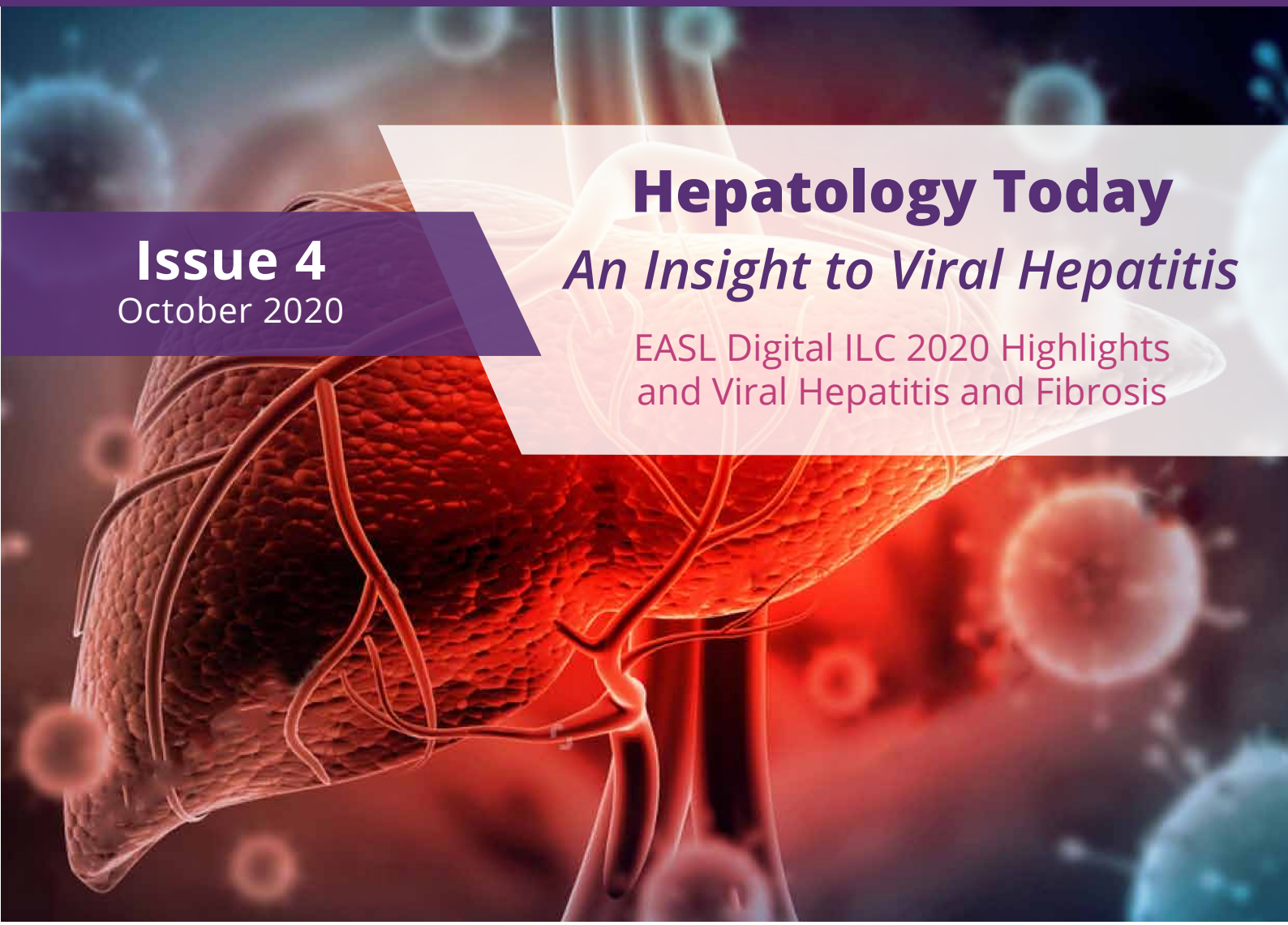

Hepatology Today

An Insight to Viral Hepatitis

EASL Digital ILC 2020 Highlights and Viral Hepatitis and Fibrosis

Issue 4
October 2020

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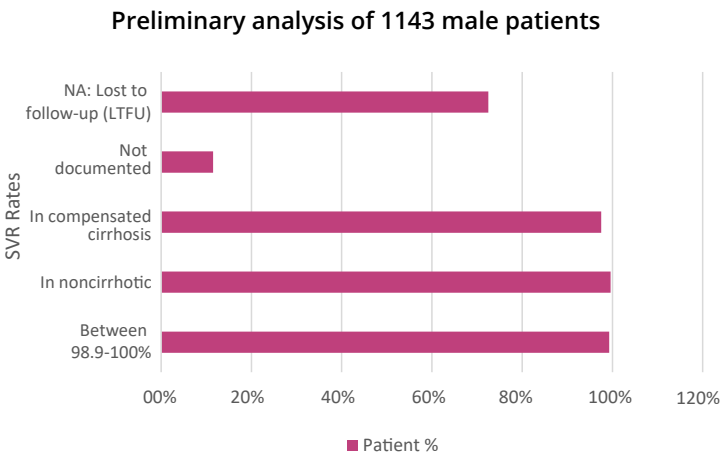
EASL Digital International Liver Congress 2020 Major Highlights and EASL-HCV Guidance

This issue mainly covers the latest updates and research findings, abstracts and poster presentations for diagnostics, treatment and management approaches for Viral Hepatitis, mainly hepatitis B virus (HBV) and hepatitis C virus (HCV) infections from the recent European Association for the Study of the Liver (EASL) Digital International Liver Congress (DLC) 2020 (August 27-29, 2020). It also incorporates the recent EASL Guidance for treatment of HCV and general management approach for hepatitis-related fibrosis.

