.60). These results emphasising the importance of reducing alcohol consumption and implementing effective viral hepatitis prevention and treatment.

Quaranta, MG, L Cavalletto, FP Russo, V Calvaruso, L Ferrigno, A Zanetto, B Mattioli, R D'Ambrosio, V Panetta, G Brancaccio, G Raimondo, MR Brunetto, AL Zignego, C Coppola, A Iannone, E Biliotti, E Rosselli Del Turco, M Massari, A Licata, F Barbaro, M Persico, F Morisco, M Pompili, F Cerini, M Puoti, T Santantonio, A Craxì, LA Kondili, L Chemello and I On Behalf Of Piter Collaborating (2024). "**Reduction of the Risk of Hepatocellular Carcinoma over Time Using Direct-Acting Antivirals: A Propensity Score Analysis of a Real-Life Cohort (PITER HCV)**." Viruses **16**(5).

The treatment of hepatitis C virus (HCV) with direct-acting antivirals (DAA) leads to high sustained virological response (SVR) rates, but hepatocellular carcinoma (HCC) risk persists in people with advanced liver disease even after SVR. We weighted the HCC risk in people with cirrhosis achieving HCV eradication through DAA treatment and compared it with untreated participants in the multicenter prospective Italian Platform for the Study of Viral Hepatitis Therapies (PITER) cohort. Propensity matching with inverse probability weighting was used to compare DAA-treated and untreated HCV-infected participants with liver cirrhosis. Kaplan-

Meier analysis and competing risk regression analysis were performed. Within the first 36 months, 30 de novo HCC cases occurred in the untreated group (n = 307), with a weighted incidence rate of 0.34% (95%CI: 0.23-0.52%), compared to 63 cases among SVR patients (n = 1111), with an incidence rate of 0.20% (95%CI: 0.16-0.26%). The 12-, 24-, and 36-month HCC weighted cumulative incidence rates were 6.7%, 8.4%, and 10.0% in untreated cases and 2.3%, 4.5%, and 7.0% in the SVR group. Considering death or liver transplantation as competing events, the untreated group showed a 64% higher risk of HCC incidence compared to SVR patients (SubHR 1.64, 95%CI: 1.02-2.62). Other variables independently associated with the HCC occurrence were male sex, increasing age, current alcohol use, HCV genotype 3, platelet count ≤ 120,000/μL, and albumin ≤ 3.5 g/dL. In real-life practice, the high efficacy of DAA in achieving SVR is translated into high effectiveness in reducing the HCC incidence risk.

Rageliene, T, A Schneider-Kamp and ST Askegaard (2024). "**Barriers and facilitators of prevention of infections related to cancer: A systematic literature review - PubMed**" Heliyon **10**(19): e37959. (https://www.ncbi.nlm.nih.gov/pubmed/39386850)

Chronic infections such as Helicobacter pylori (Hp), Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human papillomavirus (HPV) are a major cause of gastric, liver, and HPV-related cancers that contribute significantly to the global burden of human cancers. Infections related to cancers can be prevented by preventing infection through vaccination, timely detection through screening, and eradication of the underlying infections. These strategies have proven effective in different countries, but the participation rates of vaccination, screening, and eradication programs for Hp, HCV, and HPV are less than optimal. Research has shown that participation rates are influenced by various social, cultural, economic, and personal barriers and facilitators. To uncover the current evidence and enhance the understanding of the factors of prevention of infections related to cancer, we conducted a systematic literature review of such barriers and facilitators. We searched Web of Science, PubMed, and Scopus databases to identify relevant original articles published between 2013 and 2023. After screening 685 articles, a total of 23 studies were included for full-text analysis. Most of the studies analyzed factors related to the prevention of HBV, HPV, and HCV infections, while there was a relative lack of studies for Hp infections. Vaccination as a prevention measure of infections related to cancer was analyzed in most of the studies, followed by screening and treatment. We found several personal, social, economic, and cultural factors that act as barriers to the prevention of infections related to cancer and classified and connected these barriers and facilitators through the prism of health capital. Knowledge about the barriers that influence individuals' engagement with prevention measures of infections related to cancer has the potential to inform and guide health policymakers by targeting vulnerable populations through effective educational programs and improvements to the quality of healthcare services.

Roma, K, TM Chandler, Z Dossaji, A Patel, K Gupta, CD Minacapelli, V Rustgi and R Gish (2024). "**A Review of the Systemic Manifestations of Hepatitis B Virus Infection, Hepatitis D Virus, Hepatocellular Carcinoma, and Emerging Therapies**." Gastro Hep Adv **3**(2): 276-291.

