Best of ILC 2019

Viral hepatitis

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1. Viral hepatitis C: Therapy and resistance

Global real-world evidence of sofosbuvir/velpatasvir as a simple, effective regimen for the treatment of chronic hepatitis C patients

- The WHO has set a global goal to eliminate HCV as a public health threat by 2030; pangenotypic regimens provide opportunities to simplify treatment access
- SOF/VEL is a pangenotypic, panfibrotic, PI-free, single-duration, single-tablet regimen
- Efficacy of SOF/VEL for 12 weeks without RBV was evaluated in an integrated analysis of a heterogeneous real-world cohort of adults with HCV, including with compensated cirrhosis (CC)

- Data from 12 cohorts across North America, Canada and the EU included*
- CC was determined and patients treated according to local standards of care
- SVR was assessed ≥12 weeks after end of treatment (SVR12)
  - ITT: including non-virological‡ and virological failure; PP: excluding non-virological failure‡

Included	Excluded
GT 1–6	History of decompensation or HCC
Compensated or no cirrhosis	Prior NS5A inhibitor exposure
Treatment-naïve or -experienced†	Treatment duration >12 weeks
Initiated SOF/VEL prior to November 2018	RBV added to treatment

*Representing 7 countries; †pegIFN+RBV (+/- PI); ‡LTFU, discontinuation, death, reinfection, non-adherence or consent withdrawal.
Mangia A, et al. ILC 2019; GS-03

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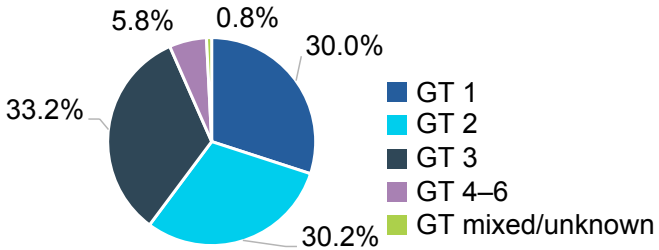
Global real-world evidence of sofosbuvir/velpatasvir as a simple, effective regimen for the treatment of chronic hepatitis C patients

- SVR data available for 5,541 patients
  - Median age 54 years; 59.5% male
  - Genotype distribution:

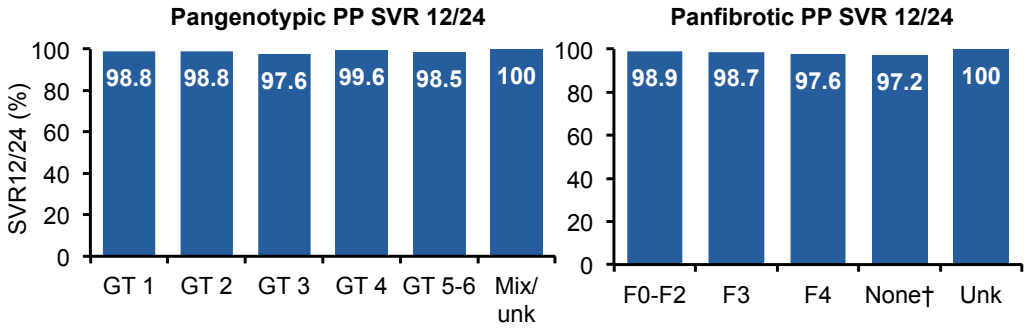


  - 20.7% (1,107) patients had CC
  - 12.4% (660) patients were treatment-experienced
- 5,134 patients achieved SVR*
  - PP: 98.5%; ITT: 92.7%

*LTFU (4%) was the most common reason for not reaching SVR;
†Confirmed no cirrhosis, but fibrosis score not recorded.

Mangia A, et al. ILC 2019; GS-03

PP SVR12/24 according to patient status



SOF/VEL for 12 weeks is a simple, highly effective regimen that cures HCV patients, irrespective of genotype, cirrhosis status or treatment history, with a manageable drug interaction profile and broad clinical utility, which will help simplify the care pathway and will contribute to the WHO 2030 targets for HCV elimination

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Glecaprevir/pibrentasvir: Real-world safety, effectiveness, and patient-reported outcomes in the German Hepatitis C-Registry

- Recent real-world data show GLE/PIB is safe and highly effective for treatment of chronic HCV infection
- However, PRO data are limited, particularly in subgroups key to HCV elimination
- This analysis from the DHC-R, an ongoing, non-interventional, multicentre, prospective registry study, reported real-world data on the safety and effectiveness of GLE/PIB, and PROs in patients with comorbidities

- Data were documented by 142 sites in Germany, 2 Aug 2017–20 Jan 2019
- The analysis included adult patients with HCV GT 1–6 infection treated with GLE/PIB according to the local label
- Primary endpoint: SVR12 (HCV RNA ≤25 IU/mL)
  - Assessed in patients who received at least 1 dose of study drug
- Safety, tolerability, and PROs also assessed

- 1,698 patients included
  - Most were TN without cirrhosis (84%) and thus treated for 8 weeks

- Reported comorbidities included: on OST (n=439; 26%); psychiatric disease (n=247;15%); alcohol abuse (n=106; 6%); HIV coinfection (n=107; 6%); active drug use (n=47; 3%)

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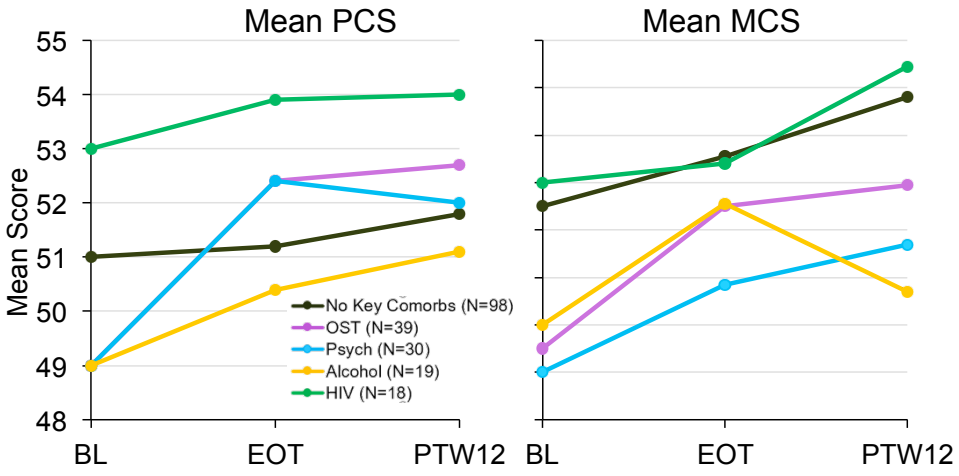
Cornberg M, et al. ILC 2019; GS-07

Glecaprevir/pibrentasvir: Real-world safety, effectiveness, and patient-reported outcomes in the German Hepatitis C-Registry

- SVR12 (ITT) rate was 96.6% (964/998)
  - 87.0% SVR12 in 23 patients with active drug use
- Excluding non-virological failures, the modified SVR12 rate was 99.5% (964/969)
- Patients with available data reported improvements in mental and physical SF-36 component scores (*Figure*)
  - Generally, patients with comorbidities had lower baseline scores and greater improvement at EOT
- Safety and tolerability:
  - 17 SAEs; 3 were considered possibly treatment related
  - 6 reinfections
  - 23 patients discontinued treatment
    - 3 due to an AE or SAE



In this real-world analysis, GLE/PIB was highly effective with few AEs, and led to significant SF-36 component score improvements.