Recent Updates in Diagnostics and Treatment Strategies in HCV

Effectiveness of sofosbuvir/velpatasvir in underserved patient populations

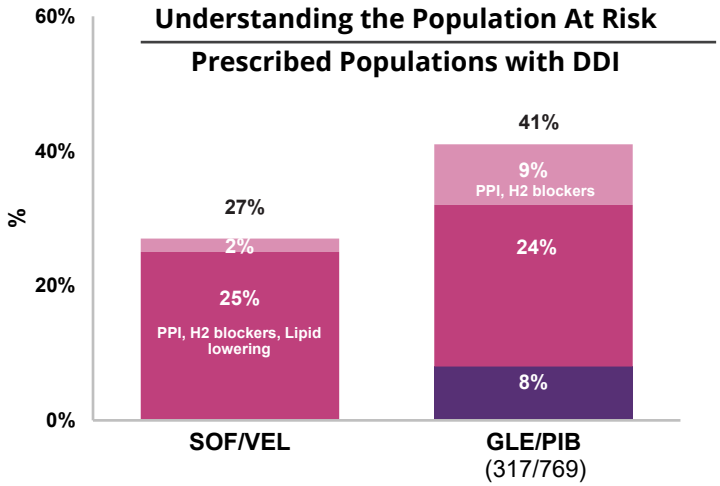
Integrated real-world analysis of Sofosbuvir /Velpatasvir (SOF/VEL) for 12 weeks in 1888 patients (incarcerated, homeless and/or with a mental health disorder) from 33 clinical cohorts from 9 countries (Australia, Belgium, Canada, France, Germany, Italy, Portugal, Spain, and the US).[1]

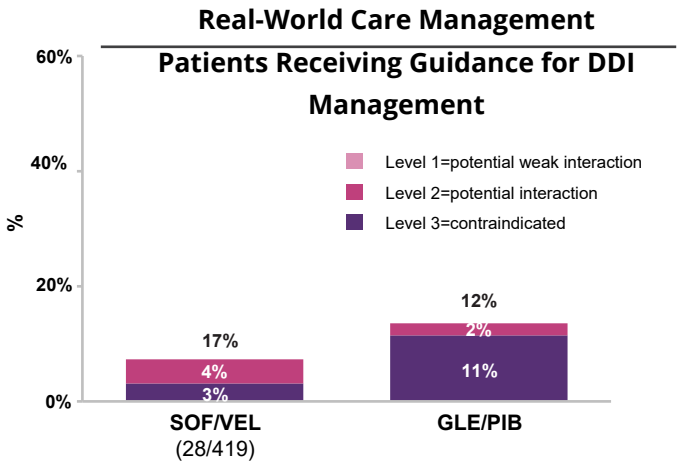


SOF/VEL (12 weeks): A well-tolerated treatment with high cure rates in traditionally challenging patient populations; allows test and treat strategy and decentralization of care, thus allowing lost to follow up (LTFU) reduction and elimination programs implementation

Drug-drug interactions (DDIs) with pangenotypic direct-acting antivirals (DAAs) in HCV: Populations at risk and real-world care management

To determine the rate of potential DDIs with DAAs in the US population and describes recommendation and course of action.[2]





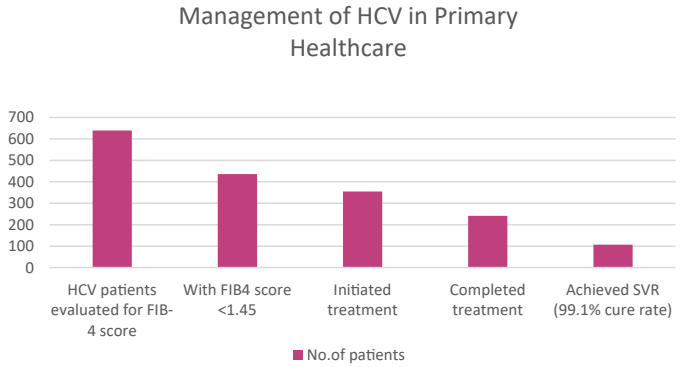
Abbreviations: DDIs, Drug□drug interactions; DAAs, direct-acting antivirals; PPI, proton pump inhibitors; SOF/VEL, Sofosbuvir/Velpatasvir; GLE/PIB, Glecaprevir/Pibrentasvir.

DDIs are more frequent with protease inhibitor-containing regimens. Pharmacists guidance is more frequently needed with protease inhibitor-containing regimens

Management of hepatitis C in primary healthcare (PHC) in Georgia

To evaluate feasibility and effectiveness of To evaluate care to HCV treatment-naïve patients (no or mild fibrosis [FIB-4 score <1.45]). The ECHO telemedicine model was used to train and support PHC providers.