Chronic hepatitis B virus (HBV) infection affects about 262 million people worldwide, leading to over 820,000 deaths each year primarily due to cirrhosis and hepatocellular carcinoma. The World Health Organization has pledged to eliminate HBV as a health threat by 2030, but currently, no countries are on track to achieve this goal. One of the barriers to HBV elimination is stigma, causing shame, denial, self-isolation, self-rejection, and depression leading to those with chronic HBV less likely to get tested or seek treatment and more likely to conceal their infection. Other barriers include limited access to care and complicated and restrictive clinical practice guidelines. Increasing public and political efforts are necessary to raise awareness, increase access to care, and change screening and treatment guidelines. The current guidance of the American Association for the Study of Liver Diseases (AASLD) recommends testing only if patients are considered at risk, but this has proven to be ineffective. We propose a simplified

"test all and treat all" approach with a 5-line guideline for HBV infection. Universal screening and treatment of adults is cost-effective and can prevent transmission by effectively managing chronic HBV. All patients who are hepatitis B surface antigen (HBsAg) positive with detectable HBV-DNA should receive treatment until HBsAg is undetectable for 12 months, as HBV-DNA transmission via blood transfusion can occur even at low viral loads of 16 copies/mL, and mother-to-child transmission is still a risk even with passive-active immunoprophylaxis. Furthermore, clinical outcomes after HBsAg clearance are significantly better than the clinical outcomes of those who remain HBsAg positive.

Shin, H, WM Choi, SU Kim, Y Ko, Y Park, J Park, MH Hur, MK Park, YB Lee, YJ Kim, JH Yoon, JH Lee and F Zoulim (2024). "**Lack of association between early on-treatment HBeAg seroclearance and development of hepatocellular carcinoma or decompensated cirrhosis.**" JHEP Rep **6**(7): 101089.

BACKGROUND & AIMS: The association between hepatitis B envelope antigen (HBeAg) seroclearance during long-term nucleos(t)ide analogue (NA) treatment and the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) remains unclear. Here, we aimed to investigate the association of HBeAg seroclearance during potent NA treatment with the development of HCC and decompensated cirrhosis. METHODS: Using a multicenter historical cohort including 2,392 non-cirrhotic adult patients with HBeAg-positive CHB who initiated NA treatment with tenofovir or entecavir, the risk of HCC and decompensated cirrhosis was compared between patients who achieved HBeAg seroclearance within 36 months of NA treatment (the HBeAg-loss group) and those who did not (the HBeAg-maintained group), using inverse probability of treatment weighting. RESULTS: Over a median of 6.6 years of NA treatment, 1,077 patients achieved HBeAg seroclearance (HBeAg loss rate = 6.0 per 100 person-years), 64 patients developed HCC (HCC incidence rate = 0.39 per 100 person-years), and 46 patients developed decompensated cirrhosis (decompensation incidence rate = 0.28 per 100 person-years). The HBeAg-loss and HBeAg-maintained groups had a similar risk of developing HCC (hazard ratio 0.89; 95% CI 0.47-1.68; p = 0.72) and decompensated cirrhosis (hazard ratio 0.98; 95% CI 0.48-1.81; p = 0.91). Compared with delayed HBeAg seroclearance beyond 10 years of NA treatment, the risk of HCC was comparable in those who achieved earlier HBeAg seroclearance at any time point within 10 years, regardless of baseline age and fibrotic burden. CONCLUSIONS: Early HBeAg seroclearance during NA treatment was not associated with a reduced risk of development of HCC or decompensated cirrhosis in non-cirrhotic HBeAg-positive patients with CHB. IMPACT AND IMPLICATIONS: The association between hepatitis B envelope antigen (HBeAg) seroclearance during long-term nucleos(t)ide analogue treatment and the risk of hepatocellular carcinoma in patients with chronic hepatitis B remains unclear. Our findings indicate that early on-treatment HBeAg seroclearance within 3 years was not associated with the development of hepatocellular carcinoma or decompensated cirrhosis. Achieving HBeAg seroclearance may not be an appropriate surrogate endpoint for preventing the development of liver-related outcomes in non-cirrhotic patients with HBeAg-positive chronic hepatitis B treated with nucleos(t)ide analogues.

Surguladze, S, PA Armstrong, GA Beckett, S Shadaker, A Gamkrelidze, M Tsereteli, V Getia and BO Asamoah (2024). "**Hepatitis C virus attributable liver cancer in the country of Georgia, 2015-2019: a case-control study**." BMC Infect Dis **24**(1): 1045.