Cornberg M, et al. ILC 2019; GS-07

DAA effectiveness in England: high response rates in GT 3 HCV infection regardless of degree of fibrosis, but RBV improves response in cirrhosis

- An estimated 100,000 people in England have chronic HCV infection
- Choice of DAAs is mandated centrally
  - Allows comparison of regimens without confounding by clinician choice
  - Mandatory national registry monitors therapy
- **Aim**: To examine the SVR12 rate achieved by different regimens

Jan 2019
anonymized data analyzed with Stata 15

Null hypothesis
no difference in SVR with different DAAs

PP analyses assessed proportions with a valid outcome achieving SVR

P<0.05 taken as the level of significance*

- 37,693 people with HCV in registry
  - 16,756 DAA-treated adults due a 12-week post-treatment outcome 8 weeks before data extraction
- 14,603 subjects had a PP outcome
  - 13,959 achieved SVR12
    - 95.6% (95% CI 95.2% to 95.9%)
  - SVR12 was significantly higher in patients with fibrosis than cirrhosis†
    - SVR with fibrosis, 96.1%
    - SVR with CC, 94.2%
    - SVR with DC, 90.0%
- Further analyses were focused on GT 3

*Chi square or Fisher's exact test;
†SVR12 in patients in PP population: fibrosis 96.1% (95% CI 95.6% to 96.6%), CC 94.2% (95% CI 93.5% to 94.9%), or DC 90.0% (95% CI 87.2% to 92.4%)
Drysdale K, et al. ILC 2019; LB-08

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DAA effectiveness in England: high response rates in GT3 HCV infection regardless of degree of fibrosis, but RBV improves response in cirrhosis

Regimen	n	SVR12, % (95% CI)	P value
Comparison 1 (SVR12 in GT 3 patients with moderate fibrosis)			
GLE/PIB (8 weeks)	92	96.6 (90.0-98.9)	0.793
SOF/VEL (12 weeks)	214	97.1 (93.7-98.7)	
Comparison 2 (SVR12 in GT 3 patients with compensated cirrhosis)			
SOF/VEL + RBV (12 weeks)	196	98.0 (94.7-99.2)	Comparator regimen
SOF/VEL	218	91.6 (87.3-94.5)	0.005*
SOF + DCV + RBV	868	92.2 (90.2-93.8)	0.002*
GLE/PIB (12 weeks)	167	96.4 (92.2-98.4)	NS†

In the large, non-selective English HCV treatment registry SVR12 rates with SOF/VEL + RBV were higher vs SOF/VEL or SOF + DCV + RBV in subjects with GT3 HCV and compensated cirrhosis. No other statsisignificant differences were found.

*vs SOF/VEL + RBV (12 weeks); †vs all other regimens.

Drysdale K, et al. ILC 2019; LB-08

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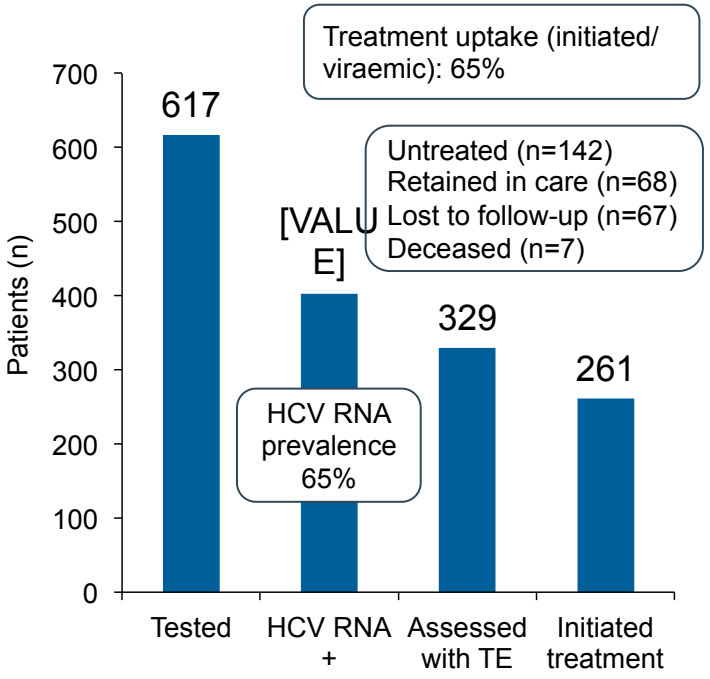
The hepatitis C cascade of care and treatment outcomes among people who inject drugs in a Norwegian low-threshold setting: A real-life experience

- Improving HCV treatment uptake and outcomes in PWID is crucial to WHO elimination goals
- **Aim:** To describe the HCV cascade of care, including treatment outcomes and reinfection rates in an urban PWID cohort attending a low-threshold clinic

- 2013: clinic established in Oslo to provide HCV care for marginalized PWID
  - Located in Oslo's harm reduction services (including NSP), with specialist support
  - Nurses draw blood, operate TE and provide tailored DAAs
    - Available without fibrosis restriction in GT 1 since 02/2017
    - Available for all patients since 02/2018
  - By 03/2019 clinic had tested 617 individuals

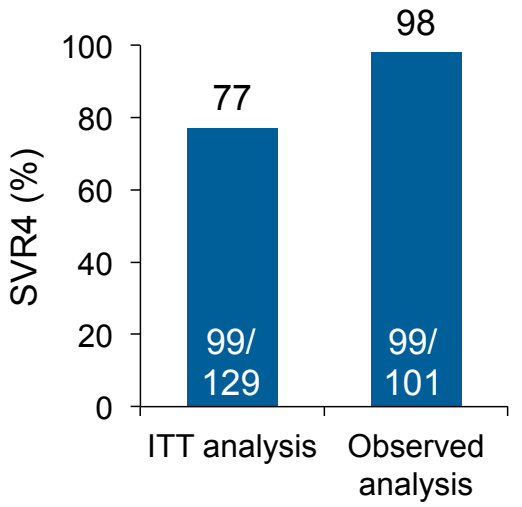


Midgard H, et al. ILC 2019; PS-068

The hepatitis C cascade of care and treatment outcomes among people who inject drugs in a Norwegian low-threshold setting: A real-life experience

- Among 129 individuals due for SVR assessment by 03/2019:
  - 48 years median age, 76% male, 26% cirrhosis, 47% GT 1
  - 81% reported injecting drug use during treatment
  - 79% received OST
- 30 patients did not achieve SVR4 in the ITT analysis (*Figure*):
  - 2 virological failures, 5 discontinued treatment, and 23 LTFU
- Adherence of >90% prescribed doses reported by 91%
- Follow-up data available in 125 patients
  - 4 cases of HCV reinfection† over 96 PY of follow-up
    - Possible reinfection: 4.2/100 PY (95% CI 1.1–10.7)
    - Probable reinfection: 3.1/100 PY (95% CI 0.6–9.1)

SVR4 rates in ITT and observed analysis*



HCV treatment uptake and virological response was high among PWID attending a low-threshold clinic. This study provides real-life data on the feasibility of a model of care that could be disseminated to other urban areas

*Excluding discontinuations and LTFU; †Post-treatment HCV RNA recurrence in presence of risk factors.
Midgard H, et al. ILC 2019; PS-068

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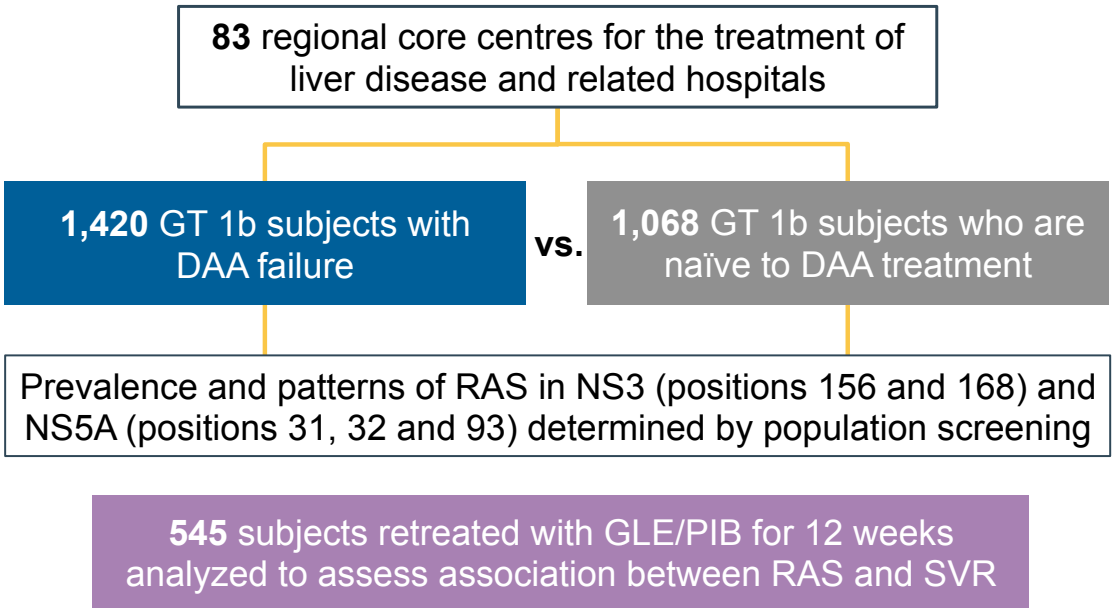
NS5A resistance profile of GT 1b virological failures that impacts outcome of re-treatment with GLE/PIB: A nationwide real-world study

- NS5A plays a key role in HCV RNA replication
- In patients with CHC and DAA failure, NS5A RASs may affect the efficacy of re-treatment with all regimens
- **Aim:** To examine the prevalence and pattern of NS5A RASs and the impact on retreatment with GLE/PIB



Kurosaki M, et al. ILC 2019; PS-180

NS5A resistance profile of GT 1b virological failures that impacts outcome of re-treatment with GLE/PIB: A nationwide real-world study