Treatment: Sofosbuvir/Ledipasvir and/or SOF/VEL for 12 weeks.[3]

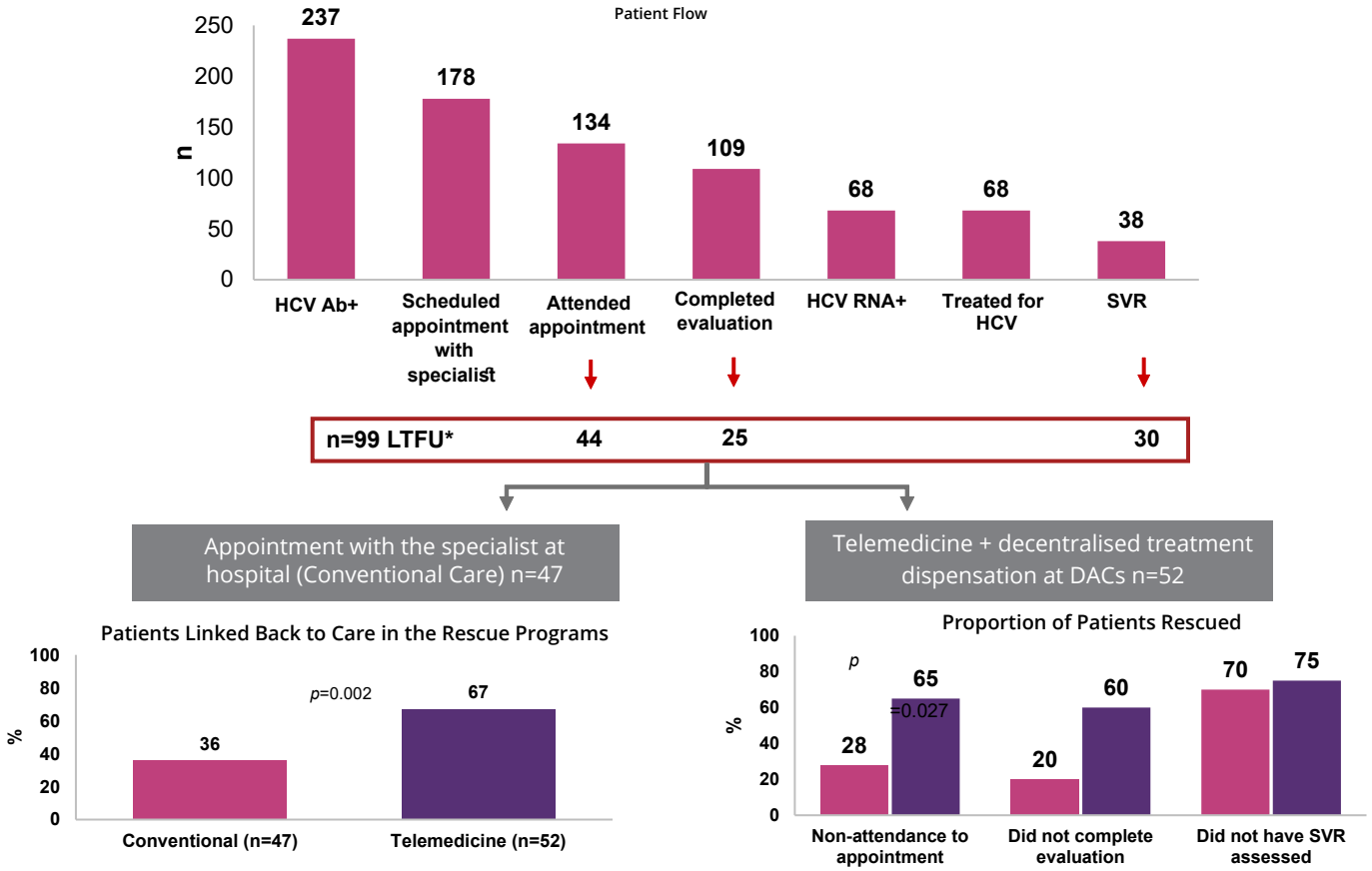


Abbreviations: HCV: Hepatitis C Virus; ECHO: Extension for Community Healthcare Outcomes; PHCs: Primary Healthcare; SOF/VEL: Sofosbuvir/Velpatasvir; SVR: sustained virology response.

Feasibility and effective model ensure continued HCV care and high rates of treatment and elimination

Telemedicine and decentralized treatment to rescue lost to follow-up HCV patients

To evaluate if feasibility and effectiveness of telemedicine linked to a decentralized dispensation of HCV treatment to rescue lost to follow up (LTFU) patients.[4]

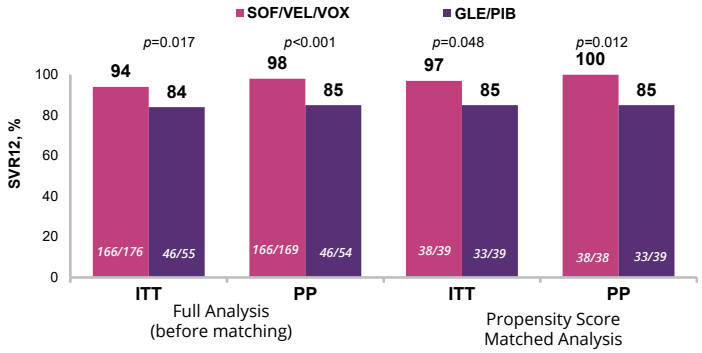


Abbreviations: LTFU, Lost to Follow-up; DAC, drug addiction center; DBS, dried blood spot testing.
*Patients rescued from LTFU included patients who did not attend the appointment with the specialist at the hospital (n=44), patients who did not receive treatment after evaluation (n=25), and patients without SVR visit (n=30)