BACKGROUND: Hepatitis C virus (HCV) infection can lead to a type of primary liver cancer called hepatocellular carcinoma (HCC). Georgia, a high HCV prevalence country, started an HCV elimination program in 2015. In addition to tracking incidence and mortality, surveillance for the HCV-attributable fraction of HCC is an important indicator of the program's impact. This study assesses HCV infection-attributable HCC in the Georgian population. METHODS: This case-control study utilized HCV programmatic and Georgian Cancer Registry data from 2015-

2019. Bivariate logistic regression and age- and sex-stratified analyses assessed HCV and liver cancer association. HCV-attributable liver cancer proportions for the HCV-exposed and total population were calculated. A sub-analysis was performed for HCC cases specifically. RESULTS: The total study population was 3874 with 496 liver cancer cases and 3378 controls. The odds for HCV-infected individuals developing liver cancer was 20.1 (95% confidence interval [CI] 15.97-25.37), and the odds of developing HCC was 16.84 (95% CI 12.01-23.83) compared to the HCV-negative group. Odds ratios varied across strata, with HCV-infected older individuals and women having higher odds of developing both liver cancer and HCC. A large proportion of liver cancer and HCC can be attributed to HCV in HCV-infected individuals; however, in the general population, the burden of liver cancer and HCC cannot be explained by HCV alone. CONCLUSION: HCV was significantly associated with a higher risk of developing liver cancer and HCC in the Georgian population. In addition, given Georgia's high HCV burden, increased HCC monitoring in HCV-infected patients is needed.

Tourkochristou, E, M Kalafateli, C Triantos and I Aggeletopoulou (2024). "**Evaluation of PAGE-B Score for Hepatocellular Carcinoma Development in Chronic Hepatitis B Patients: Reliability, Validity, and Responsiveness**." Biomedicines **12**(6).

Chronic hepatitis B (CHB) constitutes a major global public health issue, affecting millions of individuals. Despite the implementation of robust vaccination programs, the hepatitis B virus (HBV) significantly influences morbidity and mortality rates. CHB emerges as one of the leading causes of hepatocellular carcinoma (HCC), introducing a major challenge in the effective management of CHB patients. Therefore, it is of utmost clinical importance to diligently monitor individuals with CHB who are at high risk of HCC development. While various prognostic scores have been developed for surveillance and screening purposes, their accuracy in predicting HCC risk may be limited, particularly in patients under treatment with nucleos(t)ide analogues. The PAGE-B model, incorporating age, gender, and platelet count, has exhibited remarkable accuracy, validity, and reliability in predicting HCC occurrence among CHB patients receiving HBV treatment. Its predictive performance stands out, whether considered independently or in comparison to alternative HCC risk scoring systems. Furthermore, the introduction of targeted adjustments to the calculation of the PAGE-B score might have the potential to further improve its predictive accuracy. This review aims to evaluate the efficacy of the PAGE-B score as a dependable tool for accurate prediction of the development of HCC in CHB patients. The evidence discussed aims to provide valuable insights for guiding recommendations on HCC surveillance within this specific population.

Vargas-Accarino, E, M Higuera, M Buti and B Minguez (2024). "**Hepatitis-C-Related Hepatocellular Carcinoma, Still a Relevant Etiology beyond a Hepatitis C Infection Cure**." Cancers (Basel) **16**(8). (https://www.ncbi.nlm.nih.gov/pubmed/38672603)

BACKGROUND: In the past decades, global changes, including hepatitis B vaccination, hepatitis B and C antiviral therapies, and the increasing prevalence of steatotic liver disease, have influenced the landscape of liver cancer etiologies. METHODS: We performed a retrospective study focused on the etiological factors of de novo hepatocellular carcinoma (HCC) diagnoses in an academic center between 2019 and 2022. RESULTS: Among 352 consecutive patients with HCC, alcohol-related liver disease was the predominant etiology (33.3%), followed by hepatitis C (HCV) infection (30.7%). Significant associations were found between HCC etiology and patient demographics, BCLC stage at diagnosis, and cirrhosis prevalence. CONCLUSIONS: Whereas accessibility to antiviral therapy is granted, HCV infection remains as one of the main HCC etiologies. MASLD-related HCC, although growing globally, is not as relevant in our area. Strong public policies need to be implemented to prevent alcohol consumption, the main etiology of liver disease and liver cancer.

