Viral Hepatitis

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P249 **New findings in HCV genotype distribution in selected West European, Russian and Israeli regions**
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P256 **High sustained virological response rates using imported generic direct-acting antiviral treatment for hepatitis C, imported into Australia, UK, Europe and North America**
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*Indicates presenting author.

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Liu, W; Su, L; Wu, C; Wu, P; Yang, S; Zhang, J; Chang, H; Chang, S; Liu, C; Sun, H; Hung, C; Chang, S (Taipei, Taiwan)*

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Valente, C; Casella, M; Faria, D; Aleixo, M; Vaz Pinto, I; Mota, M; Mingo, A; Carvalho, A; Roxo, F; Faísca, R; Proença, P; Poças, J; Prata, M; Marques, N; Saraiva Cunha, J (Coimbra, Portugal)*

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Chen, G; Lin, K; Sun, H; Sheng, W; Hsieh, S; Chuang, Y; Hung, C; Chang, S (Taipei, Taiwan)*

*Indicates presenting author.

TURQUOISE-I, Part 2: Safety & Efficacy of Ombitasvir/ Paritaprevir/Ritonavir ± Dasabuvir With or Without Ribavirin in Patients With HIV-1 And HCV GT1 or GT4 Co-Infection

P248

Jürgen K Rockstroh[1], **Chloe Orkin**[2], Rolando M Viani[3], David Wyles[4], Anne Luetkemeyer[5], Adriano Lazzarin[6], Ruth Soto-Malave[7], Mark R Nelson[8], Sanjay R Bhagani[9], Hartwig HF Klinker[10], Giuliano Rizzardini[11], Pierre-Marie Girard[12], Niloufar Mobashery[3], Nancy S Shulman[3], Yiran B Hu[3], Linda M Fredrick[3], Tami Pilot-Matias [3], Roger Trinh[3], Edward Gane[13]

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Presented at HIV Glasgow, 24 October 2016, Glasgow, Scotland

BACKGROUND

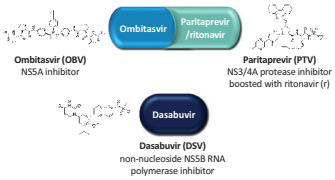
Human Immunodeficiency Virus Type 1 (HIV-1) infects approximately 37 million individuals worldwide; an estimated 20–30% of these individuals are co-infected with hepatitis C virus (HCV)[1]

HCV co-infection with HIV-1 is associated with higher incidence of:

- liver cirrhosis
- decompensation
- hepatocellular carcinoma
- liver-related mortality

Cure of HCV infection can reduce the risk of these outcomes and improve overall survival[2,3]

3D Treatment Regimen for GT1



Ombitasvir (OBV)
NS5A inhibitor

Paritaprevir (PTV)
NS3/4A protease inhibitor boosted with ritonavir (r)

Dasabuvir (DSV)
non-nucleoside NS5B RNA polymerase inhibitor

PTV was identified by AbbVie and Enanta.
Ritonavir does not have antiviral activity against HCV.

- Approval of 3D regimen based on TURQUOISE-I Part 1a, conducted in 63 patients with HIV-1/HCV genotype (GT) 1 co-infection with or without cirrhosis
  - Sustained virologic response at 12 weeks post-treatment (SVR12) was achieved by 94% and 91% of patients treated for 12 or 24 weeks, respectively[4]

2D Treatment Regimen for GT4

Ombitasvir (OBV)
NS5A inhibitor

Paritaprevir (PTV)
NS3/4A protease inhibitor boosted with ritonavir (r)

PTV was identified by AbbVie and Enanta.
Ritonavir does not have antiviral activity against HCV.

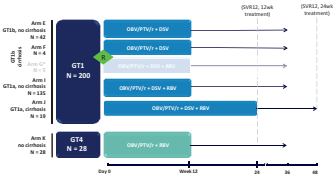
- The 3D and 2D regimens are approved in the US and EU for HCV genotype GT1/HIV-1 co-infection and HCV GT4 infection, respectively, and are recommended in national and international guidelines

OBJECTIVE

OBJECTIVE: TURQUOISE-I, Part 2 is a Phase 3, global trial assessing the efficacy and safety of OBV/PTV/r ± DSV ± RBV for 12 or 24 weeks in an expanded study population of 233 patients with HIV-1/HCV GT1 or GT4 co-infection with or without cirrhosis

METHODS

TURQUOISE-I Part 2 Study Design



*Arm G was omitted from this analysis as the recommended regimen for GT1b patients with cirrhosis is 3D without RBV.

ELIGIBILITY CRITERIA

Key inclusion criteria

- 18 to 70 years of age
- HCV GT1 or GT4 infection at time of screening

METHODS (CONTINUED)

- Treatment-naïve or treatment-experienced with pegylated interferon (pegIFN)/RBV or sofosbuvir (SOF) + RBV ± pegIFN
- Co-infection with HIV-1, with plasma HIV-1 RNA <40 copies/mL
- On a stable ART regimen containing:
  - ritonavir-boosted atazanavir (ATV/r) or darunavir (DRV/r), raltegravir (RAL), or dolutegravir (DTG)

Key exclusion criteria

- Positive test result of Hepatitis B surface antigen
- Prior treatment experience with DAAs other than SOF
- Platelets <25 000 cells/mm^3, calculated creatinine clearance <30 mL/min, albumin <2.8 g/dL, hemoglobin <11 g/dL (males) and <10 g/dL (females), or Total Bilirubin ≥6 mg/dL (for patients on ATV-containing ART) or ≥3 mg/dL

STUDY MEDICATIONS, ENDPOINTS, AND ASSESSMENTS

Study Medications

- ATV/r once daily (QD), DRV/r QD (GT4 only), RAL twice daily (BID), DTG QD or BID
- Patients on ritonavir-boosted ART stopped the ritonavir component of their ART regimen, and took OBV/PTV/r ± DSV ± RBV concurrently with ART

Primary Endpoint: number and percentage of patients achieving SVR12 (HCV RNA <LLOQ)

Additional Endpoints and Assessments

- On-treatment virologic failure and post-treatment relapse
- Maintenance of HIV-1 suppression
- Adverse events (AEs) and laboratory abnormalities
- Population resistance analyses performed to identify pre-existing and treatment-emergent amino acid substitutions in NS3, NS5A, and NS5B for patients who do not achieve SVR12

RESULTS

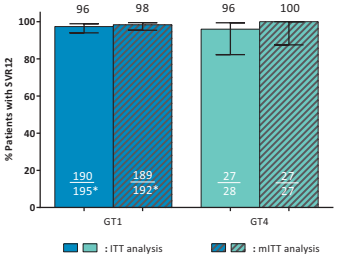
BASELINE DEMOGRAPHICS

Characteristic	GT1 N = 200	GT4 N = 28
Male, n (%)	156 (78)	26 (93)
White race, n (%)	173 (87)	25 (89)
Black race, n (%)	19 (10)	3 (11)
Age, median (range), years	50 (26–69)	47 (30–63)
BMI, median (range), kg/m^2	25 (17–41)	24 (15–38)
HCV genotype 1a, n (%)	153 (77)	—
IL28B non-CC genotype	133 (67)	21 (75)
HCV RNA, median (range), $\log_{10}$ IU/mL	6.5 (1.8–7.6)	6.0 (4.7–7.0)
CD4+ cell count, median (range), /µL	614 (133–2351)	731 (262–1533)
HIV-1 RNA <40 copies/mL, n (%)	193 (97)	27 (96)
HIV-1 RNA ≥40 copies/mL, n (%)	7 (4)	1 (4)
Cirrhosis*, n (%)	23 (12)	0
Baseline Fibrosis Stage†, n (%)		
F0–1	139 (70)	21 (75)
F2	20 (10)	2 (7)
F3	17 (9)	5 (18)
HCV Treatment-naïve, n (%)	134 (67)	17 (61)
HCV Treatment-experienced, n (%)	66 (33)	11 (39)
ART Regimen, n (%)		
Darunavir/r	—	8 (29)
Atazanavir/r	50 (25)	2 (7)
Raltegravir	94 (47)	7 (25)
Dolutegravir	56 (28)	11 (39)

GT, genotype; BMI, body mass index.
Race and ethnicity were self-reported.
Genotypes were determined by the Versant HCV Genotype Inno-LiPA Assay, version 2.0 or higher.
ART, antiretroviral therapy; PI, protease inhibitor.
*Cirrhosis documented by liver biopsy, FibroScan or FibroTest.
†Data missing for 1 patient in Arm I.