Combining telemedicine with a decentralized model of care in drug addiction centers is effective to rescue HCV patients previously LTFU

Evaluation of SOF/VEL/VOX and GLE/PIB after Failure with HCV DAA treatment

To evaluate the pangenotypic therapies glecaprevir-pibrentasvir (GLE/PIB or G-P) and sofosbuvir-velpatasvir-voxilaprevir (SOF/VEL/VOX or S-V-V) after failure with interferon-free DAA for HCV treatment.[5]



Failure to achieve SVR
SOF/VEL/VOX: VF (3/10 or 3/176 [2%]), D/C (4/10), death (2/10), LTFU (1/10)
GLE/PIB: VF (8/9 or 8/55 [15%]), D/C (1/9)

Abbreviations: GLE/PIB, glecaprevir-pibrentasvir; SOF/VEL, sofosbuvir-velpatasvir-voxilaprevir; eGFR - Estimated glomerular filtration rate; GT, Genotype; FIB, Fibrosis score; LDV/SOF, Ledipasvir/Sofosbuvir; SVR, sustained virologic response.

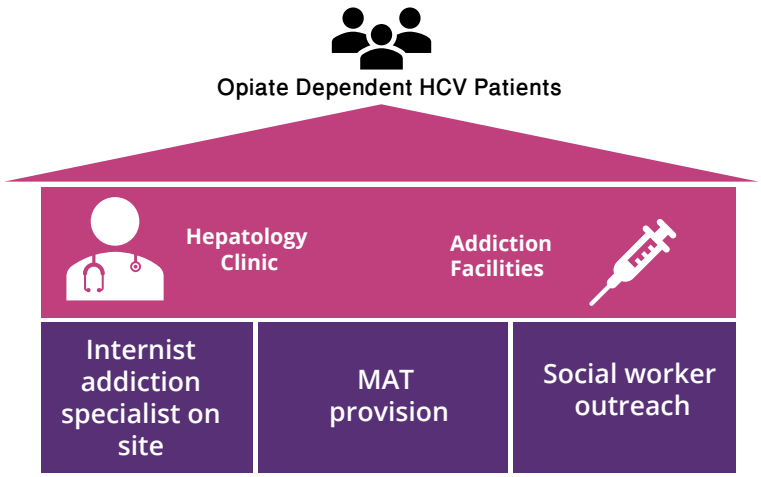
DAA failure patients, SOF/VEL/VOX achieved significantly higher SVR rates compared to GLE/PIB, both before and after adjustment for clinical difference

Recent Updates on Micro-elimination of HCV

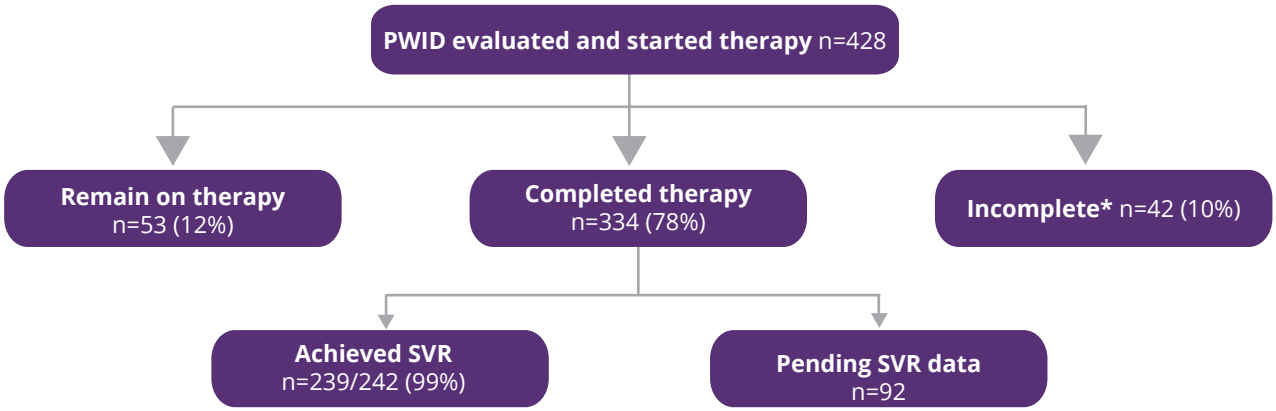
Managing HCV in people who inject drugs (PWID) using the internist-addiction medicine-hepatology (IAHC) model to achieve HCV micro-elimination

To evaluate the opiate-dependent patients for HCV infection using IAHC, an integrated, co-located program.[6]

IAHC Colocalization Model



Outcomes



*Incomplete included: n=15 LTFU, n=8 achieved SVR despite incomplete regimen, n=19 no data

Abbreviations: IAHC, Internist-addiction medicine-hepatology; PWID, People who inject drugs; SVR, sustained virologic response; MAT, Medication-assisted treatment.