Vuković, MN, M Jakšić, D Stojanović and B Smolović (2024). "**Time trends in liver cancer mortality rates in Montenegro from 1990 to 2018.**" Eur J Gastroenterol Hepatol **36**(5): 622-627.

OBJECTIVE: Liver cancer is the third most common cause of cancer-related deaths worldwide. Hepatitis B and C infections are the main factors affecting mortality. During recent years, Montenegro conducted activities on eradication of viral hepatitis according to the global strategy for the primary prevention of liver cancer mortality. The objective of this study was to assess the liver cancer mortality trend in Montenegro for the period of 1990-2018 using regression techniques. METHODS: liver cancer mortality data in Montenegro from 1990 to 2018 were collected. Mortality rates were age standardized to the World Standard Population. The joinpoint, linear and Poisson regressions were used to assess liver cancer mortality trends both overall and gender specific. RESULTS: The mortality trend was constant, with no significant increase or decrease in mortality rates both at the overall level and by gender. The number of cases, however, increases significantly at the overall level by an average of 1.4% per year [average annual percentage change (AAPC) (95% confidence interval, CI): 1.4 (0.5-2.3); P = 0.004] and in women by 1.9% per year [AAPC (95% CI): 1.9 (0.8-3.1); P = 0.002]. In men, there was no change in the number of cases. The three age groups most burdened by mortality from liver cancer were 65-74 (34.9%), 75-84 (26.6%) and 55-64 (25.8%). CONCLUSION: The consistent implementation of prevention measures and hepatitis virus infection treatment has played a role in partially favorable liver cancer mortality trends in Montenegro. It is crucial to closely monitor guidelines for this cancer and give particular attention to the elderly population as the most affected.

Zheng, J, X Li, AM Masci, H Kahn, A Huffman, E Asfaw, Y Pan, J Guo, V He, J Song, AI Seleznev, AY Lin and Y He (2024). "**Empowering standardization of cancer vaccines through ontology: enhanced modeling and data analysis**." J Biomed Semantics **15**(1): 12.

BACKGROUND: The exploration of cancer vaccines has yielded a multitude of studies, resulting in a diverse collection of information. The heterogeneity of cancer vaccine data significantly impedes effective integration and analysis. While CanVaxKB serves as a pioneering database for over 670 manually annotated cancer vaccines, it is important to distinguish that a database, on its own, does not offer the structured relationships and standardized definitions found in an ontology. Recognizing this, we expanded the Vaccine Ontology (VO) to include those cancer vaccines present in CanVaxKB that were not initially covered, enhancing VO's capacity to systematically define and interrelate cancer vaccines. RESULTS: An ontology design pattern (ODP) was first developed and applied to semantically represent various cancer vaccines, capturing their associated entities and relations. By applying the ODP, we generated a cancer vaccine template in a tabular format and converted it into the RDF/OWL format for generation of cancer vaccine terms in the VO. '12MP vaccine' was used as an example of cancer vaccines to demonstrate the application of the ODP. VO also reuses reference ontology terms to represent entities such as cancer diseases and vaccine hosts. Description Logic (DL) and SPARQL query scripts were developed and used to query for cancer vaccines based on different vaccine's features and to demonstrate the versatility of the VO representation. Additionally, ontological modeling was applied to illustrate cancer vaccine related concepts and studies for in-depth cancer vaccine analysis. A cancer vaccine-specific VO view, referred to as "CVO," was generated, and it contains 928 classes including 704 cancer vaccines. The CVO OWL file is publicly available on: http://purl.obolibrary.org/obo/vo/cvo.owl , for sharing and applications. CONCLUSION: To facilitate the standardization, integration, and analysis of cancer vaccine data, we expanded the Vaccine Ontology (VO) to systematically model and represent cancer vaccines. We also developed a pipeline to automate the inclusion of cancer vaccines and associated terms in the VO. This not only enriches the data's standardization and integration,

but also leverages ontological modeling to deepen the analysis of cancer vaccine information, maximizing benefits for researchers and clinicians. AVAILABILITY: The VO-cancer GitHub website is: https://github.com/vaccineontology/VO/tree/master/CVO.