RESULTS (CONTINUED)

Efficacy: ITT and mITT Analyses



*5 out of 200 patients have not yet reached the SVR12 timepoint and are excluded from the analyses.
ITT: intent-to-treat population, which includes patients missing data as virologic failures.
mITT: modified ITT population, which excludes non-virologic failures and patients missing data.

- 3 patients with GT1 infection did not achieve SVR12: 1 on-treatment virologic failure; 2 relapses

Characteristics of 3 Virologic Failures

Patient Characteristics	On-treatment VF, Week 12	Relapse PTW4	Relapse PTW12*
HCV genotype	GT1b	GT1a	GT1a
Prior treatment	PegIFN/RBV (Null Responder)	Naïve	Naïve
Cirrhosis status	Cirrhosis	No Cirrhosis	No Cirrhosis
Resistance-associated substitutions			
In NS3 at baseline	None	None	None
at virologic failure	Y56H, D168V	None	None
In NS5A at baseline	None	None	None
at virologic failure	Y93H	None	None
In NS5B at baseline	S556G	None	None
at virologic failure	S556G	None	None

*Evidence of re-infection based on phylogenetic analysis.

MAINTENANCE OF HIV-1 SUPPRESSION

- 10/228 (4%) patients experienced episodes of intermittent viremia during treatment
- HIV-1 RNA was <200 copies/mL in 10/10 (100%) of these patients
- No episodes met criteria for HIV-1 genotypic resistance testing

Summary of Adverse Events (AE)

Event, n (%)	GT1 N = 200	GT4 N = 28
Any AE*	169 (85)	24 (86)
AEs leading to study drug discontinuation	0	0
Serious AE	9 (5)†	1 (4)
Common AEs‡		
Fatigue	47 (24)	5 (18)
Nausea	41 (21)	5 (18)
Diarrhea	32 (16)	1 (4)
Headache	28 (14)	5 (18)
Insomnia	30 (15)	2 (7)
Pruritus	22 (11)	1 (4)
Hgb Decrease	19 (10)	4 (14)

*Includes all AEs regardless of relation to study drugs. †1 SAE of anxious depressive syndrome on Day 123 was deemed as having a reasonable possibility of being related to DAAs.
‡Occurring in ≥10% of patients overall.
Hgb, Hemoglobin.

Summary of Laboratory Abnormalities

Characteristic, n (%)	GT1 N = 200	GT4 N = 28
Alk. Phos. Grade ≥3 (>5 × ULN)*	0	0
AST Grade ≥3 (>5 × ULN)*	0	0
ALT Grade 3 (>5 × ULN)*	1 (1)	0
AST Grade 4 (>10 × ULN)*	0	0
Total Bilirubin Grade 3 (3–5 × ULN)	25 (13)	2 (7)
Total Bilirubin Grade 4 (>5 × ULN)	1 (0.5)	0
Patients with Grade 3–4 Bilirubin Elevations Receiving ATV-containing ART, n/N (%)	23/26 (88)	2/2 (100)
Hemoglobin Grade 2 (8–10 g/dL)	15 (8)†	0
Hemoglobin Grade 3 (<8 g/dL)	0	0
RBV dose modifications due to Hgb decline	26 (13)	3 (11)

Alk. Phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; ATV, atazanavir; ART, antiretroviral therapy.
*Post-nadir.
†14/15 patients with Hgb reductions were on RBV-containing regimen.

CONCLUSIONS

- 99% (225/228) overall SVR12 rates were achieved in HIV-1 patients co-infected with HCV GT1 or GT4 following treatment with OBV/PTV/r ± DSV ± RBV, regardless of prior treatment history, baseline variants, or cirrhosis status
- The regimen was well tolerated, with no hepatic decompensation and no discontinuations due to AEs
- OBV/PTV/r ± DSV ± RBV treatment had no significant impact on HIV control, and there were no HIV-1 virologic failures
- These results suggest that HIV-1 co-infected patients on certain stable ART regimens can be treated safely with OBV/PTV/r ± DSV ± RBV

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New Findings in HCV Genotype Distribution in selected West European, Russian and Israeli Regions

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BACKGROUND:

HCV affects 185 million people worldwide and leads to death and morbidities. HCV has a high genetic diversity and is classified into seven genotypes and 67 subtypes. Novel anti-HCV drugs (Direct-Acting-Antivirals) eligibility, resistance and cure rates depend on HCV geno/subtype (GT).

MATERIALS AND METHODS:

Anonymised GT and epidemiological information gained in 2011-2015 was analysed retrospectively. Data were obtained from 52 centres in Austria, Belgium, Germany, Israel, Italy, Luxembourg, Portugal, Russia, Spain, and the UK (Table 1).

RESULTS:

37,839 samples were included in the study. The most prevalent was GT1 (64.9%), followed by GT3 (20.9%) and GT4 (9.0%). Three samples classified as the recombinant genotype-P were identified in Munich (Germany) (Fig. 1).

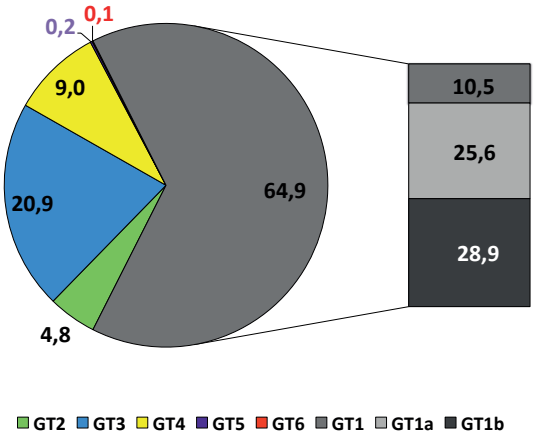

Fig. 1: GT distribution in the dataset

We show that the GT distribution is similar throughout Western European countries, with some local differences (Fig. 2). Here, GTs 1b and 2 prevalences are lower and of GT 1a and 4 higher than in all previous reports. Israel has a unique GT pattern with only GT1b, 1a and 4 (78.6%, 20.2% and 1.2%, respectively). In South Russia the GT proportions are more similar to Asia, with prevalent GTs 1, 3 and 2 (50.8%, 37.9% and 11.2%, respectively). GTs 5 and 6 were detected in very low proportions. Three cases of the recombinant genotype P were reported in Munich (Germany).

Variable		Number of samples
year of testing	2011	8301 (21.9%)
	2012	7939 (20.9%)
	2013	8410 (22.2%)
	2014	8761 (23.1%)
	2015	4533 (12.0%)
genotype	GT1[a]	3860 (10.2%)
	GT1a	9910 (26.2%)
	GT1b	10832 (28.6%)
	GT2	1952 (5.2%)
	GT3	7754 (20.5%)
	GT4	3415 (9.0%)
	GT5	70 (0.2%)
	GT6	36 (0.1%)
	non-1, 2 or 3	10 (0.0%)
gender	M	20282 (53.6%)
	F	9279 (24.5%)
	unknown	8278 (21.9%)
transmision route / risk group	parenteral	2282 (9.9%)
	vertical	13 (0%)
	nosocomial	442 (2%)
	tattoo / piercing	93 (0.5%)
	IVDA	1231 (5.8%)
	sexual	257 (0.9%)
	unknown	34685 (91.7%)
age at testing	≥65	4496 (11.9%)
	64-55	6663 (17.6%)
	54-45	10423 (27.5%)
	44-35	6034 (15.9%)
	34-25	2209 (5.8%)
	24-15	307 (0.8%)
	≤14	78 (0.2%)
	unknown	7629 (20.2%)
coinfections	HIV+	2095 (5.5%)
	HIV-	1311 (3.5%)
	HIV unknown	34433 (91%)
	HBV+	1314 (3.5%)
	HBV-	9325 (24.6%)
	HBV unknown	27200 (71.9%)

Table 1: Dataset

In addition, we observed that GT proportion was dependant on patients´ gender, age and transmission route (Fig. 3). Multivariate analysis (Fig. 4) showed that GTs 1b and 2 were significantly more common in female, older, nosocomially-infected patients, while GTs 1a, 3 and 4 were more frequent in male, younger patients infected by tattooing, drug consume, and/or sexual practices. In infections acquired by drug consume, GTs 1a (35.0%) and 3 (28.1%) prevailed. In infections related to sexual practices lower proportion of GT3 (14.0%) and higher of GT4 (20.2%) were detected. GT4 was mostly abundant in MSM (29.6%). HIV coinfection was significantly associated with higher proportions GTs 1a and 4 (42.5% and 19.3%, respectively).