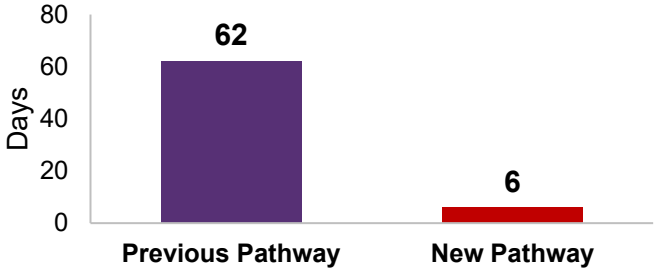
A co-located program such as the IAHC model is an effective strategy for HCV microelimination in PWID, resulting in improved treatment uptake and high SVR rates

Rapid test and treat program facilitating HCV micro-elimination in a prison

To develop a 'Rapid Test & Treat (RT&T)' program in a woman's prison to increase testing, initiation, and completion of treatment.[7]

Rapid HCV care pathway using Cepheid HCV GeneXpert testing for opt-out screening at entry, followed by treatment with pan-genotypic DAA

Median Time from Testing to Treatment



Previous Pathway

- First **24 hours in a "reception area"** upon arrival
- **Initial healthcare check within 24 hours**, no opt-out HCV test
- **Formal healthcare check** (+ opt-out HCV test)
- Results communicated and **referral to specialist**
- **Specialist review**
- **HCV treatment start**

Approx. 2 weeks

Approx. 6 weeks

Approx. 2-3 months

New Pathway

- First 24 hours in a "reception area" upon arrival
- **Full healthcare check,** including opt-out rapid HCV test
- Results communicated within 24h
- On-line multidisciplinary team starts patient on pan-genotypic regimen
- Medications issued and provided.

Within 24 hours

Aim for Within 5 Days

Opt-out point-of-care testing at prison entry is feasible and markedly increases testing and treatment, with time to treatment start less than 1 week

Latest EASL Guidance for Treatment of HCV

Recent final update from the EASL Guidance on treatment of HCV intends to assist healthcare providers, patients, and others in the clinical decision-making and describes the optimum management of patients with HCV infections.[8]

- Treatment initiation without delay in treatment-naïve or treatment-experienced patients with recently acquired or chronic HCV infection (A1)
- Immediate treatment for patients with significant fibrosis (F2-F4), cirrhosis (compensated and decompensated), clinically significant extrahepatic manifestations; HCV recurrence post liver transplant; Rapid evolution risk of liver disease due to concurrent comorbidities; and in individuals at risk of transmitting HCV(PWID, homeless, prisoners, rural communities, migrants, mentally disabled, people wt substance use, sex workers, men having sex with men (MSM) and indigenous population) (A1)
- Treatment not recommended in patients with limited life expectancy due to non-liver-related comorbidities (B2)

Considerations for Treatment Regimens

- Simplified, genotyping-/subtyping-free pangenotypic treatment is recommended to increase access to HCV treatment and increase cure rates globally in a setting where genotype and subtype determination is unavailable, unaffordable and/or would limit access to therapy (A1)
- Pre-treatment assessment can include detecting the presence of HCV viremia and the presence or absence of cirrhosis using a non-invasive method (A1)
- All Possible DDIs should be thoroughly checked and dose modifications should be implemented where necessary (A1)
- Testing for sustained virologic response (SVR) in 12 weeks (SVR12) can be limited to cases of high-risk behaviors and risk of reinfection (B1)

Genotype/subtype Determination-based Treatment

<table>
<tr><th>Genotype</th><th>Cirrhosis status</th><th>Treatment History</th><th>SOF/VEL/VOX</th><th>GLE/PIB (weeks)</th><th>SOF/VEL/VOX (weeks)</th><th>GZR/EBR (weeks)</th></tr>
<tr><td rowspan="4">GT 1a, 1b, 2, 4, 5, 6</td><td rowspan="2">NC</td><td>T-n</td><td rowspan="4">12</td><td rowspan="2">8</td><td rowspan="3">No</td><td rowspan="3">12 (GT 1b only)</td></tr>
<tr><td>T-e</td></tr>
<tr><td rowspan="2">CC (CTP A)</td><td>T-n</td></tr>
<tr><td>T-e</td><td>12</td></tr>
<tr><td rowspan="4">GT 3</td><td rowspan="2">NC</td><td>T-n</td><td rowspan="2">12</td><td>8</td><td rowspan="2">No</td><td rowspan="4">No</td></tr>
<tr><td>T-e</td><td>12</td></tr>
<tr><td rowspan="2">CC (CTP A)</td><td>T-n</td><td rowspan="2">12 + weight-based RBV†</td><td>8–12 ‡</td><td rowspan="2">12 †</td></tr>
<tr><td>T-e</td><td>16</td></tr>
<tr><td rowspan="4">Subtype 1l, 4r, 3b, 3g, 6u, 6v or any other subtype naturally harboring one or several NS5A RASs§</td><td rowspan="2">NC</td><td>T-n</td><td rowspan="4">Unknown</td><td rowspan="4">Unknown</td><td rowspan="4">12</td><td rowspan="4">No</td></tr>
<tr><td>T-e</td></tr>
<tr><td rowspan="2">CC (CTP A)</td><td>T-n</td></tr>
<tr><td>T-e</td></tr>
</table>