Demographics (DAA failure cohort)

Characteristic	Patients (%)
Number of failed DAA regimens	
1	83
2	15
3	2
Regimen used	
DCV/ASV	84
LDV/SOF	13
GZR/EBR	2

- Prevalence of NS3* and NS5A† RAS significantly higher in subjects with DAA failure vs. DAA-naïve subjects
- Dual NS3 + NS5A RAS:
  - 35% failing DCV/ASV
  - 20% failing GZR/EBR

  Prevalence increased with number of failed regimens
  34% failing 1 regimen
  55.3% failing 2 regimens
  86.7% failing 3 regimens
- Prevalence of NS5A P32del:
  - DAA naïve: 0%
  - LDV/SOF: 2.0%
  - DCV/ASV: 3.7%
  - GZR/EBR: 4.3%
- In GLE/PIB re-treated subjects SVR12 was 95.8%
  - SVR not affected by presence of NS3 or NS5A L31/Y93
  - SVR 25% in patients with P32del vs. 97% in WT P32 (p=0.0002)

Retreatment with GLE/PIB was highly effective except in patients with a RAS P32del in NS5A

*Position 156 and 168; †Position L31, P32, and Y93.
Kurosaki M, et al. ILC 2019; PS-180

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Unacceptably low SVR rates in African patients with unusual HCV sub-genotypes: Implications for global elimination

- Rare HCV subtypes are underrepresented in clinical trials but are prevalent in some regions
- **Aim:** To describe the genotype distribution and antiviral treatment outcome in a south London cohort of African patients

- All patients born in Africa attending clinic* from 2015–2018 were identified
  - HCV genotype, treatment regimen and outcome were recorded
- Samples were analyzed locally
  - VERSANT HCV Geno 2.0 Assay
  - Non-subtypeable GT 1 samples further analyzed on Glasgow NimbleGen NGS

- 47/91 (52%) had an unusual genotype, including (*Table*)
  - Non-subtypeable GT 1
  - Non 1a/1b GT 1
  - Non 4a/4d GT 4
  - Among non-subtypeable GT 1 samples that underwent NGS
    - 15 samples met criteria to be novel unconfirmed subgenotype 1 (u/c GT 1)
    - These 15 samples included 12 novel subtypes (2 separate samples for 3 of the novel subtypes)

*King's College Hospital, Institute of Liver Studies, London, UK.

Childs K, et al. ILC 2019; PS-181

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Unacceptably low SVR rates in African patients with unusual HCV sub-genotypes: Implications for global elimination

- SVR rate was 46/51 (90%) overall
  - Only 19/26 (73%) in unusual GT 1 subtypes
  - Failure in 4/16 u/c G1 and 3/4 in GT 1L
- SVR failure associated with unusual GT 1 subtype and NS5a, but not PI treatment
  - After re-treatment
    - 1 patient with u/c GT 1 failed to achieve SVR with G/P
    - 2 patients with GT 1L achieved SVR with G/P
    - 2 patients with u/c GT 1 achieved SVR with SOF/VEL/VOX

Mean age (range)	**54 (47, 64)**	
Sex	42/91 (46%) female	
HIV+	8 (9%)	
Cirrhosis	20/91 (21.9%)	
Country of birth	**n**	**Genotype**
Cameroon	9	1,u/cGT 1,1b,2x1e,1l,2,4,4f
Congo	7	2,4,4c,3x4k,4r
Cote D'Ivoire	4	1a,3xu/cGT 1
Egypt	3	2x1g,4
Eritrea	3	1a,4a,5a
Ghana	6	1a,2xu/cGT 1,2a/c,4,6
Nigeria	26	2x1a,4xun1,3x1b,1c,2x1g,1h,3x1l,5xu/cGT 1,3a,3x4a,4f
Other African countries	33	8x1a,3xu/cGT 1,un1,3x1b,1l,1e,1b/2k,2k,2a,2x3h, 4x4a,4r,4x4e

The majority (52%) of African patients had an unusual genotype. SVR with unusual GT 1 was 73%; unacceptably low in the current era. This was driven by 6 failures with SOF/LDV vs. only 1 failure with a PI, raising concerns about first-generation NS5A inhibitor-based schemes across Africa. Depending on regimen, failure rates in African cohorts could be higher than in clinical trials, jeopardizing HCV elimination agendas

Childs K, et al. ILC 2019; PS-181

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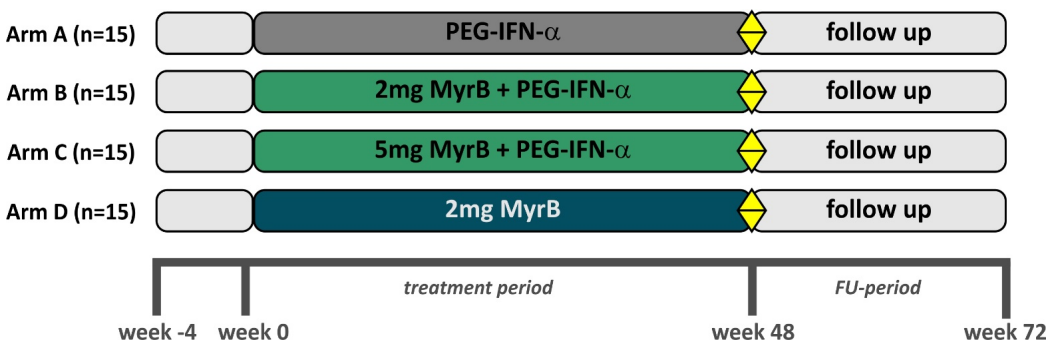
2. Viral hepatitis B/D: Therapy

Myrcludex B with PEG-interferon α 2a: Safety and efficacy in patients with chronic HBV/HDV co-infection in a phase 2 trial (MYR203)

- Myrcludex B (MyrB, Bulevirtide) is a first-in-class entry inhibitor for HBV/HDV infection
- In a phase 2 study MYR202, MyrB monotherapy led to HDV RNA decline and improvement of ALT levels
- End-of-treatment data from a MyrB ± PegIFNα2a 48 weeks combination study (MYR203) have been reported[1]
- Here, the 24-week treatment-free follow-up data are presented



- Primary endpoint: undetectable serum HDV RNA at Week 72 (w72)
- Secondary endpoints: ALT normalization, combined treatment response*, and HBsAg reduction >1 $\log_{10}$

*≥2 log serum HDV RNA decline + normal ALT levels.

1. Wedemeyer H, et al. Hepatology 2018;68(Suppl):11.
Wedemeyer H, et al. ILC 2019; GS-13

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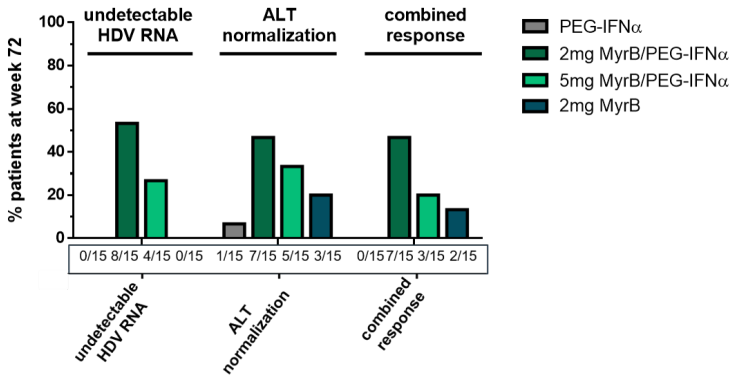
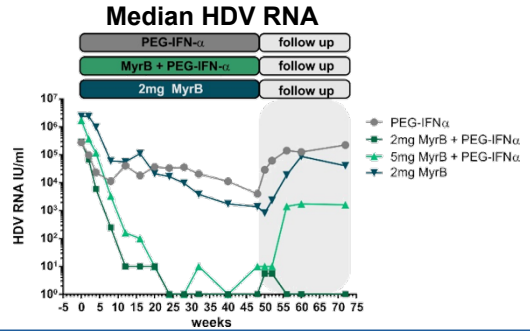
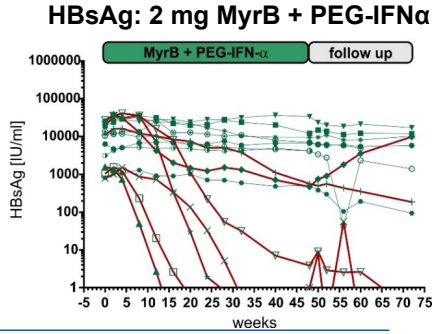
Myrcludex B with PEG-interferon α 2a: Safety and efficacy in patients with chronic HBV/HDV co-infection in a phase 2 trial (MYR203)