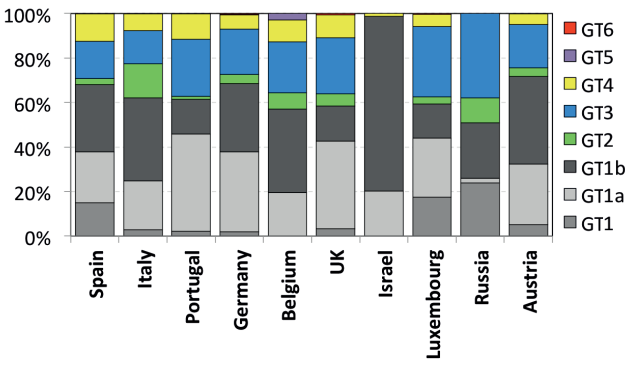

Fig. 2: GT distribution per country

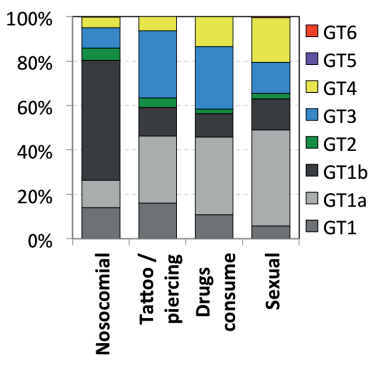

Fig. 3: GT distribution mode of transmission

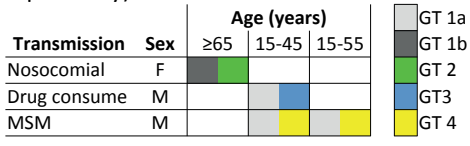

Fig. 4: GT associations found in the multivariate analysis

CONCLUSIONS:

Genotype prevalence evolves and correlates to epidemiological factors. Continuous surveillance is necessary to better assess hepatitis C infection in Europe and to take appropriate health actions.

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Hepatitis C can be cured for less than $100 per person - analysis of drug exports from India

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Background: Novel direct-acting antivirals (DAAs) for chronic hepatitis C (HCV) achieve high sustained virological response (SVR) rates of >90%. Current high prices limit access to DAAs both globally and in high-income countries. While Gilead (originator company of sofosbuvir) offers voluntary licenses to generic producers in a limit number of countries, these countries represent only 50% of the worldwide epidemic. Costs of production can be estimated by tracking the average cost-per-kilogram of the active pharmaceutical ingredient (API) exported internationally from India, and combining the estimated per-pill API expenditure with other components of production cost (e.g., formulation, packaging). The per-kilogram price of active pharmaceutical ingredient (API) and steady, high demand volumes are key determinants of the total production cost of any medicine.

Methods: Data were extracted from an online database of Indian export ledgers for per-kilogram prices and volumes of DAA APIs exported from India over Jan-Jun 2016. Average API costs were calculated for Jun 1, using linear regression models, weighted by individual export size. For velpatasvir, which is the newest DAA in this study and lacks export data, per-kilogram API cost was estimated from analysis of chemical synthesis processes described in originator patents. Costs of per-pill API requirements were combined with estimated costs for formulation and excipients ($0.04/pill), packaging ($0.35/month). Finally, a profit margin of 50% was added to estimate a price at which generic producers could profitably enter the market.
Current US and Indian prices were collected, for comparison, from multiple databases.

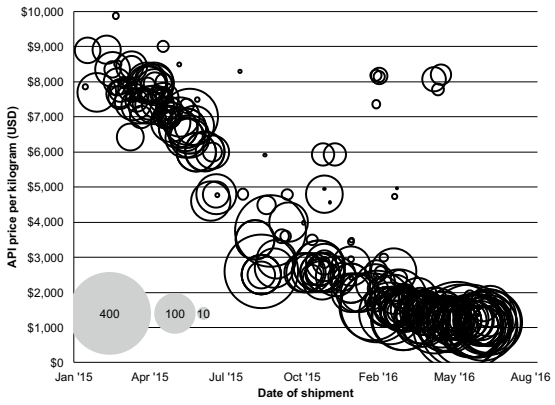
Results: Export volumes from India in Jan-Jun 2016 were, sofosbuvir: 10,200 kg, (equivalent to 303,000 12-week treatment courses), daclatasvir: 5,443 kg (1,080,000 courses), ledipasvir: 240 kg (32,000 courses). API prices decreased throughout the time frame. Mean API prices on June 1st 2016 were: sofosbuvir $1,094/kg, daclatasvir $998/kg, ledipasvir $2,441/kg. API cost for velpatasvir was estimated at $8,900-11,700/kg. US prices were 1,355 times higher than the target price for sofosbuvir, 4500 times for daclatasvir, 984 times higher for sofosbuvir+ledipasvir, and 346-413x times higher for sofosbuvir+velpatasvir.

Conclusions: HCV DAAs production costs are falling rapidly. 12-week treatments of sofosbuvir can be manufactured for $62, sofosbuvir+ledipasvir $96, daclatasvir $14, sofosbuvir+velpatasvir $181-216. These target prices all include a 50% profit margin for generic suppliers. These estimated generic prices for DAAs are comparable to those that have allowed massive treatment scale-up in HIV/AIDS.

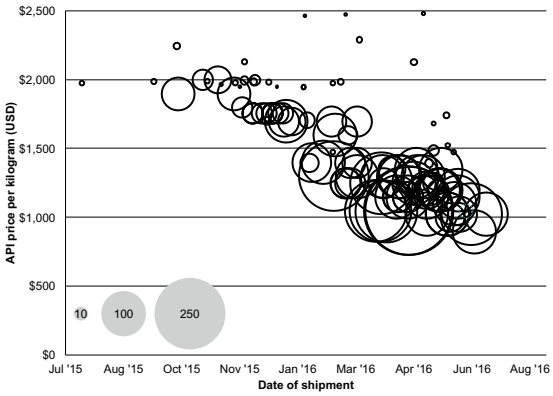
Costs of API, calculated target prices, and current prices

Drug	June 2016 API cost/kg	Target price per 12-week treatment	Current global lowest price per 12-week treatment	Current US price per 12-week treatment
Sofosbuvir (SOF)	$1,094	$62	$324	$49,860-84,000
Daclatasvir	$998	$14	$153	$50,653-63,000
Ledipasvir (LDV)	$2,441	$34	unknown	unknown
SOF+LDV	N/A	$96	$507	$56,700-94,500
Velpatasvir (VEL)	$8,900-11,700	$119-154	unknown	unknown
SOF+VEL	N/A	$181-216	unknown	$74,760

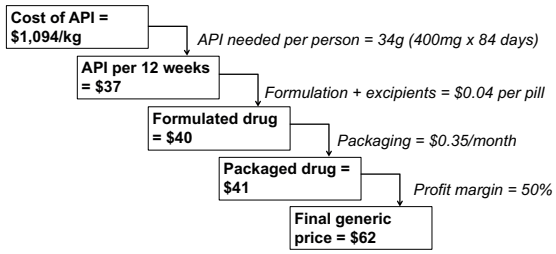
Cost/kg of sofosbuvir API exports Jan 2015 to Jul 2016, weighted by size of shipment