Zovich, B, SJ Block, F Borondy-Jenkins, T Chen, K Moraras, J Afoakwah, M Dong and C Cohen (2024). "**The Role of Culturally Appropriate Mediated Communication Strategies to Reduce Hepatitis B and Liver Cancer Disparities.**" J Health Commun **29**(7): 440-449. (https://www.ncbi.nlm.nih.gov/pubmed/38832597)

Asian, Pacific Islander, African, and Caribbean communities in the U.S. are heavily impacted by chronic hepatitis B (HBV) and hepatocellular carcinoma (HCC). Educating these groups about the link between the two diseases is imperative to improve screening rates and health outcomes. This study aims to identify and incorporate preferred mediated communication methods into community-specific educational campaigns which emphasize the connection between the conditions, to promote uptake of prevention and management behaviors for HBV and HCC. Fifteen focus groups and two key informant interviews were conducted with Micronesian, Chinese, Hmong, Nigerian, Ghanaian, Vietnamese, Korean, Somali, Ethiopian, Filipino, Haitian, and Francophone West African communities. Data were analyzed using thematic coding and analysis. Findings demonstrate that all communities preferred materials be offered in both English and native languages and requested that materials highlight the connection between HBV and HCC. Delivery channel preferences and messaging themes varied by group. This study provides insight into community-specific preferences for learning about HBV and HCC. The findings can be used to design culturally and linguistically tailored, multi-platform, health education campaigns to facilitate improved HBV screening and vaccination rates and increase knowledge about HCC risk among highly impacted communities in the U.S.

*2025*

Berenguer, J, T Aldámiz-Echevarría, V Hontañón, C Fanciulli, C Quereda, C Busca, L Domínguez, C Hernández, J Vergas, G Gaspar, LJ García-Fraile, C Díez, M De Miguel, JM Bellón, R Bañares and J González-García (2025). "**Clinical outcomes and prognostic factors after HCV clearance with DAA in HIV/HCV-coinfected patients with advanced fibrosis/cirrhosis.**" Hepatology **81**(1): 238-253.

BACKGROUND AND AIMS: We assessed long-term clinical outcomes and prognostic factors for liver disease progression after sustained viral response with direct-acting antivirals in patients coinfected with HIV/HCV with advanced fibrosis or cirrhosis. APPROACH AND RESULTS: A total of 1300 patients who achieved sustained viral response with direct-acting antivirals from 2014 to 2017 in Spain were included: 1145 with compensated advanced chronic liver disease (384 advanced fibrosis and 761 compensated cirrhosis) and 155 with decompensated cirrhosis. The median follow-up was 40.9 months. Overall, 85 deaths occurred, 61 due to non-liver non-AIDS-related causes that were the leading cause of death across all stages of liver disease. The incidence (95% CI) of decompensation per 100 person-years (py) was 0 in patients with advanced fibrosis, 1.01 (0.68-1.51) in patients with compensated cirrhosis, and 8.35 (6.05-11.53) in patients with decompensated cirrhosis. The incidence (95% CI) of HCC per 100 py was 0.34 (0.13-0.91) in patients with advanced fibrosis, 0.73 (0.45-1.18) in patients with compensated cirrhosis, and 1.92 (1.00-3.70) per 100 py in patients with decompensated cirrhosis. Prognostic factors for decompensation in patients with compensated advanced chronic liver disease included serum albumin, liver stiffness measurement (LSM), and fibrosis 4. In this population, LSM and LSM-based posttreatment risk stratification models showed their predictive ability for decompensation and HCC. CONCLUSIONS: Non-liver non-AIDS-related events were the leading causes of morbidity and mortality after direct-acting antiviral cure among coinfected patients with advanced fibrosis/cirrhosis. Among those with compensated advanced chronic liver disease, baseline LSM and posttreatment LSM-based models helped to assess decompensation and HCC risk.

Eilard, A, J Ringlander, ME Andersson, S Nilsson, G Norkrans and M Lindh (2025). "**Long-Term Outcome of Chronic Hepatitis B-Histological Score and Viral Genotype Are Important Predictors of Hepatocellular Carcinoma.**" J Viral Hepat **32**(3): e70008.

Current guidelines to prevent hepatocellular carcinoma (HCC) by chronic hepatitis B virus (HBV) infection are based on risk assessments that include age, sex, and virological and biochemical parameters. The study aim was to investigate the impact of predictive markers on long-term outcomes. The clinical outcomes of 100 patients with chronic hepatitis B were investigated 30 years after a baseline assessment that included liver biopsy. A favourable outcome-HBsAg loss or HBeAg-negative infection (ENI; previously termed 'inactive carrier')-was observed in 74% of all patients, whereas 7% developed HCC. HBsAg loss was observed in 75% of patients with genotype A, compared with 42%, 33% and 0% with genotypes D, B and C, respectively ($p < 0.0001$). HCC developed in 3 patients (33%) with genotype C as compared with 3 (17%), 1 (2%) and 0 patients with genotypes B, D and A, respectively ($p < 0.0001$). In multiple logistic regression analysis, both HBsAg loss and HCC were associated with HBV genotype and baseline HBV DNA level, and HCC also with histological score. The results suggest that genotyping and histological assessment may improve outcome prediction and help decisions about HCC screening, particularly in populations with HBV-infected individuals of mixed geographic origin.