- **Safety:** MyrB was well tolerated, with 155 drug-related AEs up to w72 (mild n=122, moderate n=28, serious n=5), primarily increased total bile salts
  - Most AEs (n=524) related to PegIFNα2a
  - All cases resolved; bile salts returned to baseline by follow-up Week 50
  - Two SAEs (anal fistula and proctitis) not-related to MyrB occurred in 1 patient of Arm B in follow-up
- **Efficacy:** MyrB + PegIFNα2a induced a significant enhancement of HDV RNA response
  - 40% (12/30) patients had undetectable HDV RNA at Week 72

  2 mg MyrB + PegIFNα2a induces HBsAg response in HBeAg negative patients at Week 72
  - 40% of patients experienced HBsAg response
  - In this group 27% lost HBsAg and 20% seroconverted







In contrast to PegIFNα2a monotherapy, MyrB + PegIFNα2a demonstrated high rates of HDV RNA suppression. HBsAg loss was achieved in 27% of patients, indicating a potential role for MyrB in future HBV cure regimens

Wedemeyer H, et al. ILC 2019; GS-13

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Tenofovir treatment has lower risk of hepatocellular carcinoma than entecavir in patients with chronic hepatitis B

- TDF and ETV have potent hepatitis B antiviral effects and are recommended first-line for CHB
- **Aim:** To compare TDF and ETV on HCC risk in a territory-wide CHB cohort

- Adult CHB patients initially treated with ETV or TDF for ≥6 months between 01/2008–06/2018
  - In/out-patient data from all Hong Kong public hospitals and clinics
  - Exclusions: patients with cancers or LT before or within first 6 months of treatment
  - Missing data replaced by MI by chained equations, then PS weighted to balance BL clinical characteristics

- 29,350 CHB patients identified (mean age 52.9 ± 13.2 years; 63.7% male)
  - 1,309 (4.5%) and 28,041 (95.5%) first received TDF and ETV, respectively
- At a median 3.6 years FU, 8 (0.6%) TDF and 1,386 (4.9%) ETV-treated patients developed HCC
  - TDF associated with lower HCC risk than ETV*

*Before (aHR 0.36, p=0.042) and after MI, with (weighted HR 0.36, p=0.013) and without (aHR 0.32, p=0.002) PS weighting.
Yip TCF, et al. ILC 2019; LB-03

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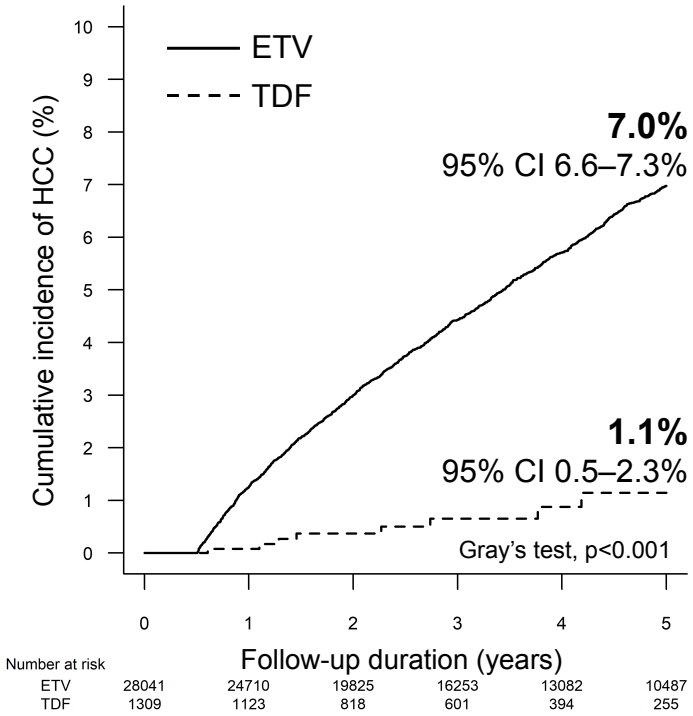
Tenofovir treatment has lower risk of hepatocellular carcinoma than entecavir in patients with chronic hepatitis B

5-year cumulative HCC incidence



*Log-transformed in the model; †p=0.002 for TDF vs. ETV; ‡p=0.003 for TDF vs. ETV; All others p<0.001.

Yip TCF, et al. ILC 2019; LB-03

HCC risk analysis

Parameters	Univariate analysis†		Multivariable analysis†	
	SHR	95% CI	Adjusted SHR	95% CI
TDF vs. ETV	0.15	0.07–0.29	0.32	0.16–0.65
Age	1.06	1.06–1.06	1.05	1.04–1.05
Male sex	2.17	1.90–2.47	2.42	2.11–2.76
Cirrhosis	5.73	5.16–6.36	2.30	2.01–2.64
Platelet*	0.35	0.31–0.40	0.54	0.49–0.60
Albumin	0.91	0.91–0.92	0.97	0.97–0.98
ALT*	0.81	0.77–0.84	0.87	0.83–0.91
Total bilirubin*	1.48	1.41–1.56	–	–
HBeAg+‡	0.82	0.73–0.93	1.44	1.26–1.65

TDF treatment associated with lower HCC risk than ETV in a territory-wide CHB cohort

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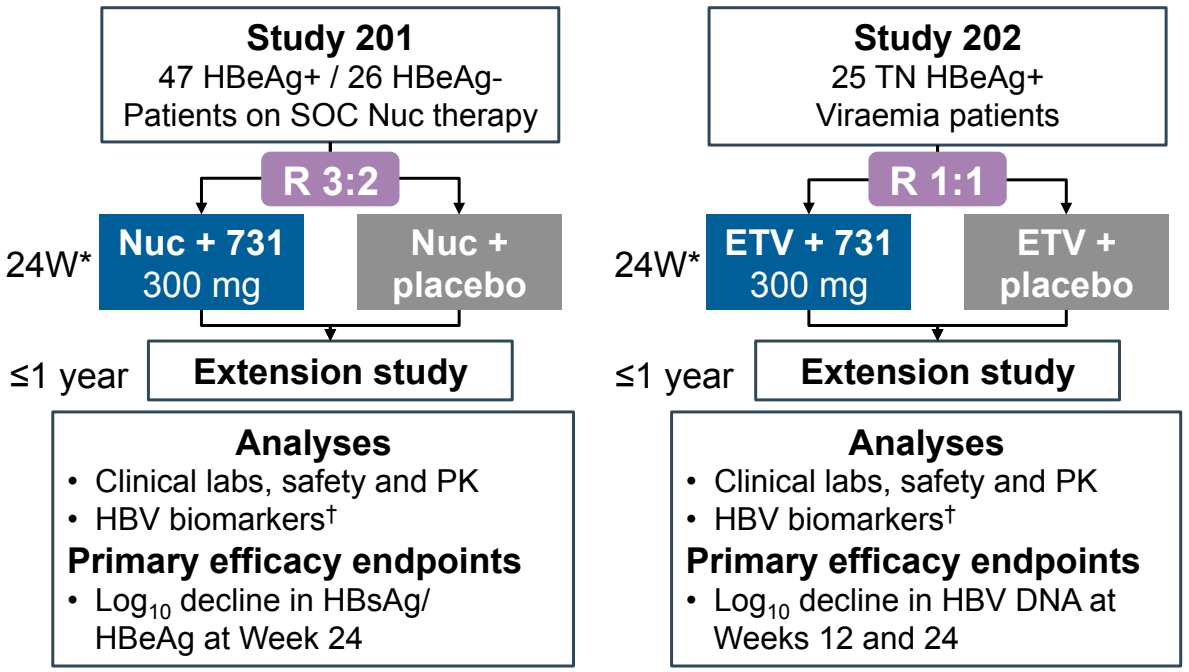
Interim safety and efficacy results of the phase 2a program of ABI-H0731 + Nuc therapy in treatment-naïve and treatment-suppressed patients with CHB

- Nucs are the standard of care (SOC) for CHB
  - But achieve low rates of sustained response off therapy
- The novel core inhibitor ABI-H0731 (731) exhibited potent anti-HBV activity over 28 days as monotherapy
- 731 + Nuc combo is being evaluated in two double-blind, placebo-controlled phase 2a trials in patients with CHB and F0–2 fibrosis



*Including follow-up at Weeks 2, 4 and then monthly; †Including HBV DNA, HBV RNA, HBsAg and HBeAg.
Ma X, et al. ILC 2019; LB-06

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Interim safety and efficacy results of the phase 2a program of ABI-H0731 + Nuc therapy in treatment-naïve and treatment-suppressed patients with CHB