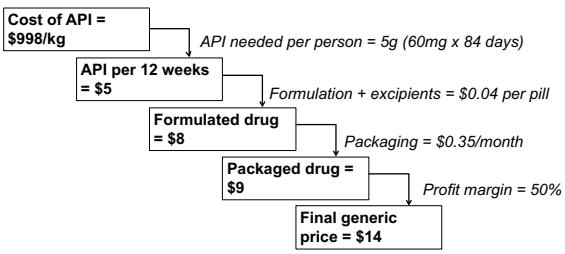
Cost/kg of daclatasvir API exports Jul 2015 to Jul 2016, weighted by size of shipment



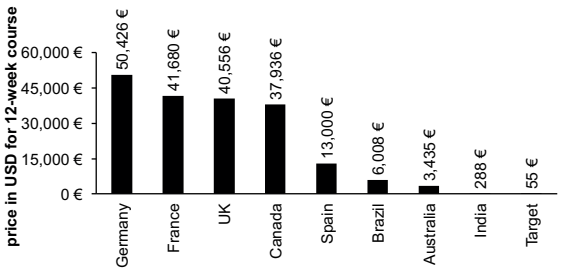
Cost-based generic price calculation for sofosbuvir (12 weeks)



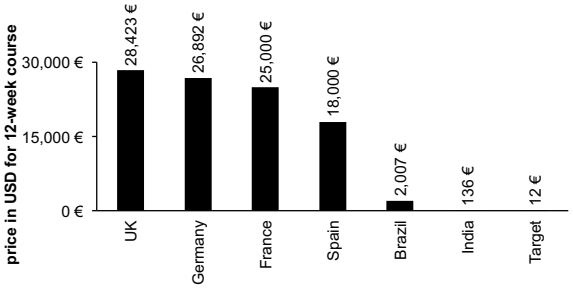
Cost-based generic price calculation for daclatasvir (12 weeks)



Lowest prices of sofosbuvir in selected countries (references 1-9)



Lowest prices of daclatasvir in selected countries (references 10-14)



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Sofosbuvir prices:
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2. France: http://www.medecinsdumonde.org/actualites/presse/2016/09/29/mdm-soppose-au-brevet-sur-le-sovaldir-decision-le-5-octobre-2016
3. Germany: medizinfuchs.de
4. Spain: http://politica.elpais.com/politica/2016/04/05/actualidad/1459873421_480033.html?id_externo_rsoc=TW_CC
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8. Australia: Authors' own calculation based on an annual budget of AU$200 million (138 million EUR), and 40,000 people treated in 2016.
9. India: http://hepcasia.com/wp-content/uploads/2016/03/31-Jan-2016-Indian-generic-sofosbuvir.pdf

Daclatasvir prices:
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Presented at the International Congress on Drug Therapy in HIV Infection. Glasgow, 2016.

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P 252

Hepatitis C Virus Screening Project of Patients on current anti-HCV Therapy

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BACKGROUND:

Clinical outcome of HCV therapy of direct acting antivirals (DAAs) depends on host and viral factors.

This observational, retrospective and non-interventional study collects data from viral geno/subtypes (GTs), DAA-resistance-associated-mutations (RAMs) within the viral NS3/protease, NS5A and NS5B genes, and host factors, to predict clinical outcome using the geno2pheno$_{[HCV]}$ tool. The current geno2pheno$_{[HCV]}$ version interprets resistance according to viral GT background.

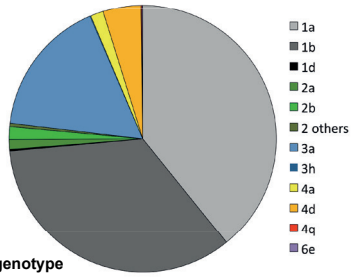

FIG. 1: Baseline genotype

MATERIALS AND METHODS:

Viral NS3/protease, NS5A and NS5B sequences from baseline plasma samples were obtained. Subtyping and presence of RAMs against Asunaprevir (ASV), Boceprevir (BOC), Grazoprevir (GZV), Paritaprevir (PTV), Simeprevir (SMV), Telaprevir (TVR), Daclatasvir (DCV), Elbasvir (EBR), Ledipasvir (LDV), Ombitasvir (OBV), Dasabuvir (DSV) and Sofosbuvir (SOF) was determined by sequencing (either Sanger or NGS) of the corresponding viral gene and subsequent interpretation with geno2pheno$_{[HCV]}$ (http://hcv.bioinf.mpi-inf.mpg.de/).

NS5B amplification and sequencing protocols were optimised for detection of specific DSV RAMs.

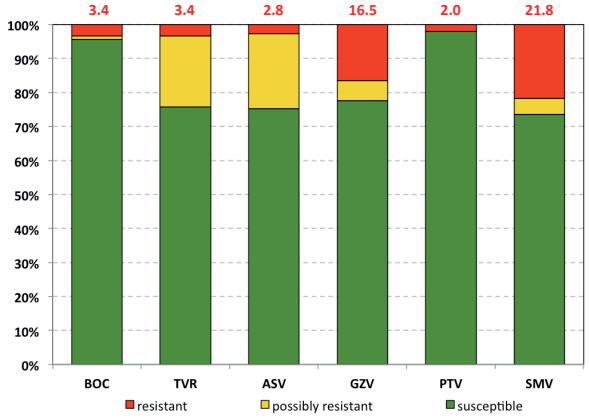

FIG. 2: Resistance to NS3/protease inhibitors

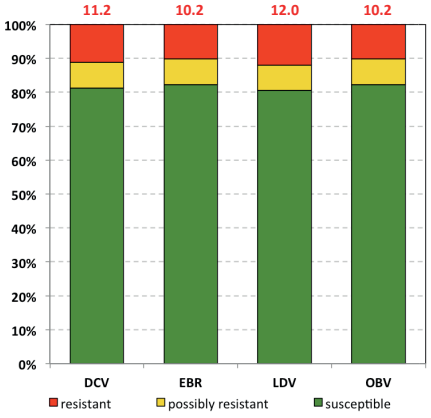

FIG. 3: Resistance to NS5A inhibitors

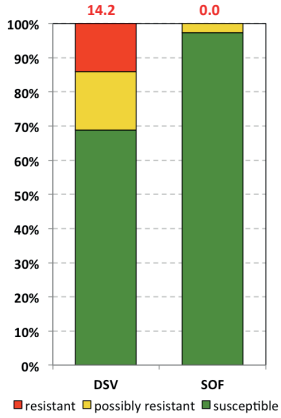

FIG. 4: Resistance to NS5B inhibitors

RESULTS:

1570 HCV-infected patients from the PEPSI Project have been enrolled until June 30th 2016. We could obtain 1024 NS5B sequences, which were used for genotyping. The most prevalent GTs were: GT1a= 39.1%; GT1b=34.2%; GT3a=16.6%; and GT4d=4.6% (Fig. 1).

Treatment susceptibility at baseline:

- **NS3/protease:** 595 baseline sequences were obtained and used for baseline NS3/protease-inhibitors resistance prediction (Fig. 2). Baseline resistance was found: ASV=2.8%; BOC=3.4%; GZV=16.5%; PTV=2.0%; SMV=21.8%; TVR=3.4%. For ASV, 22.0% of the samples were predicted as possibly resistant.
- **NS5A:** The susceptibility of 402 sequences was analysed. The percentage of resistant samples was similar for all four NS5A inhibitors, 10.2%-12.0% (Fig. 3).
- **NS5B:** The sequence sets used for the analysis of each of the NS5B inhibitors varied, since the described RAM-patterns for each drug encomprise different amino acid residues. While 14.2% of the 502 sequences used for DSV screening were reported as resistant, none of the 912 samples screened for SOF were predicted as resistant (Fig. 4).