Abbreviations: NC, No cirrhosis; CC, Compensated cirrhosis; T-n, Treatment-naïve; T-e, Treatment-experienced; CTP, Child–Turcotte–Pugh; EBR, elbasvir; GLE, glecaprevir; GT, genotype; GZR, grazoprevir; PEG-IFN, pegylated interferon; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

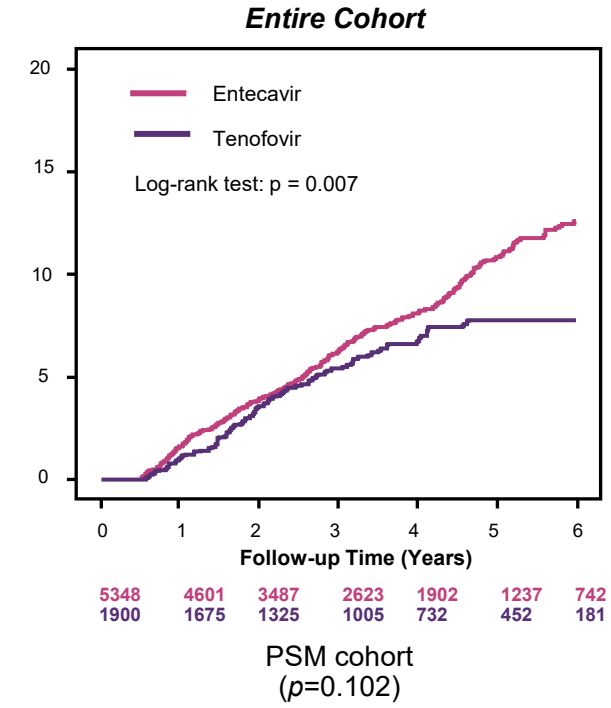
Treatment-experienced defined as previously treated with PEG-IFN + RBV; SOF + PEG-IFN + RBV; or SOF + RBV.
†If resistance testing is performed, only patients with the NS5A Y93H RAS at baseline should be treated with SOF/VEL + RBV or with SOF/VEL/VOX, whereas patients without the Y93H RAS should be treated with SOF/VEL alone;
‡In treatment-naïve patients infected with GT 3 with compensated (CTP A) cirrhosis, treatment with GLE/PIB can be shortened to 8 weeks, but more data are needed to consolidate this recommendation;
§As determined by sequence analysis of the NS5A region by means of population sequencing or deep sequencing (cut-off 15%).

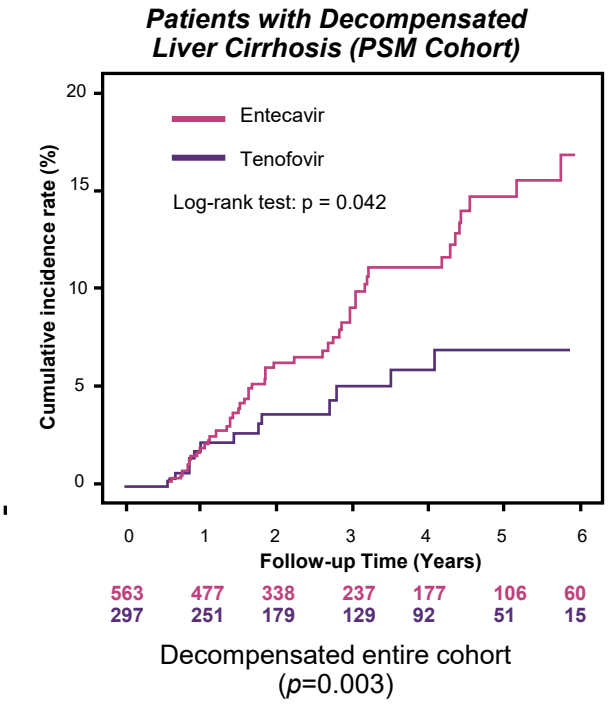
Recent Updates in HBV

Long-term risk of primary liver cancers in tenofovir disoproxil fumarate vs. entecavir treatment in CHB

To compare the long-term risk of tenofovir disoproxil fumarate (TDF) and entecavir (ETV) treatment on primary liver cancers (HCC and intrahepatic cholangiocarcinoma [CCC]) in chronic hepatitis B (CHB) patients from a database analysis of 7,248 patients in Taiwan.[9]

Cumulative Incidence of HCC





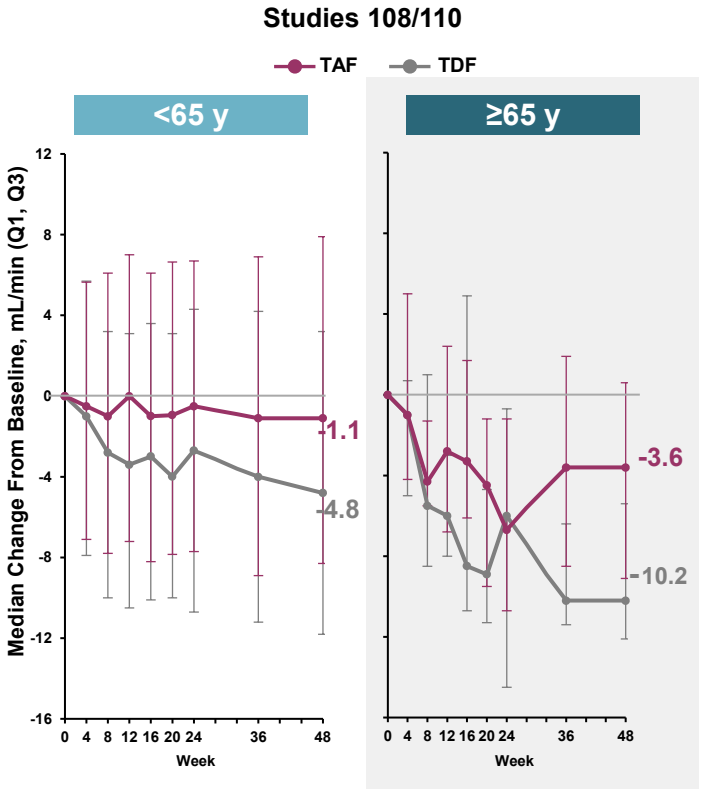
Abbreviations: ETV, Entecavir; TDF, Tenofovir disoproxil fumarate; SD, Standard deviation; NUC, Nucleos(t)ide analogue; HCC, Hepatocellular carcinoma.