Giannini, EG, A Pasta, MC Plaz Torres, G Pieri, G Cabibbo, A Sangiovanni, F Piscaglia, C Campani, G Missale, G Vidili, G Ghittoni, F Pelizzaro, FG Foschi, F Morisco, V Santi, G Svegliati-Baroni, F Azzaroli, C Saitta, MR Brunetto, R Sacco, FR Ponziani, S Boninsegna, G Nardone, A Martini, A Mega, D Sacerdoti, D Magalotti, A Vitale, L Bucci and F Trevisani (2025). "**Absence of Viral Replication Is Associated With Improved Outcome in Anti-HCV-Positive Patients With Hepatocellular Carcinoma.**" Liver International **45**(2): e16185.

BACKGROUND AND AIMS: Presence of active hepatitis C virus (HCV) infection may influence the outcome of patients treated for hepatocellular carcinoma (HCC), although this issue has never been adequately assessed in a large series of patients. The aim of this study was to evaluate whether the presence of active HCV affects the survival of patients treated for HCC. METHODS: This study assessed the outcome of 3123 anti-HCV-positive patients with HCC, subdivided according to the presence of active HCV infection or previous sustained virological response (SVR). Comparisons were also carried out after propensity score matching (PSM) considering demographic, clinical and oncological characteristics. RESULTS: The median overall survival from HCC treatment was longer in patients with SVR than in those with active HCV infection both before ($n = 2118$: 61.0 months [95% confidence internal (CI): 56.5-65.5] vs. $n = 1005$: 51.0 months [95% CI: 43.4-58.6]; $p = 0.003$) and after PSM ($n = 1285$: 60.0 months [95% CI: 55.3-64.7] vs. $n = 926$: 54.0 months [95% CI: 46.7-61.3]; $p = 0.030$). Active HCV infection was associated with a greater risk of mortality (hazard ratio: 1.22-1.27, $p = 0.001$) independently of liver- and tumour-related variables, and modality of HCC treatment. Death due to liver failure was more common in patients with active HCV infection (24.5% vs. 17.1%; $p = 0.001$), while non-liver-related causes of death were more common in patients with SVR (25.0% vs. 17.0%; $p = 0.001$). CONCLUSIONS: SVR is associated with a better outcome in patients undergoing HCC treatment, thus suggesting that these patients may benefit from antiviral therapy for HCV independently of cure of HCC.

Lybeck, C, D Bruce, R Szulkin, S Montgomery, S Aleman and AS Duberg (2025). "**Long-term risk of HCC in a DAA-treated national hepatitis C cohort, and a proposed risk score.**" Infect Dis (Lond) **57**(3): 211-223.

BACKGROUND: The risk of hepatocellular carcinoma (HCC) remains elevated in cirrhotic hepatitis C patients with sustained virological response (SVR) after DAA treatment. We assessed long-term HCC risk stratified by pretreatment liver stiffness measurement (LSM) and

developed a risk score algorithm. METHODS: This register-based nationwide cohort study of 7,227 DAA-treated patients with SVR evaluated annual HCC incidence rates (IRs) and cumulative incidences stratified by pretreatment LSM. The association between LSM and HCC risk was analyzed using multivariate Cox regression. A risk score algorithm was developed and internally validated in 2,664 individuals with LSM >9.5 kPa, assigning each patient a score based on risk factors, proportionally weighted by the association with HCC risk. RESULTS: During a median follow-up of 1.8 years (3.2 years for LSM ≥12.5 kPa), 92 patients (1.3%) developed HCC. The IRs for LSM 9.5-12.4, 12.5-19.9 and ≥20 kPa were 0.21, 0.99 and 2.20 HCC/100 PY, respectively, with no significant risk reduction during follow-up. The HRs (and 95% CI) for LSM 9.5-12.5, 12.5-19.9 and ≥20 kPa are 1.19 (0.43-3.28), 4.66 (2.17-10.01) and 10.53 (5.26-21.08), respectively. Risk score models including FIB-4, alcohol, diabetes, age and LSM effectively stratified patients with LSM >9.5 kPa into low-, intermediate- and high-risk groups, with a Harrell's C of 0.799. Notably, 48% with LSM ≥9.5 kPa and 27% ≥12.5 kPa were classified as low-risk. CONCLUSION: Pretreatment LSM is associated with HCC risk, which remains stable during the initial five years post-SVR. The HCC risk score algorithm effectively identifies low-risk patients, who may not require HCC surveillance.