- Enrolment complete in both studies
- Few TEAEs or laboratory abnormalities; generally mild or moderate
  - 3 AEs (rash) “possibly related” or “related” to treatment
  - None had associated systemic symptoms and none required treatment interruption
  - No discontinuations due to AE or ALT flares
- Significantly greater declines in HBV viraemia (DNA/RNA) seen on combination therapy
- Individuals have shown decreases in HBeAg and HBsAg, but no meaningful conclusions can be drawn on antigen reductions at this early interim time point

Study 202 (TN HBeAg+ subjects), mean log_{10} declines				
Marker	Week	ETV (n)	731+ETV (n)	P values
RNA, copies/mL	12	0.44 (12)	2.27 (12)	<0.005
	24	0.61 (5)	2.54 (6)	<0.005
DNA, IU/mL	12	3.29 (12)	4.54 (12)	<0.011
	24	3.99 (6)	5.94 (6)	<0.005

Study 201 (Nuc-suppressed HBeAg+ subjects), mean log_{10} declines				
Marker	Week	Nuc (n)	731+Nuc (n)	P values
RNA, copies/mL	12	0.05 (18)	2.34 (23)	<0.001
	24	0.15 (4)	2.20 (6)	0.012
Study 201 (Available subjects at Week 24), HBV DNA (+/-)				
DNA, PCR TND*	24	0 (4)	5 (6)	N/A

Interim data suggest ABI-H0731+Nuc was well tolerated over the dosing period and exhibited early and enhanced antiviral benefit in suppressing HBV DNA and HBV RNA levels to a greater extent than seen with Nuc therapy. These interim data support the use of CIs in a next-generation regimen as potential advance in treatment

*Target not detected using ASMB <5 copies/mL semi-quantitative PCR assay.
Ma X, et al. ILC 2019; LB-06

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HDV co-infection modifies the immunoproteasome profile of HBV infected hepatocytes leading to increased CD8 T-cell recognition

- Immunological therapy with engineered virus-specific T cells might eradicate HBV/HDV-infected hepatocytes; impact of HDV on the T-cell recognition is unknown
- **Aim:** To analyze how HDV modifies HBV antigen presentation to CD8 T cells and test the antiviral efficacy of engineered T cells in HBV/HDV co-infected humanized chimeric mice

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- HBV CD8 T-cell epitope:MHC complexes were measured concomitantly with Primeflow HDV RNA specific probes on PHH infected with HBV alone or HBV/HDV
  - Antibodies and CD8 T cells specific for either core or envelope HLA-A0201 restricted HBV epitopes
- Differentially expressed genes during HDV infection characterized using Nanostring technology
- In vivo adoptive T-cell transfer to HBV/HDV co-infected mice* repopulated with HLA-A02-matched PHH
- HBV-specific TCR T cells were engineered using TCR mRNA electroporation on T cells of healthy and HDV chronically infected subjects

*Adoptive transfer of T cells engineered with TCR specific for envelope/A0201 complexes into HBV/HDV co-infected human liver chimeric mice (uPA-SCID/beige/IL2rg-/- [USG]).
Tham CYL, et al. ILC 2019; PS-079

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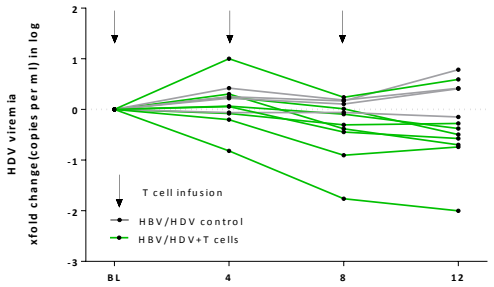
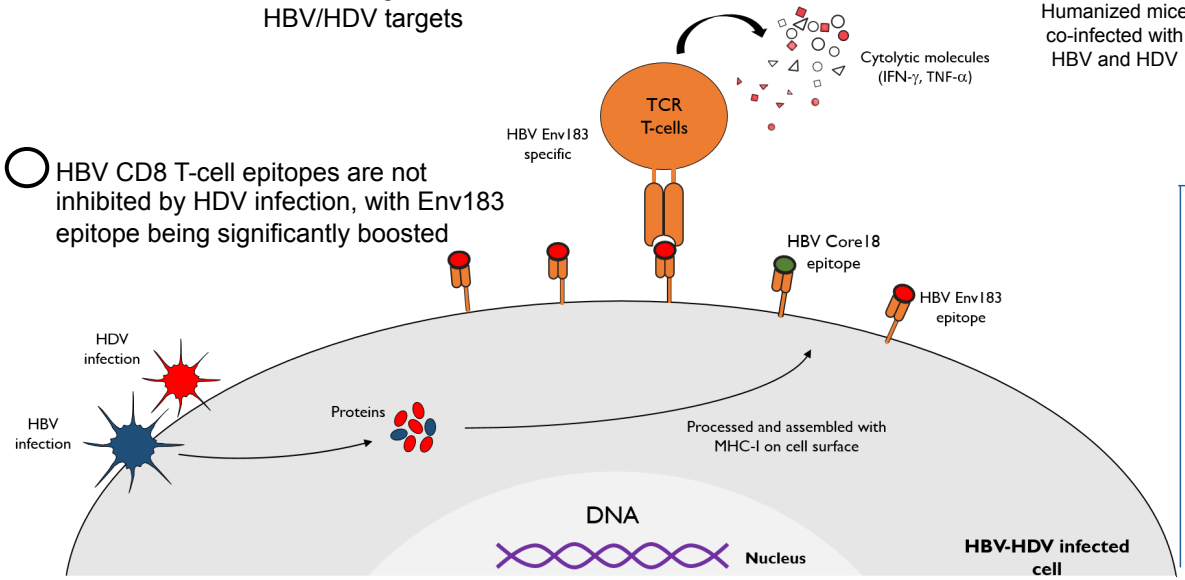
HDV co-infection modifies the immunoproteasome profile of HBV infected hepatocytes leading to increased CD8 T-cell recognition

- Introduction of HBV Env183-specific T cells into HBV/HDV humanized mice rapidly reduces HDV and HBV viraemia

Humanized mice co-infected with HBV and HDV



- Enhanced HBV Env183-specific CD8 T cell recognition and activation of HBV/HDV targets



- HBV CD8 T-cell epitopes are not inhibited by HDV infection, with Env183 epitope being significantly boosted

The ability of HDV to activate immunoproteasome activity in HBV-infected hepatocytes and boost the presentation of envelope-derived HBV epitopes support the therapeutic use of HBV envelope-specific TCR engineered T cells in HBV/HDV co-infection

Tham CYL, et al. ILC 2019; PS-079

Lenvervimab, a mAb against HBsAg, can induce sustained HBsAg loss in a chronic hepatitis B mouse model

- Sustained loss of HBsAg is regarded as a marker for functional cure in HBV
- As HBsAg is known to suppress HBV immune responses, this study hypothesized that HBsAg removal could result in immune response restoration

- Therapeutic potential of surrogate lenvervimab (sLenvervimab) was evaluated in an HDI-based CHB mouse model

- Sustained HBsAg loss for 6 months was observed after end of sLenvervimab treatment in 5/12 mice (41.7%)
  - HBV replication and HBcAg+ hepatocytes barely detectable
  - >1 log reduction in copy number of injected DNA (pAAV-HBV1.2*) was observed and at a level comparable to self-limited mice
  - IHC showed lymphocyte infiltration and structural changes of hepatocytes, resembling ballooning degeneration
    - Upregulation of inflammatory markers, such as Cox-2, interleukin-1β and prostaglandin E2
  - Statistically meaningful mild–moderate increase in ALT
  - Existence of protective immunity was confirmed by further challenge experiments to the HBsAg loss mice
    - 60% showed immunity vs. 0% of HBsAg-persistent mice

*Acts as a template for HBV replication as cccDNA does in natural infection.
Kim J-H, et al. ILC 2019; PS-077