Risk of HCC was lower with TDF in patients with decompensated liver cirrhosis

Safety and Efficacy of tenofovir alafenamide in geriatric patients with CHB

To study the efficacy of tenofovir alafenamide (TAF) as first line treatment for a subset of geriatric CHB patients.[10]

Geriatric patients (aged ≥65 years) were more likely to have history of cirrhosis and an increased incidence of comorbidities, evidence of bone loss, and reduced renal function



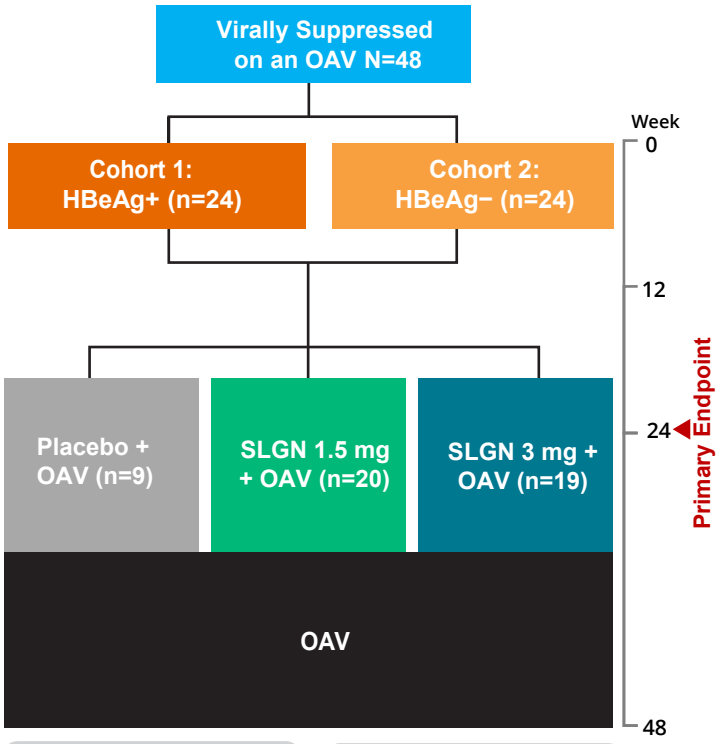
Abbreviations: TAF, Tenofovir alafenamide; TDF, Tenofovir disoproxil fumarate; eGFR - Estimated glomerular filtration rate

Consistent with advanced age, declines in $eGFR_{CG}$ were greater in geriatric vs nongeriatric patients, but smaller for TAF vs TDF treatment in both age subgroups

Safety of TAF in Geriatric Patients with CHB: No new safety signals or concerns were seen

Efficacy and safety of 24 weeks treatment with ral toll-like receptor 8 (TLR8) agonist, selgantolimod, in CHB patients: A phase 2 study

To evaluate the safety and tolerability of selgantolimod at Week 24 in virally suppressed adult patients with CHB and patients with ≥1.0-log_{10} IU/mL Hepatitis B surface antigen (HBsAg) decline from baseline at Week 24.[11]



5% (2/39) SLGN-treated patients achieved HBsAg loss

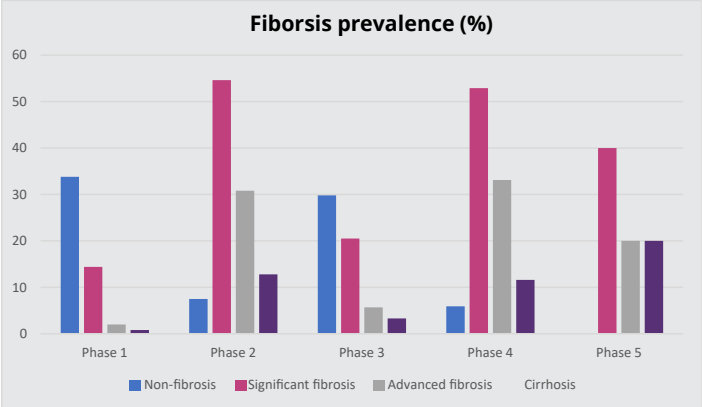
16% (3/19) HBeAg-positive SLGN-treated patients achieved HBeAg loss

Abbreviations: OAV, Oral antiviral; HBsAg, Hepatitis B surface antigen; HBeAg, Hepatitis B e antigen; SLGN, Selgantolimod.