Gene	RAM	hits	%
NS3	36A/G/M	9	1,5
	43I/L/S/V	0	0,0
	80K	108	18,2
	122R	1	0,2
	155C/C/G/M/Q/T	1	0,2
	155K	9	1,5
	156F/G/N/S/T/V	2	0,3
	1687A/E/G/H/I/K/N/Q/T/V	9	1,6
	170I/T	86	15,1
NS5A	28A/T/V	19	4,7
	30D/E/H/K/R/S	18	4,5
	31F/I/M/V	12	3,0
	32L	0	0,0
	58D	0	0,0
	92K	0	0,0
	93C/H/N	16	4,0
NS5B	282T	0	0,0
	316Y	3	0,3
	368T	0	0,0
	411S	0	0,0
	414T	0	0,0
	448C/C	3	0,3
	553T/V	4	0,8
	554S	2	0,4
	556G/N/R	58	13,0

Table 1: DAA-RAMs detected at baseline

Baseline RAM analysis:

The prevalence of the mutations NS3 80K and 170I (18.2% and 14.8% respectively; Table 1), leads to baseline resistance to SMV and GZV (21.8% and 16.5%, respectively). In addition, substitutions on other five amino acid positions were found in lower proportions.

In the NS5A, amino acids exchanges at positions 28, 30, 31 and 93 were found, leading to NS5A baseline resistance of 10%. In the NS5B, the mutations 556GNR were found in 13.0% of the cases.

CONCLUSIONS:

DAA susceptibility may be compromised at baseline. Baseline sequencing of target genes is cost-effective procedure to asses viral genotype in the DAA target genes and to determinate resistance. These two parameters can help the physician to determine the best treatment and avoid misclassification of viral recombinant GTs.

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ARE HIV/HCV CO-INFECTED PATIENTS MORE LIKELY TO EXPERIENCE MULTIPLE LINES OF ANTIRETROVIRAL THERAPY (ART) THAN HIV MONO-INFECTED PATIENTS?

P 253

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Background

New antiretroviral drugs show a favorable liver safety profile and are currently recommended by guidelines for HIV/ HCV co-infection.

The impact of cART on liver fibrosis is debated. Some data suggested that cART itself may accelerate the progression of HCV-related liver disease (Rancinan C et al, AIDS, 2002). Other studies supported the beneficial role of cART in slowing HCV progression (Benhamou Y et al, Hepatology, 2001; Moshen AH et al, Gut, 2003) and in reducing mortality among HIV/HCV co-infected patients (Qurishi N et al, Lancet, 2003).

It is unclear whether HCV status would lead to more or less frequent ART use over time for fear of hepatoxicity or poor adherence.

Despite a common perception that HIV-HCV co-infected patients seem to be exposed to more lines of antiretroviral therapy due to hepatotoxicity and/or poor adherence, confirmatory data are strongly needed.

Aims

We aimed to asses whether HIV-HCV co-infected patients are subjected to higher frequency of ART changes as compared to HIV mono-infected patients for a given time in care.

Methods

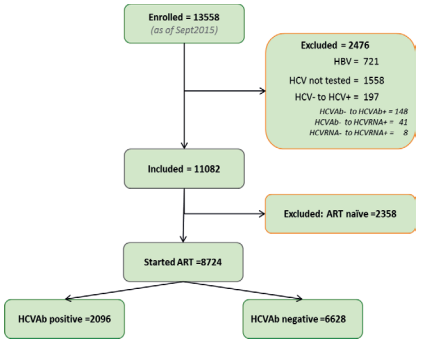
We selected patients enrolled in ICONA Foundation Study Cohort who started cART and were ever tested for HCV Ab at least once over follow-up. Patients were defined to be :

-HCV infected if they tested postive for anti-HCV (HCVAb+).

-Patients HBV co-infected, those who seronverted for HCV and those who never started ART were excluded from the analysis [Figure 1].

- Total ART lines exposed to were calculated :
  - counting all changes regardless of reason of changing
  - counting only switches that occurred for a specific reasons as reported by the clinician including: treatment failure (virological or immunological), toxicity/intolerance, treatment simplification and other/unknown.
- All analyses were stratified by HCVAb status. ART use was assessed a continuous and categorical variable with cut-offs using quartiles.
- Summary statistics were presented for description purposes and formal statistical tests were used to compared differences in ART use in both groups.
- Unadjusted and adjusted logistic regression models were fitted to assess the association between HCV infection and ART use for all reasons and separately for specific reasons.
- For adjusted analysis, models were fitted first with only ART use as the covariate, secondly with variables (age, CD4 HIV-RNA, mode of HIV transmission, calendar year, follow-up duration, gender, nationality, smoking, alcohol consumption) and finally another model including also previous use of individual drugs.

Figure 1. Patient selection flow diagram



HCV-RNA neg was defined as HCV-RNA<615 IU/L

Results I

Table 1. Patient characteristics stratified by HCVAb status

Characteristics	HCVAb+	HCVAb-	Total	*p-value
	N= 2096	N= 6628	N= 8724	
Age, years				
Median (IQR)	37 (33, 42)	38 (31, 46)	38 (32, 45)	<.001
Mode of HIV Transmission, n(%)				
PWID	1590 (75.9%)	193 (2.9%)	1783 (20.4%)	<.001
MSM	135 (6.4%)	2691 (40.6%)	2826 (32.4%)	
Heterosexual contacts	307 (14.6%)	3229 (48.7%)	3536 (40.5%)	
Other/Unknown	64 (3.1%)	515 (7.8%)	579 (6.6%)	
CD4 count , cells/mmc				
≤350	1321 (63.0%)	3652 (55.1%)	4973 (57.0%)	<.001
351-500	434 (20.7%)	1437 (21.7%)	1871 (21.5%)	
>501	285 (13.6%)	1006 (15.2%)	1291 (14.8%)	
Unknown	56 (2.7%)	533 (8.0%)	589 (6.7%)	
CD4 count nadir, cells/mmc				
≤350	1435 (68.5%)	4116 (62.1%)	5551 (63.6%)	<.001
351-500	407 (19.4%)	1461 (22.0%)	1868 (21.4%)	
>501	239 (11.4%)	897 (13.5%)	1136 (13.0%)	
Unknown	15 (0.7%)	154 (2.3%)	169 (1.9%)	
Viral load, log10 copies/mL				
≤1000	137 (6.5%)	291 (4.4%)	428 (4.9%)	<.001
1001 – 5000	166 (7.9%)	429 (6.5%)	595 (6.8%)	
5001- 10,000	119 (5.7%)	355 (5.4%)	474 (5.4%)	
10,001- 100,000	885 (42.2%)	2584 (39.0%)	3469 (39.8%)	
>100,001	700 (33.4%)	2336 (35.2%)	3036 (34.8%)	
Unknown	89 (4.2%)	633 (9.6%)	722 (8.3%)	
Gender, n(%)				
Female	578 (27.6%)	1674 (25.3%)	2252 (25.8%)	0.034
Nationality, n(%)				
Italian	1990 (94.9%)	5484 (82.7%)	7474 (85.7%)	<.001
Smoking, n(%)				
No	245 (11.7%)	2786 (42.0%)	3031 (34.7%)	<.001
Yes	729 (34.8%)	1910 (28.8%)	2639 (30.2%)	
Unknown	1122 (53.5%)	1932 (29.1%)	3054 (35.0%)	
Alcohol consumption, n(%)				
Abstainer	411 (19.6%)	2292 (34.6%)	2703 (31.0%)	<.001
Moderate	232 (11.1%)	1294 (19.5%)	1526 (17.5%)	
+Hazardous	150 (7.2%)	375 (5.7%)	525 (6.0%)	
Unknown	1303 (62.2%)	2667 (40.2%)	3970 (45.5%)	

Results II

Table 2 - Number of changes in ART use stratified by HCVAb status: HCVAb+ were more likely to be exposed to multiple lines of ART than HCVAb mono-infected individuals