Mennini, FS, P Sciattella, C Simonelli, A Marcellusi, S Rosato and LA Kondili (2025). "**Long-Term Effects of Direct-Acting Antivirals on Hepatitis C: Trends in Liver Disease-Related Hospitalisations in Italy.**" J Viral Hepat **32**(2): e14061.

This study aimed to evaluate the effectiveness of direct-acting antivirals (DAAs) on hepatitis C virus (HCV) hospitalisation trends in Italy, the country with not only the highest burden of HCV-related disease but also the highest number of patients treated for chronic HCV infection in Europe. Incident hospital discharge records in Italy from 2012 to 2019 that included a liver cirrhosis diagnosis without mention of alcohol, hepatocellular carcinoma (HCC), HCV and liver cirrhosis without mention of alcohol and/or HCC, cirrhosis with mention of alcohol, as defined by the International Classification of Diseases (ICD-9-CM) were reviewed. An interrupted time series analysis compared the incidence of cirrhosis and HCC before and after the introduction of DAAs (Year 2015). Overall, non-alcoholic cirrhosis significantly decreased after the introduction of DAAs (β(3) = 0.03) and for those 40-59 years of age (β(3) = 0.025). HCV with cirrhosis and/or HCC significantly reduced overall for those aged 40-59 and older than 60 ( β3 = 0.002 ). HCC-related hospitalisation rates significantly decreased in patients younger than 60 ( β3 = 0.03 ). Cirrhosis-related hospitalisations with mention of alcohol did not differ during the study period before and after the year 2015 ( β3 = 0.4 ). There was a significant reduction in HCV-related hospitalisations throughout Italy after introducing DAAs.

Meszaros, M, MN Hilleret, J Dumortier, L D'Alteroche, A Abergel, M Latournerie, T Antonini, F Conti, P Borentain, S Dharancy and GP Pageaux (2025). "**Bulevirtide in Chronic Hepatitis D Patients Awaiting Liver Transplantation Results From a French Multicentric Retrospective Study.**" Liver International **45**(3): e70033.

BACKGROUND AND AIMS: The impact of bulevirtide in patients awaiting liver transplantation (LT) for decompensated liver disease and/or hepatocellular carcinoma (HCC) is unclear. We assessed clinical, virological, and biochemical responses to bulevirtide in patients with chronic hepatitis delta virus (HDV) awaiting LT and compared outcomes with a cohort of similar untreated patients. METHODS: Consecutive HDV-infected patients waiting for LT since bulevirtide approval were included. Patients receiving 2 mg of bulevirtide daily had clinical, biological, and virological data collected at baseline, Week 24, Week 48, at LT, and post-LT. Patients not receiving bulevirtide had data collected at baseline, LT, and post-LT for comparison. RESULTS: Forty-one patients from nine LT centers were included. In the bulevirtide group (20 patients; mean age 52.8 ± 9.98 years; 75% male), 65%, 10% and 25% were Child-Pugh A, B and C, respectively. Fifteen completed 48 weeks of therapy. At 48 weeks, median HDV RNA decreased by 2.56 log IU/mL (p = 0.004). Virological and biochemical

responses were obtained in 73.3% and 66.6% of patients. Twelve patients (60%) underwent LT. No serious adverse events occurred. Bulevirtide improved liver function, enabling one (7.1%) HCC patient to undergo chemoembolization while on the WL and leading to delisting of three (15%) other patients. In untreated patients (mean age 42.9 ± 7.9 years; 76.2% Child-Pugh C), none were delisted. Three-month transplant-free survival was 76.9% in the bulevirtide group versus 36.7% (p = 0.007) in the control group. CONCLUSIONS: Bulevirtide demonstrates safety and efficacy in HDV-infected patients listed on the LT waiting list and may potentially improve pre-transplant outcomes.

Singal, AG, KR Reddy, M Colombo, HL Morris, AR Mospan, R Cabrera, RK Kelley, RD Kilpatrick, F Trevisani, F Farinati, EG Giannini, N Mehta, MW Fried and B Sangro (2025). "**DAA-PASS: A Prospective Evaluation of HCC Recurrence After Direct Acting Antiviral Therapy.**" J Viral Hepat **32**(2): e14056.