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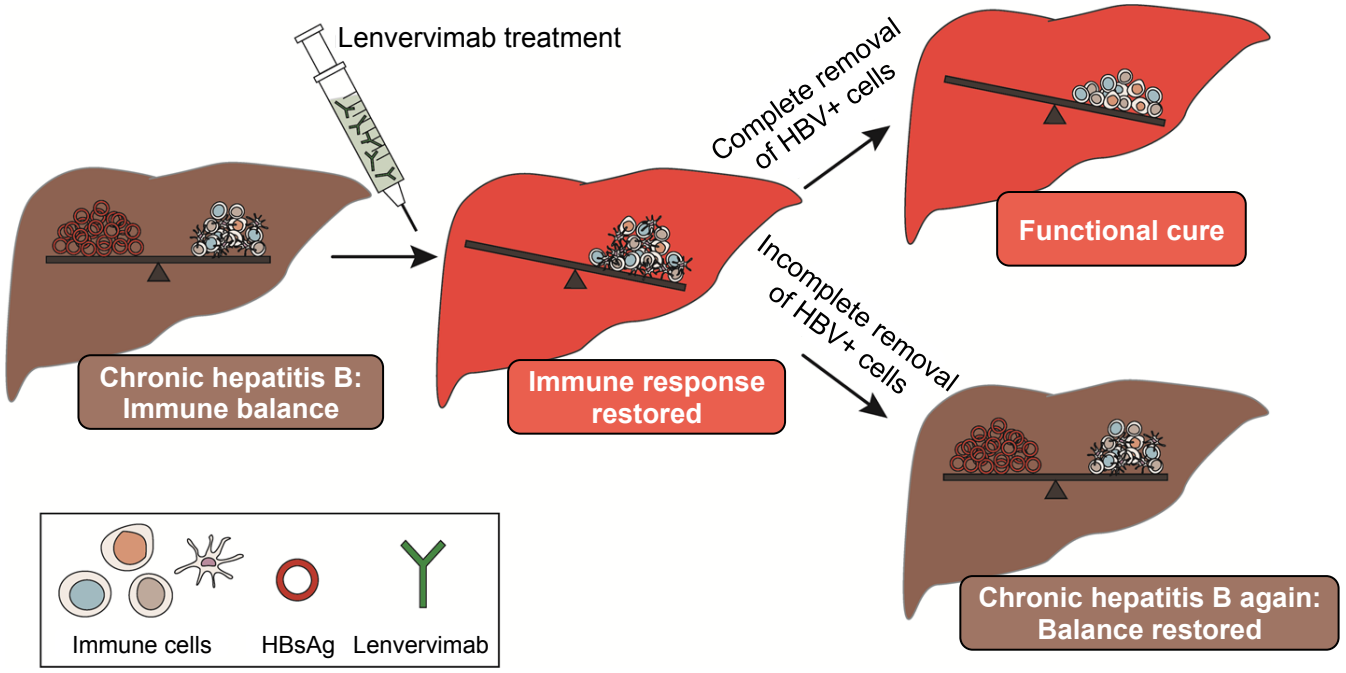
Lenvervimab, a mAb against HBsAg, can induce sustained HBsAg loss in a chronic hepatitis B mouse model



Removal of HBsAg by Lenvervimab resulted in restoration of HBV immune responses. Sustained HBsAg loss was achieved by elimination of HBV+ hepatocytes. This study provides proof of concept for Ab-based therapies for CHB functional cure

Kim J-H, et al. ILC 2019; PS-077

Short-term RNA interference therapy in chronic hepatitis B using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold

- To explore the effect of 3 doses of JNJ-3989 (formerly ARO-HBV) on HBsAg reductions below certain thresholds

- Patients with chronic HBV received 3 SC doses of JNJ-3989 weekly to monthly together with ETV or TDF
- HBsAg levels were assessed in patients that had ≥24 weeks of HBsAg data (n=40)
- Safety and tolerability were assessed in all patients in these cohorts (n=56)

- JNJ-3989 was well tolerated
- JNJ-3989 reduced viral products in HBeAg+ and HBeAg-, NUC experienced or naïve patients
- HBsAg was reduced as follows:
  - To <100 IU/mL in 88%
  - By ≥1 Log_{10} IU/mL in 100%
  - Both thresholds have been associated with increased probability of HBsAg clearance when stopping NUC treatment[1]

1. Jeng WJ, et al. Hepatology 2018;68:425-34.
Yuen MF, et al. ILC 2019; PS-080

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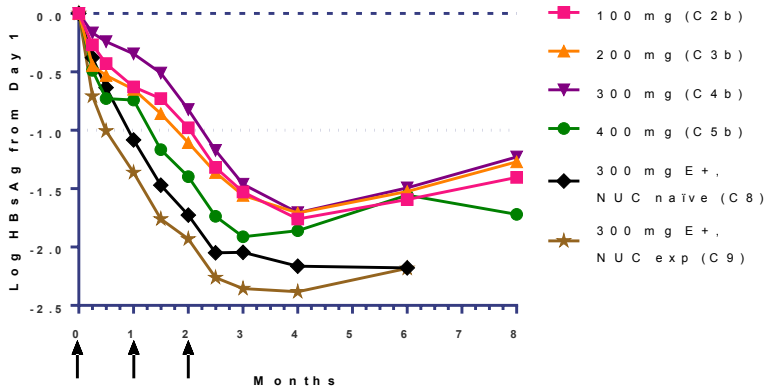
Short-term RNA interference therapy in chronic hepatitis B using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold

FIGURE **Mean HBsAg reductions from baseline**



Baseline HBsAg		
Threshold	N	Percent
>100 IU/ml	37 of 40	93%
NADIR HBsAg		
Threshold	N	Percent
≤100 IU/ml	35 of 40	88%
≤10 IU/ml	17 of 40	43%

JNJ-3989 exhibits characteristics desirable for a cornerstone therapy in finite regimens aimed at HBsAg seroclearance in patients with chronic hepatitis B infection

Yuen MF, et al. ILC 2019; PS-080

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3. Viral hepatitis A/E: Clinical aspects

Mortality and morbidity of hepatitis E in Scotland: A multicentre study

- HEV has become the most common acute viral hepatitis in Scotland
  - Little is known about the burden of disease
- **Aim:** To record morbidity/mortality for all HEV cases in four Scottish health boards

- Data* were collected retrospectively from all reported cases of HEV between 01/2013–01/2018 (N=416)
  - NHS Greater Glasgow and Clyde (n=187)†
  - NHS Grampian (n=96)†
  - NHS Tayside (n=117)
  - NHS Lothian (n=16)

- Mean age 61 years; 63% were male
- Cirrhosis present in 45 (10.8%)
- Diabetes present in 91 (21.9%)
- HEV infection affected 15 transplant patients
  - In 69 (16.6%) immunosuppressed cases
- 257 (61.8%) patients required hospitalization
- 15 (3.6%) HEV-related deaths
- 21 (5%) patients required critical care
- 30 (7.2%) patients developed liver failure
  - 2 required transplantation

*Demographic, clinical and laboratory; †Complete 5-year data sets obtained.

Wallace S, et al. ILC 2019; PS-051

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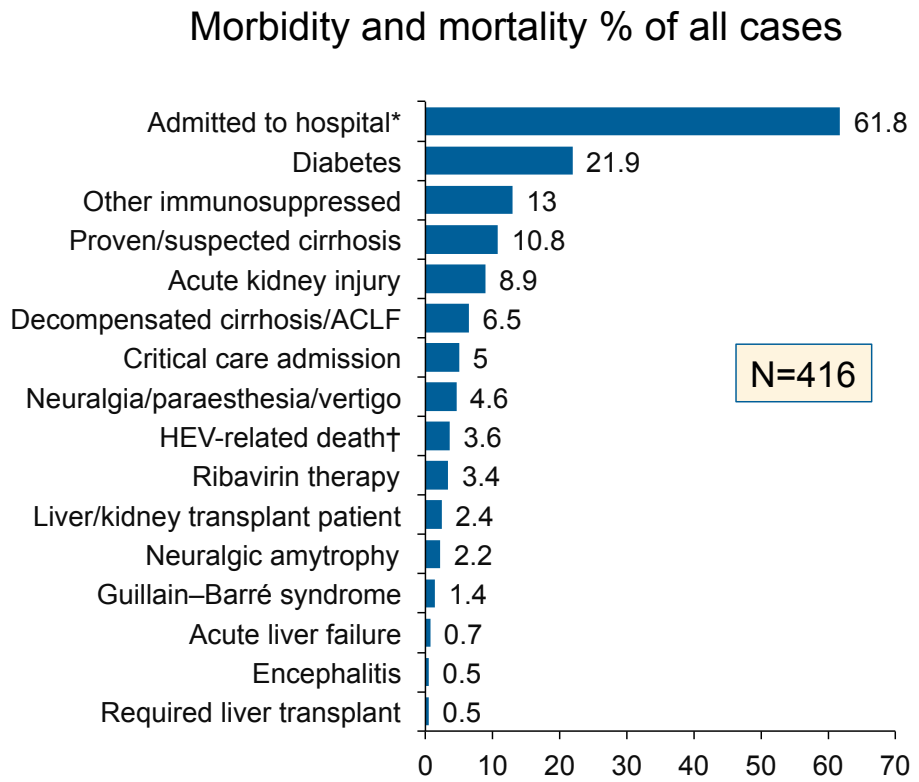
Mortality and morbidity of hepatitis E in Scotland: A multicentre study



*2,329 inpatient bed days (median stay 3 days); †11 with pre-existing liver disease, 4 with immunosuppression.