All switches (N =8724)	HCVAb+ N= 2096	HCVAb- N= 6628	Total N= 8724	p-value
N. of ARV lines				
Median (IQR)	2 (1, 4)	2 (1, 3)	2 (1, 3)	<.001
No of ARV lines, n(%)				<.001
1	671 (32.0%)	2756 (41.6%)	3427 (39.3%)	
2-3	713 (34.0%)	2563 (38.7%)	3276 (37.6%)	
>3	712 (34.0%)	1309 (19.7%)	2021 (23.2%)	
Only switches due to virological/immunological failure (N =841)	**HCVAb+**	**HCVAb-**	**Total**	**p-value**
N. of ARV lines				
n	273	568	841	
Median (IQR)	3 (1,4)	2 (1,4)	3 (1,4)	0.335
No of ARV lines, n(%)				<.001
None	1823 (87.0%)	6060 (91.4%)	7883 (90.4%)	
1	76 (3.6%)	148 (2.2%)	224 (2.6%)	
2-3	94 (4.5%)	231 (3.5%)	325 (3.7%)	
>3	103 (4.9%)	189 (2.8%)	292 (3.4%)	
Only switches due to toxicity/ intolerance (N = 1613)	**HCVAb+**	**HCVAb-**	**Total**	**p-value**
N. of ARV lines				
n	509	1104	1613	
Median (IQR)	3 (2,5)	3 (2,4)	3 (2,4)	0.032
No of ARV lines, n(%)				<.001
None	1587 (75.9%)	5524 (83.3%)	7111 (81.5%)	
1	106 (5.1%)	216 (3.3%)	322 (3.7%)	
2-3	208 (9.9%)	559 (8.4%)	767 (8.8%)	
>3	195 (9.3%)	329 (5.0%)	524 (6.0%)	
Only switches due to simplification (N = 1427)	**HCVAb+**	**HCVAb-**	**Total**	**p-value**
N. of ARV lines				
n	272	1155	142	
Median (IQR)	3 (2,5)	2 (2,4)	2 (2,4)	0.043
No of ARV lines, n(%)				<.001
None	1824 (87.1%)	5473 (82.6%)	7297 (83.6%)	
1	17 (0.8%)	126 (1.9%)	143 (1.6%)	
2-3	143 (6.8%)	738 (11.1%)	881 (10.1%)	
>3	112 (5.3%)	291 (4.4%)	403 (4.6%)	
Other/Unknown (n =6489)	**HCVAb+**	**HCVAb-**	**Total**	**p-value**
N. of ARV lines				
n	1547	4942	6489	
Median (IQR)	2 (1,4)	1 (1,3)	1 (1,3)	<.001
No of ARV lines, n(%)				<.001
None	549 (26.2%)	1686 (25.4%)	2235 (25.6%)	
1	640 (30.5%)	2704 (40.8%)	3346 (38.4%)	
2-3	446 (21.3%)	1417 (21.4%)	1863 (21.3%)	
>3	461 (22.0%)	819 (12.4%)	1280 (14.7%)	

*Kruskall Wallis test and chi-squared tests

Results III

Table 3 - Adjusted logistic regression models for HCV Ab+: HCV Ab co-infection was associated with an increased independent OR of changing ART

All switches (N=8724)	Unadjusted ORs (95% CI)	p-value	**Adjusted OR(95%CI)	**p-value	***Adjusted OR(95%CI)	***p-value
No. of ARV lines						
per additional	1.14 (1.12, 1.16)	<.001	1.0 (0.96, 1.05)	0.807	1.02 (0.98, 1.10)	0.536
1	1.0		1.0		1.0	
2-3	1.14 (1.02, 1.29)	0.027	0.977 (0.80, 1.20)	0.820	1.171 (0.98, 1.47)	0.176
>3	2.234 (1.97, 2.53)	<0.001	1.144 (0.87, 1.50)	0.333	1.622 (1.11, 2.32)	0.008
Only switches due to treatment failure (N =841)	**Unadjusted ORs (95% CI)**	**p-value**	**Adjusted OR(95%CI)**	**p-value**	**Adjusted OR(95%CI)**	**p-value**
per additional	1.09 (1.05, 1.13)	<.001	0.975 (0.92, 1.04)	0.400	0.928 (0.87, 0.99)	0.034
None	1.0		1.0		1.0	
1	1.700 (1.29, 2.26)	<.001	0.750 (0.47, 1.20)	0.233	0.800 (0.45, 1.31)	0.375
2-3	1.353 (1.06, 1.73)	0.016	0.824 (0.54, 1.25)	0.362	0.777 (0.50, 1.20)	0.254
>3	1.812 (1.42, 2.32)	<.001	0.881 (0.58, 1.34)	0.552	0.999 (0.64, 1.12)	0.139
Only switches due to simplification (N = 1427)	**Unadjusted ORs (95% CI)**	**p-value**	**Adjusted OR(95%CI)**	**p-value**	**Ajusted OR(95%CI)**	**p-value**
per additional	0.977 (0.94, 1.01)	0.190	0.947 (0.89, 1.00)	0.0617	0.949 (0.94, 1.01)	0.081
None	1.0		1.0		1.0	
1	0.405 (0.24, 0.67)	<.001	0.282 (0.13, 0.63)	0.002	0.312 (0.14, 0.69)	0.004
2-3	0.581 (0.48, 0.70)	<.001	0.888 (0.66, 1.20)	0.444	0.938 (0.68, 1.29)	0.691
>3	1.155 (0.92, 1.45)	0.208	0.839 (0.57, 1.23)	0.368	0.879 (0.59, 1.31)	0.528
Only switches due to toxicity/ intolerance (N = 1613)	**Unadjusted ORs (95% CI)**	**p-value**	**Adjusted OR(95%CI)**	**p-value**	**Ajusted OR(95%CI)**	**p-value**
per additional	1.11 (1.08, 1.14)	<.001	1.01 (0.96, 1.05)	0.835	0.993 (0.94, 1.05)	0.779
None	1.0		1.0		1.0	
1	1.708 (1.35, 2.17)	<.001	1.121 (0.74, 1.69)	0.586	1.220 (0.86, 1.86)	0.354
2-3	1.295 (1.09, 1.53)	0.003	1.096 (0.83, 1.45)	0.522	1.380 (0.8, 1.43)	0.602
>3	2.063 (1.71, 2.48)	<.001	0.918 (0.65, 1.29)	0.623	0.896 (0.6, 1.31)	0.572
Other/Unknown (N =6489)	**Unadjusted ORs (95% CI)**	**p-value**	**Adjusted OR(95%CI)**	**p-value**	**Ajusted OR(95%CI)**	**p-value**
per additional	1.11 (1.08, 1.13)	<.001	1.01 (0.97, 1.05)	0.497	1.01 (0.97, 1.06)	0.587
None	1.0		1.0		1.0	
1	0.726 (0.64, 0.83)	0.001	0.971 (0.76, 1.23)	0.808	0.801 (0.6, 1.05)	0.105
2-3	0.967 (0.84, 1.12)	0.643	0.903 (0.71, 1.15)	0.415	0.889 (0.68, 1.15)	0.361
>3	1.729 (1.49, 2.01)	<.001	1.138 (0.88, 1.47)	0.329	1.211 (0.91, 1.61)	0.187

** Adjusted only factors used in matching age, cd4, HIV-RNA, mode of HIV transmission, gender, nationality, smoking, alcohol consumption and calendar year, follow-up duration

*** Adjusted for age, CD4+, HIV-RNA, mode of HIV transmission, gender, nationality, smoking, alcohol consumption, calendar year, follow-up duration and previous use of individual drugs.

Conclusions

- Overall, HCVAb+ individuals are more likely to be exposed to multiple lines of antiretroviral therapy than HIV mono-infected while in care, especially when comparing people who used at least three ART lines.
- The higher probability of changing ART in HCVAb+ versus HCVAb-negative patients seems driven by reasons that are not captured by the investigation of viro-immunological failure, toxicity and simplification as reported by the physician.