Direct-acting antiviral (DAA) therapy is associated with a significant reduction in hepatocellular carcinoma (HCC) incidence among patients with cirrhosis, but data are conflicting about the risk of recurrence following DAA therapy. DAA-PASS was a prospective, pragmatic, observational study designed to estimate the risk of HCC recurrence associated with DAA therapy exposure during routine clinical care. Eligible patients were DAA treatment naive with Barcelona Clinic Liver Cancer (BCLC) stage A. Patients were followed at regular intervals for up to 24 months. To provide additional data, outcomes were compared to the Italian Liver Cancer Group (ITA.LI.CA) cohort. Of 42 patients enrolled, 24 were treated with DAA therapy. Ten HCC recurrence events were observed during the study, with 5 each in DAA-treated and DAA-untreated patients (cumulative incidences of 23 and 37 per 100 PY, respectively). The overall crude hazard ratio (HR) for HCC recurrence associated with DAA therapy was 0.6 (95% CI, 0.2-2.2). In the ITA.LI.CA cohort, HCC recurrence was observed in 193 patients during 24 months of follow-up, resulting in a cumulative incidence rate of 28 per 100 PY. Although limited by small sample size, this prospective study suggests DAA therapy is not associated with increased HCC recurrence risk among patients with a history of complete response to prior HCC therapy.

Singh, SP, T Madke and P Chand (2025). "**Global Epidemiology of Hepatocellular Carcinoma.**" J Clin Exp Hepatol **15**(2): 102446.

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and a significant global health challenge due to its high mortality rate. The epidemiology of HCC is closely linked to the prevalence of chronic liver diseases, the predominant etiology being hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol consumption, and metabolic disorders such as metabolic dysfunction-associated steatotic liver disease (MASLD). HCC incidence varies widely globally, with the highest rates observed in East Asia and sub-Saharan Africa. This geographic disparity is largely attributed to the endemicity of HBV and HCV in these regions. In Western countries, the incidence of HCC has been rising, driven by increasing rates of alcohol abuse and the presence of steatosis liver disease. MASLD-associated HCC has a higher body mass index, a higher rate of type 2 diabetes mellitus, hyperlipidemia, hypertension, and association with cardiovascular diseases. Steatosis-associated HCC is also known to develop in the absence of cirrhosis, unlike alcohol-related liver disease and viral hepatitis. Prevention strategies vary by region, focusing on vaccination against HBV, antiviral treatments for HBV and HCV, alcohol moderation, and lifestyle interventions along with weight reduction to reduce obesity and incidence of MASLD-related HCC incidence.

Toy, M, D Hutton, EE Conners, H Pham, JA Salomon and S So (2025). "**Cost-effectiveness of monitoring and liver cancer surveillance among patients with inactive chronic hepatitis B.**" PLoS One **20**(1): e0313898.

Patients with chronic hepatitis B infection (CHB) have an increased risk for death from liver cirrhosis and hepatocellular carcinoma (HCC). In the United States, only an estimated 37% of adults with chronic hepatitis B diagnosis without cirrhosis receive monitoring with at least an annual alanine transaminase (ALT) and hepatitis B deoxyribonucleic acid (DNA), and an estimated 59% receive antiviral treatment when they develop active hepatitis or cirrhosis. A Markov model was used to calculate the costs, health impact and cost-effectiveness of increased monitoring of adults with HBeAg negative inactive or HBeAg positive immune tolerant CHB who have no cirrhosis or significant fibrosis and are not recommended by the current American Association for the Study of Liver Diseases (AASLD) clinical practice guidelines to receive antiviral treatment, and to assess whether the addition of HCC surveillance would be cost-effective. For every 100,000 adults with CHB who were initially not recommended for treatment, if the monitoring rate increased from the current 37% to 90% and treatment rate increased from 59% to 80%, 4,600 cases of cirrhosis, 2,450 cases of HCC and 4,700 HBV-related deaths would be averted with a gain of 45,000 QALYs and a savings of $180 million in lifetime health care costs. At a willingness to pay threshold of $100,000/QALY, the addition of HCC surveillance with the standard recommended biannual liver ultrasound and alfa fetoprotein levels is likely cost-effective if the HCC risk ≥ 0.55%/year. Regular monitoring of persons with inactive or immune tolerant CHB who are initially not recommended to receive antiviral treatment in the United States is cost-saving. The addition of HCC surveillance with biannual US and AFP would be cost-effective for individuals with HCC incidence ≥ 0.55%/year.