Selgantolimod (up to 3 mg once weekly for 24 weeks) was well tolerated. Selgantolimod (24 weeks) achieved modest decline in HBsAg levels from baseline (sustained off-treatment for 24 weeks at week 48)

Recent Updates in Chronic Hepatitis-related Fibrosis

Prevalence of fibrosis (non-fibrosis [NF], significant fibrosis [SF], advanced fibrosis [AF], and cirrhosis) in 9,718 CHB adults from 13 countries (Asia, Europe US, and Africa).[12]



Risk of fibrosis persists through CHB natural course

Viral Hepatitis and Liver Fibrosis

The World Health Organization (WHO) Eastern Mediterranean region had an estimated prevalence of HBV and HCV infections as 3.3% and 2.3%, respectively in 2015. HBV and HCV have resulted into 887,000 (2015) and 399,000 (2016) deaths, mostly because of cirrhosis and hepatocellular carcinoma (HCC).[13,14]

The degree of liver fibrosis (LF) or finally cirrhosis is an independent factor leading to mortality in chronic hepatitis patients, with higher 1-year mortality rates in those with severe cirrhosis than in patients with early-stage LF. About 10–17% liver cirrhosis patients develop HCC in 5 years.[15,16]

In patients with HBV-HCV co-infection, the incidence of fibrosis progression to cirrhosis is found to be higher as compared to HCV monoinfection.[17]

Diagnosis, Evaluation and Management of Liver Fibrosis in Hepatitis Patients

Table 1 shows the evidence-based cut-off references of LF in HBV and HCV infection.[18-20]

Table 1: Cut-off values for LF in HBV and HCV

HBV	F0-FI <6.0	Significant fibrosis ≥9.0
	F2 >6.0	
	F3 ≥9.0	Cirrhosis ≥11.7
	F4 ≥12.0	
HCV (HCV and HIV)	F0-F1 ≤7.0 (≤7.0)	Significant fibrosis >7.3
	F2 >7.0 (≤10.0)	
	F3 ≥9.5 (≤11.0)	Cirrhosis ≥12.5
	F4 ≥12.0 (≥14.0)	

Liver biopsy and non-invasive tests (NITs) are extensively used for staging hepatic fibrosis and evaluating CLD progression. Combination testing using NITs has been shown to be more effective prognostic tool as compared to any single non-invasive method.[21,22] Common modalities used are elastography using ultrasound and magnetic resonance technology, and serum biomarkers. Transient elastography (TE) or Fibroscan is a reliable LF diagnostic method that uses ultrasound and has been validated for chronic viral hepatitis.[21,23]

EASL-Latin American Association for the Study of the Liver (EASL-ALEH 2015) recommends TE in viral hepatitis with equivalent performance in hepatitis B and C and in HIV-HCV coinfection.[24]

American Association for the Study of Liver Diseases (AASLD) recommends treatment in chronic hepatitis B (CHB) patients if elastography and serum biomarkers indicate significant fibrosis (≥F2) or moderate or severe inflammation (A2 or A3).[25]

Table 2 illustrates the practical considerations to be used while using NITs for diagnostic evaluation of LF in hepatitis patients.[21]

Table 2: Considerations while using NITs in hepatitis infection

	Hepatitis C	Hepatitis B
Confirmation	VCTE +++ Indirect markers +++ Direct markers +	VCTE ++ Indirect markers ++ Direct markers +
Cut-off values	≥F2 F4	≥F2 F4
Applicability	Interpretation of elastography after SVR	Risk of false positive results of VCTE with abnormal ALT levels
Clinical importance	Pretreatment detection of cirrhosis enabling screening for HCC and esophageal varices	Detection of cirrhosis to enable screening for HCC (in patients not in high risk categories independently of fibrosis stage), and esophageal varices; Detection of significant liver fibrosis

Abbreviations: VCTE, vibration-controlled transient elastography; SVR, sustained virologic response; HCC, hepatocellular carcinoma; ALT, Alanine transaminase

General Management Approach for Chronic Hepatitis-related Fibrosis[20]

HBV

- Tenofovir alafenamide, tenofovir disoproxil fumarate with adefovir dipivoxil
- Entecavir
- Lamivudine

HCV

- Interferon-derived therapy
- Direct-acting antivirals

Takeaways

Clinical care aspects for chronic hepatitis have progressed noticeably with better diagnostic procedures and advancements in the therapeutic and preventative approaches.

EASL's recent Digital International Liver Congress 2020 (August 27-29, 2020) covers latest updates and new research findings, abstracts and poster presentations for diagnostics, treatment and management approaches related to Viral Hepatitis (HBV and HCV).

EASL has recently released their latest recommendations on treatment of hepatitis C including guidance for treatment indications and genotype-based treatment regimens.

Liver fibrosis (LF) may go unrecognized unless symptoms manifest due to cirrhosis complications. The primary goal of therapies is to prevent, reduce, and reverse the fibrosis progression to cirrhosis.

Liver biopsy is extensively used as a gold standard for diagnosis and evaluation of advanced LF. However, recent advances are suggestive of non-invasive methods for staging hepatic fibrosis and evaluating CLD progression in the clinical practices today.

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NAVIGATE HEPATOCYTE IN PRACTICE

GILEAD Creating Possible

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