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Rapid decline of anti-HCV antibodies following treatment of incident HCV infection in HIV-infected MSM in the Swiss HIV Cohort Study (SHCS)

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POSTER 254

BACKGROUND

- Following clearance of Hepatitis C virus (HCV) infection, HCV antibody titers (anti-HCV) may decline resulting in seroreversion
- It is unclear, whether changes in antibody levels differ between patients with spontaneous HCV clearance, those treated during early HCV infection and those with chronic hepatitis C.

METHODS

- We compared anti-HCV dynamics following an incident HCV infection after HIV diagnosis in 67 HIV-seropositive men who have sex with men (MSM)
- Anti-HCV antibody levels were measured at baseline and annually for 3 years using a commercial ELISA kit (ARCHITEKT, Abbott Laboratories).
- Results were compared to 12 SHCS participants with chronic HCV infection acquired before HIV-diagnosis and SVR following treatment during chronic HCV-infection.
- We compared the relative change [%] in antibody levels between patient groups by estimating: i) the maximum drop over the study period and ii) rates of decline per year over time.
- We assessed the relationship between time from HCV infection to treatment start and the speed of decline in antibody levels.

RESULTS

Table 1: Sociodemographic and clinical characteristics of MSM cohort within the SHCS with an incident HCV infection at time of HCV diagnosis.

	All n=67	Spontaneous clearance n= 12 (%)	SVR after treatment n=33 (%)	Chronic Infection n=22(%)	p-value
Median age in years (IQR)	35(31-42)	34(31-36)	34 (31-41)	35(29-45)	
Median CD4 in cells/µL (IQR)	544(350-675)	637(569-926)	508(356-602)	443(300-616)	
CD 4 cells <350	14(22.2)	0(0)	7(21.2)	8(36.4)	0.025
On ART	57(90.5)	12(100)	30(90.9)	19(86.4)	0.384
Suppressed HIV VL	45(71.4)	8(66.7)	27(81.8)	13(59.1)	0.471
Occasional sexual partners (n=60)	55(87.3)	11(91.6)	31(93.9)	17(77.3)	0.289
Inconsistent condom use (n=63)	46(73.0)	10(83.3)	26(78.8)	13(59.1)	0.303
History of syphilis (n=63)	27(42.9)	5(41.7)	20(60.6)	6(27.3)	0.163
HCV genotype (n=57)					
1	34(51)	6(50.0)	16(48.5)	12(54.6)	0.224
2	1(1.5)		1(3.0)	1(4.5)	
3	8(11.9)		7(21.2)	2(9.1)	
4	14 (20.9)	1(8.3)	6(18.1)	5(22.7)	
IL28B	38(56.7)	9(75.0)	16(48.5)	12(54.6)	0.494
HCV antibody drop within 3 years >20%	35(55.6)	7(58.3)	31(93.9)	1(4.6)	<0.001

- MSM with SVR following treatment of incident HCV infections experienced a more pronounced decrease in anti-HCV levels within the first 3 years after treatment (median decline 71%) compared to patients with spontaneous clearance (median decline 37.6%, P<0.001, fig. 1A).

- 5/33 (15%) with SVR and 1/12 (8%) with spontaneous clearance had a seroreversion (figure 1A, grey dots)

- **Exponential rate of decline in relative antibody levels (Figure 1B)**

  Patients with **SVR following an incident acute HCV infection:** rate[IQR] = -0.47[-0.18 to-0.85]),
  Patients with **spontaneous clearance**: -0.15[-0.06 to -0.27])
  Patients with **SVR due to HCV treatment during chronic HCV infection:** +0.05[-0.05-0.13].

- Shorter delay between time of infection and treatment start was associated with higher rates of decline in antibody levels (**Figure 2**).

- 7 subjects experienced a re-infection during follow-up, 2 of those 2 re-infections: anti-HCV levels increased above the level of primary infection

- We found no association between antibody decline and HCV genotype, IL28B, CD4+ T cell count and HIV viral load

Figure 1 A : Maximum change in antibody titers during follow-up

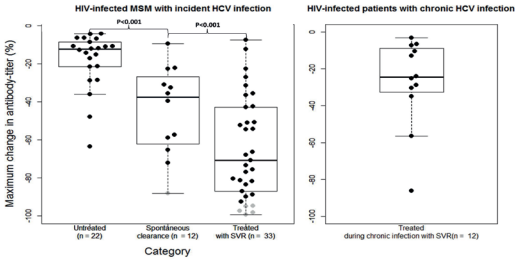

Figure 1 B : Relative change in antibody titers during follow-up

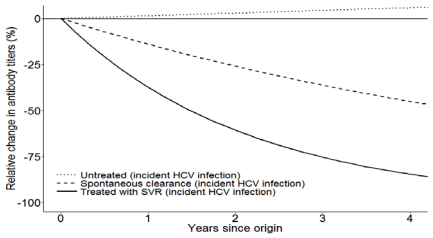

Figure 2: Relationship of the time intervall between diagnosis and treatment and the decline of antibody titer

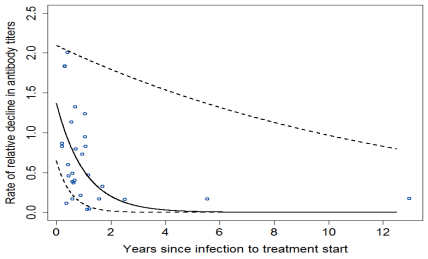

Figure 2. Estimated rates per patient (blue dots), exponential fit (solid line), 95% confidence intervals (dashed line), Residual standard error: 0.4881

CONCLUSION

- Treatment-induced HCV clearance was associated with a more pronounced decline in anti-HCV antibody levels and with higher rates of sero-reversions compared to spontaneous HCV clearance or to chronic HCV infection among HIV-infected MSM with incident HCV infections.
- Shorter time between diagnosis and treatment was associated with a faster decline of anti-HCV antibodies.
- These results suggest that fast clearance of HCV-RNA following treatment of incident HCV-infections might lead to a limited viral antigen stimulation required for a persistent antibody response.

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The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers).

Members of the Swiss HIV Cohort Study

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P255

Effectiveness of hepatitis A vaccination in HIV-positive men who have sex with men during an ongoing hepatitis A outbreak in Taiwan

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Introduction

1. During June 2015 to September 2016, more than 750 indigenous cases of acute HAV infections were reported in Taiwan, with more than half in patients being HIV-positive men who have sex with men (MSM).
2. Hepatitis A vaccination has been recommended for MSM.
3. The serological response to hepatitis A vaccination is reduced in HIV-positive patients compared with HIV-negative persons.
4. This ongoing study aimed to evaluate the effectiveness of hepatitis A vaccination among HIV-positive patients.

Methods

1. Design: prospective cohort study, June 2015 to September 2016.
2. Study site: National Taiwan University Hospital, the major designated hospital for HIV care in Taiwan.
3. Included subjects: HIV-positive patients aged 20 years or greater with negative baseline anti-HAV IgG since June 2015.
4. Outcomes:
   (1) Serological outcomes: seroconversion rates after the first dose of hepatitis A vaccination.
   (2) Clinical outcome: incident acute HAV infection.
5. Generalized estimating equation (GEE) was used to determine the associations between the predictor variables and repeated measured serological outcomes.

Results

1. 1597 HIV-positive patients tested negative for anti-HAV IgG at baseline (Figure 1).
   - 1053 patients (65.9%) had received the first dose of HAV vaccine (Table 1).
   - 324 patients (20.3%) had completed the 2-dose HAV vaccine series.
2. The overall seroconversion rate before the last dose of HAV vaccination was 32.9% (347/1056). One month after the last dose, the seroconversion rate increased to 94.6% (191/202) (Figure 2).
3. In multivariable GEE analysis, the independent factors associated with seroconversion between the first and the last doses of HAV vaccination were receiving VAQTA®, time to anti-HAV IgG testing, and previous hepatitis A vaccination (Table 2).
4. Three vaccinees and 48 non-vaccinees had incident acute HAV infections, resulting in vaccine effectiveness of 93.8% (Figure 3).