Wallace S, et al. ILC 2019; PS-051

- 35 (8.4%) patients reported neurological symptoms
  - 8 neuralgic amyotrophy
  - 6 Guillain–Barré
  - 2 encephalitis
- 37 (8.4%) patients had acute kidney injury
  - 16 (3.4%) cases documented as chronic HEV, with 14 receiving ribavirin

Locally acquired HEV causes significant burden of disease. Cirrhosis, diabetes, and immunosuppression are associated with symptomatic infection. Neurological and renal complications occur in a minority

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4. Viral hepatitis A/E: Therapy

Efficacy and safety of sofosbuvir monotherapy in patients with chronic hepatitis E: The HepNet SofE pilot study

- cHEV is an emerging problem in immunocompromised patients
  - Treatment is limited to RBV
  - RBV is contraindicated in many
- SOF inhibits HEV replication *in vitro*
  - Case reports are conflicting

- Investigator-initiated, multicentre, phase 2 pilot trial*
- Patients with confirmed cHEV† received SOF 400 mg QD for 24 weeks
  - Primary endpoint: undetectable HEV RNA at Week 24
  - Secondary outcomes: analysis of antiviral efficacy (log_{10} HEV RNA decline)

- 9 patients were evaluated‡:
  - Mean age: 44±14 years
  - 7 patients failed prior RBV (median 15 months); 2 ineligible for RBV
  - Median ALT before SOF: 126 U/L
  - Median BL HEV RNA: $6x10^5$ IU/ml
- 5/9 (56%) patients experienced HEV RNA decline of ≥1 log_{10} IU/ml
  - Strongest median decline observed between BL and Week 2 (1.1 log_{10})
  - No patient reached the primary endpoint
  - 2 maintained >1 log_{10} HEV RNA reduction at Week 24

*3 German centres (NCT03282474); †10 patients for whom RBV failed or was contraindicated;
‡1 patient was excluded from further analysis.
Cornberg M, et al. ILC 2019; LB-04

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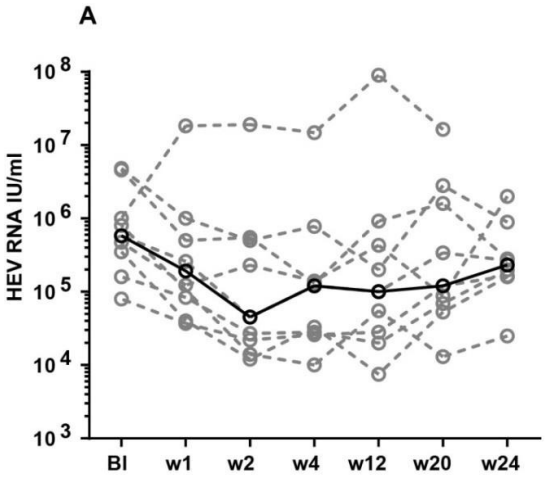
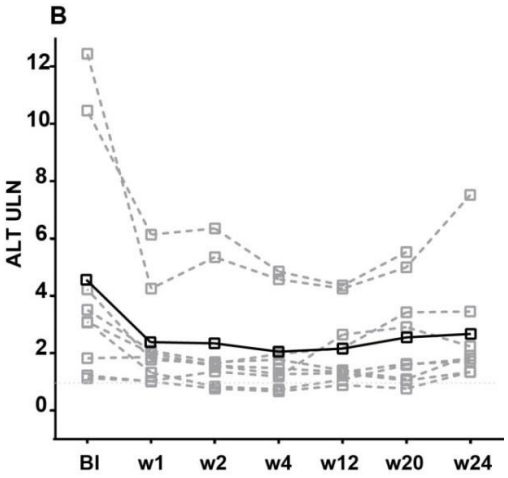
Efficacy and safety of sofosbuvir monotherapy in patients with chronic hepatitis E: The HepNet SofE pilot study

- ALT showed significant decline
  - From 4.6 to 2.2 ULN at Week 12 and 2.7 ULN at Week 24
- SOF was well tolerated
  - CrCl stable during therapy
    - GFR >30 mL/min in all patients
  - 6 SAEs in 3 patients
    - Only 1 (elevated lipase) considered SOF related
    - Patient experienced sepsis and died 4 weeks after SOF was stopped

HEV RNA in 9 patients
(black line = median)



ALT in 9 patients
(black line = mean)



SOF shows moderate antiviral efficacy but does not cure cHEV.
Further study of SOF + RBV is warranted in immunocompromised patients with cHEV

Cornberg M, et al. ILC 2019; LB-04

5. Viral hepatitis A, B, C, D, E: Virology

A first-in-class orally available HBV cccDNA destabilizer ccc_R08 achieved sustainable HBsAg and cccDNA reduction in the HBV circle mouse model

- Persistence of cccDNA is a major barrier to cure in CHB patients with existing therapies
- **Aim:** To evaluate the effect of a novel small molecule ccc_R08 on the level of pre-existing cccDNA both *in vitro* and *in vivo*

- HBV-infected primary human hepatocytes (PHH) were used for evaluating antiviral activities *in vitro*
- ccc_R08 was orally administered in HBV circle mouse model* to study its in vivo efficacy
  - Levels of HBV DNA, HBsAg, HBeAg, pgRNA, and cccDNA were measured

HBV-infected PHH

- Potent inhibition of HBV DNA, HBsAg, HBeAg, and pre-existing cccDNA
- No effect on mitochondrial DNA level and cytotoxicity

HBV circle mice

- Levels of serum HBV DNA, pgRNA, HBsAg, HBeAg reduced significantly
  - Sustained during the off-treatment period
- Levels of cccDNA in the liver of ccc_R08 treated mice were < LLOQ
  - ETV had no such effect on cccDNA level in this model

*Yan Z, et al. HBV circle: A novel tool to investigate hepatitis B virus covalently closed circular DNA. J Hepatol 2017;66:1149–57.
Wang L, et al. ILC 2019; PS-074

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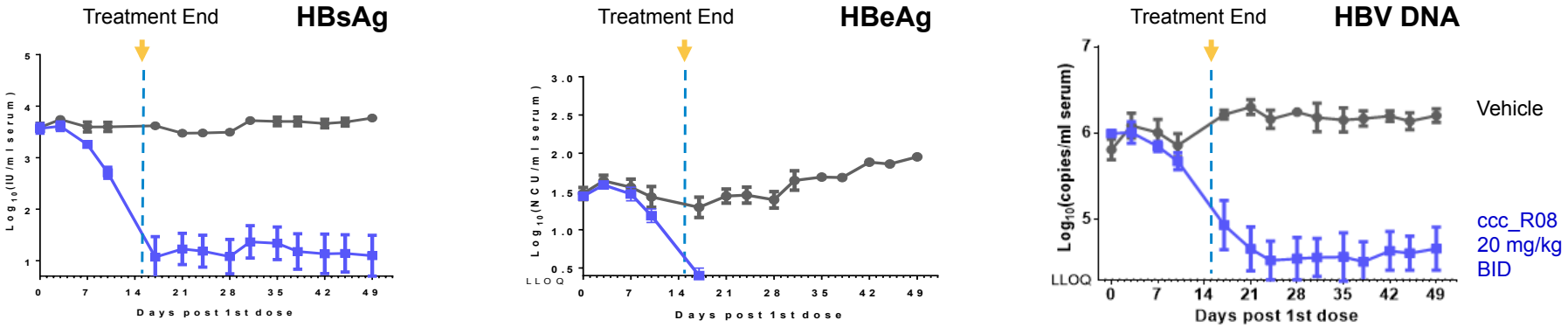
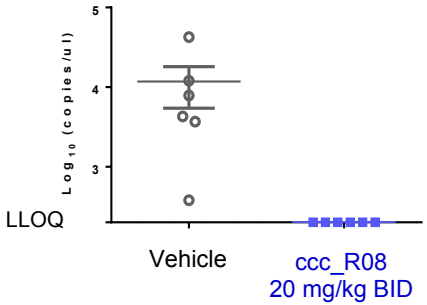
A first-in-class orally available HBV cccDNA destabilizer ccc_R08 achieved sustainable HBsAg and cccDNA reduction in the HBV circle mouse model

HBV circle mouse model: serum levels of HBsAg, HBeAg, and HBV DNA and cccDNA levels in the liver



Liver cccDNA level



A novel small molecule ccc_R08 can sustainably reduce serum HBsAg and liver cccDNA levels in the HBV circle mouse model

Wang L, et al. ILC 2019; PS-074

HBV entry inhibition after IFNα treatment hinders HBV rebound in hepatocytes negative for all HBV markers during IFN treatment

- IFNα treatment can exert both immunomodulatory and antiviral effects
- **Aims:**
  - Investigate these antiviral effects in HBV-infected human hepatocytes *in vivo* and whether they can persist after treatment cessation
  - Employ HBV entry inhibition to assess the role of new infections in HBV rebound

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- HBV-infected human liver chimeric mice were treated with PEG-IFNα for 6 weeks (n=13 + 5 untreated controls)
  - Mice were either sacrificed (n=5) or treatment was stopped to assess serological/intrahepatic viral changes for 6 further weeks, either in the presence (n=4) or absence of the entry inhibitor MyrB* (n=4)
  - HBV load analyzed in serum and liver by qPCR
  - RNA-ISH and immunofluorescence to visualize HBV transcription and presence of SMC6 (potential marker of cccDNA suppression/clearance)

*MyrB treatment started 3 days before the last IFNα injection.

Allweiss L, et al. ILC 2019; PS-155

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HBV entry inhibition after IFNα treatment hinders HBV rebound in hepatocytes negative for all HBV markers during IFN treatment

- 6 weeks of IFNα treatment reduced median viraemia (1.3 log), HBV transcripts (3.4x) and cccDNA (7.6x)
- SMC6 was degraded in most HBV-infected controls, but detectable in IFNα-treated mice
- After stopping IFNα, HBV rebound occurred in 3-6 weeks, with renewed SMC6 degradation in most human hepatocytes
- Viraemia also increased in MyrB-treated mice
  - BUT entry inhibition blocked intrahepatic HBV rebound in >40% of human hepatocytes, which remained SMC6+, HBcAg- and HBV RNA-
- Intrahepatic cccDNA levels in MyrB-treated mice during rebound remained as low as in mice sacrificed at the end of IFNα treatment

Reappearance of SMC6 in IFNα-treated human liver chimeric mice did not hinder HBV reactivation after drug withdrawal. MyrB maintained HBV negativity in a large proportion of hepatocytes, suggesting that they had cleared cccDNA during treatment and that new infection events play a key role in HBV rebound post IFN treatment

Allweiss L, et al. ILC 2019; PS-155

6. Viral hepatitis A, B, C, D, E: Immunology

Impact of antigen recognition on memory-like HCV-specific CD8+ T cells

- In chronic HCV infection, exhausted HCV-specific CD8+ T cells consist of terminally exhausted CD127-PD1hi and memory-like CD127+ PD1+ subsets
- **Aim:** To determine the impact of antigen recognition on memory-like HCV-specific CD8+ T cells

- scRNAseq analyses of HCV-specific CD8+ T cells
- Low-input RNAseq analyses of CD127/PD1-based HCV-specific CD8+ T-cell subsets

- Memory-like cHCV-specific CD8+ T cells exhibit an exhausted scar while showing memory-like characteristics
- HCV-specific CD8+ T cells targeting escaped epitopes also show an exhausted scar, however, to a different extent compared to memory-like HCV-specific CD8+ T cells after DAA-mediated viral elimination
- Dynamics of antigen recognition modulate the characteristics of memory-like HCV-specific CD8+ T cells

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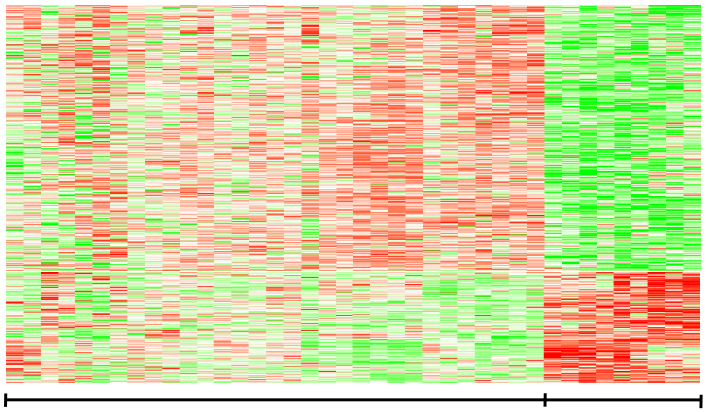
Hensel N, et al. ILC 2019; PS-032

Impact of antigen recognition on memory-like HCV-specific CD8+ T cells

Unsupervised clustering reveals exhausted signature of chronic HCV-specifc CD8+ T cells independent of antigen recognition



Chronic infection **(cHCV)**

Memory-like and terminally exhausted
With/without viral recognition (EXH/ESC)
Baseline and end of therapy

Resolved Infection **(rHCV)**

Chronic HCV infection is strictly linked to an 'exhaustive' T-cell differentiation . The exhausted programme is not reverted by loss of antigen recognition or removal of antigen. Dynamics of antigen recognition modulate the T-cell differentiation

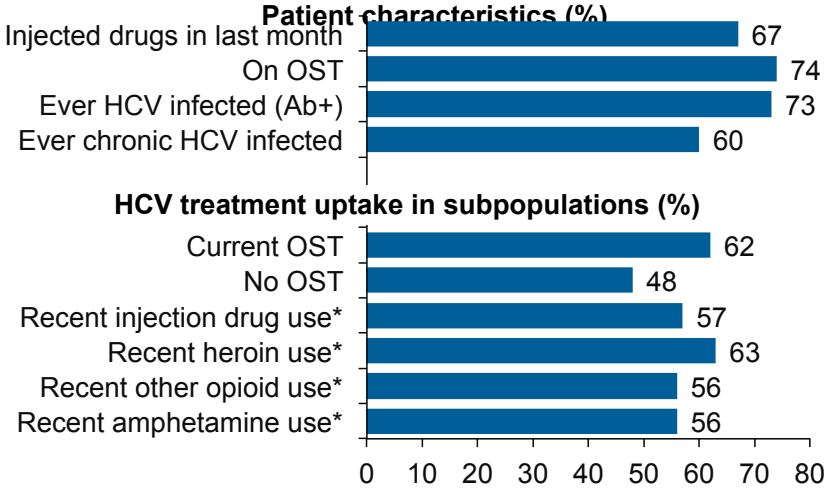
Hensel N, et al. ILC 2019; PS-032

7. Public Health

Uptake of testing, linkage to care, and treatment for hepatitis C infection among people who inject drugs in Australia: The ETHOS Engage study

- PWID are at high risk of HCV infection
- Access to treatment in PWID is poor
- Unrestricted DAA availability in Australia since 2016
- **Aim:** Evaluate HCV burden and factors associated with the cascade of care in PWID

- ETHOS Engage
  - Observational cohort study
  - Collects data† from PWID attending drug treatment clinics and NSPs in Australia
- All PWID (N=1001) had POC HCV RNA testing
- Multivariate logistic regression used to identify factors associated with treatment uptake



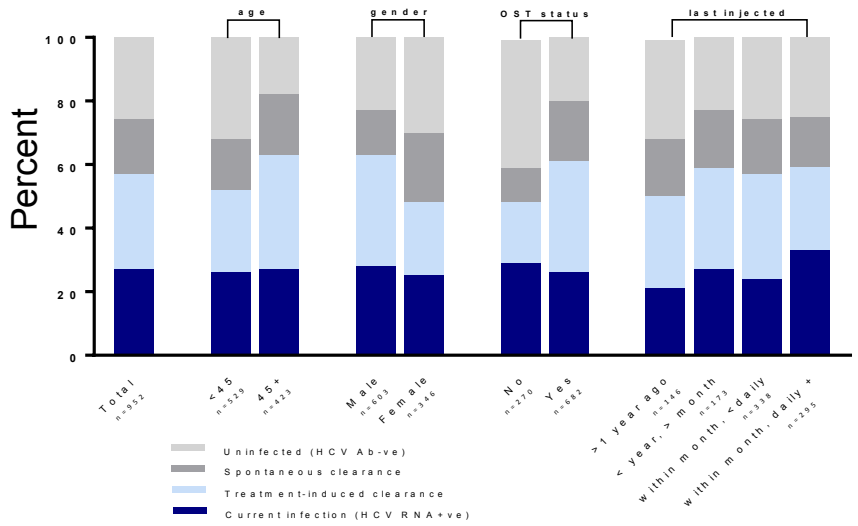
- Patients with current/past chronic HCV:
  - 86% had been linked to care
  - 68% received treatment
- Male sex and current OST significantly associated with treatment uptake

*≤1 month; †Demographic, behavioural and clinical.

Valerio H, et al. ILC 2019; PS-070

Uptake of testing, linkage to care, and treatment for hepatitis C infection among people who inject drugs in Australia: The ETHOS Engage study

HCV prevalence among participants with known POC HCV RNA result at enrolment (n=952)



- Proportion with current HCV infection was similar across demographic and behavioural sub-populations

The DAA era in Australia has produced high treatment uptake and lowered HCV viraemia among PWID attending treatment and NSPs. To reach elimination targets, subgroups of PWID may require additional support

Valerio H, et al. ILC 2019; PS-070

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