Figure 1. Study flow diagram

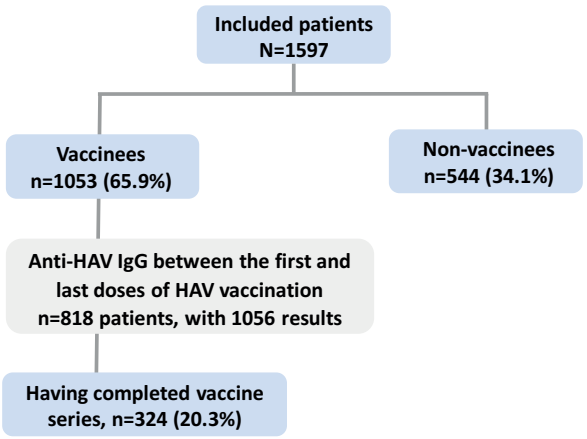


Table 1. Comparisons of the clinical characteristics between vaccinees and non-vaccinees

	Vaccinees (n=1053)	Non-vaccinees (N=544)	*p*
Age, mean (SD), years	35.7 (7.9)	34.0 (7.8)	<0.001
Male, n (%)	1035 (98.3)	523 (96.1)	0.008
Men who have sex with men, n (%)	1004 (95.4)	503 (92.5)	0.018
HBsAg positivity, n (%)	114 (10.8)	44 (8.1)	0.082
Anti-HCV positivity, n (%)	66 (6.3)	56 (10.3)	0.004
Antiretroviral therapy use, n (%)	1022 (97.1)	495 (91.0)	<0.001
Baseline CD4 count, median (range), cells/μL	573 (5-1772)	559 (4-2342)	0.006
Baseline PVL, median (range), $\log_{10}$ copies/mL	UD (UD-5.18)	UD (UD-7.23)	<0.001
Previous hepatitis A vaccination, n (%)	79 (7.5)	13 (2.4)	<0.001

Figure 2. Seroconversion rates after the first dose of hepatitis A vaccination

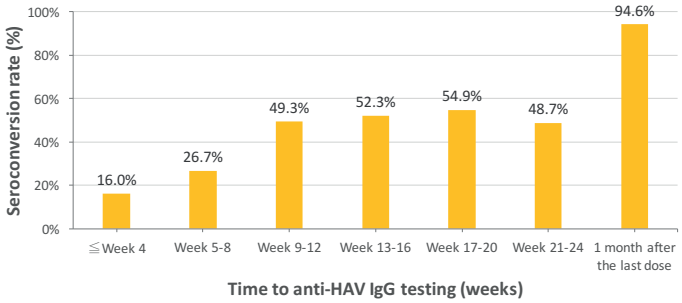
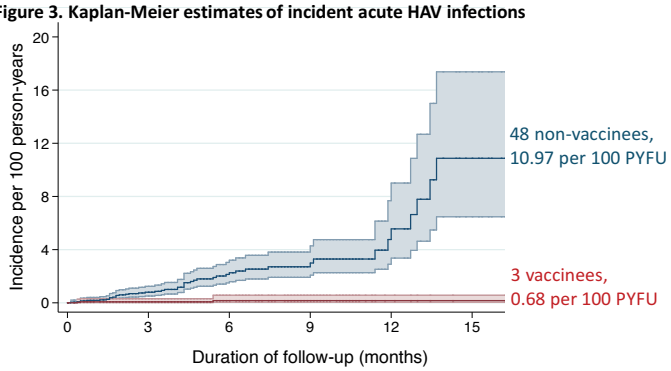


Table 2. Factors associated with HAV seroconversion between the first and the last doses

Multivariable GEE analysis	Adjusted OR (95% CI)	*p*
Age, per 1-year increase	0.99 (0.96-1.01)	0.390
Men who have sex with men	1.26 (0.50-3.18)	0.624
Weight, per 1-kg increase	1.00 (0.99-1.02)	0.914
Smoking	1.09 (0.73-1.63)	0.689
HBsAg positivity	0.57 (0.32-1.02)	0.059
Anti-HCV positivity	0.99 (0.39-2.50)	0.987
Nadir CD4, , per 1-cells/μL increase	1.001 (1.000-1.002)	0.250
CD4 count at vaccination, per 1-cell/μL increase	1.001 (1.000-1.001)	0.113
PVL at vaccination, per 1-$\log_{10}$ copies/mL increase	0.95 (0.77-1.18)	0.657
Vaccine type, VAQTA® vs. HAVRIX®	2.43 (1.63-3.62)	<0.001
Time to anti-HAV IgG testing, per 1-week increase	1.12 (1.09-1.14)	<0.001
Previous hepatitis A vaccination	29.99 (11.76-76.47)	<0.001

Figure 3. Kaplan-Meier estimates of incident acute HAV infections



Conclusions

Despite the delayed serologic response to hepatitis A vaccination in HIV-positive patients, the risk of acute HAV infection was significantly reduced among the vaccinated patients during the HAV outbreak setting.

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High Sustained Virological Response rates using imported Generic Direct Acting Antiviral Treatment for Hepatitis C, imported into Australia, UK, Europe and North America

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Introduction:
High prices of Direct Acting Antivirals (DAAs) can prevent access to treatment.
Generic versions of DAAs are being mass produced for prices under 1% of the current US retail price.
Under UK and Australian law, individual patients have the legal right to import 3 months of treatment for Hepatitis C, for their personal use.
This analysis assessed the efficacy and safety of generic DAAs legally imported into countries where treatment access is limited.

Methods:
Sofosbuvir (SOF), ledipasvir (LDV) and daclatasvir (DCV) were imported from generic companies into Europe, Australia, North America and other countries worldwide.
Selection of DAAs and treatment duration depended on baseline HCV Genotype and fibrosis stage.
Initial generic supplies were evaluated using High Precision Liquid Chromatograhy (HPLC) and Nuclear Magnetic Resonance (NMR) to evaluate presence of active drug.
Patients taking generic DAAs were evaluated pre-treatment, and at Weeks 4 (to evaluate Rapid Virological Respone (RVR), at the end of Treatment (EOT) and then for Sustained Virological Response (SVR) 4 and 12 weeks after the end of treatment.
This analysis includes data from 448 patients, whose imported treatment was organised from the FixHepC website.

Results:
Of the 448 patients treated, 237 received SOF/LDV, 208 SOF/DCV and 3 SOF/RBV. By HPLC and NMR, all imported drugs passed quality control standards for active DAA drugs.
Overall, the patients were 57% male with a mean age of 55 years; 66% were Genotype 1, 25% Genotype 3 and mean baseline HCV RNA was 6.5 log10 IU/mL.
Based on currently available data, the percentage with HCV RNA <25 IU/mL was 376/380 (98.9%) at end of treatment (EOT), 192/211 (91%) at SVR 4 and 130/144 (90%) at SVR12.
Summary baseline and outcome data from the patients given SOF/LDV or SOF/DCV are shown in Table 1 and Table 2.

Conclusions:
In this analysis, treatment with legally imported generic DAAs achieved SVR4 rates of 92% on SOF/LDV and 85% on SOF/DCV.
These SVR rates are comparable to those seen in Phase 3 trials of the same, but more expensive, branded treatments. Mass treatment with legally imported generic DAAs is a feasible, low-cost option where high prices prevent access to branded treatment.

Acknowledgements:
We would like to thank all of the authors and their institutions for collaborating on this work, and all of the patients from the FixHepC community for pioneering this style of treatment and data collection.

Table 1: Baseline Characteristics

Patients	SOF/RBV N=3	SOF/DCV N=198	SOF/LDV N=237
% Male	67%	58%	53%
% Cirrhosis	67%	34%	21%
% GT 1	0%	41%	90%
% GT 3	0%	46%	5%
+ RBV	100%	11%	9%

Figure 1: Patients by Genotype

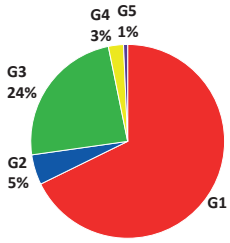


Figure 2: Fibrosis scores of patients

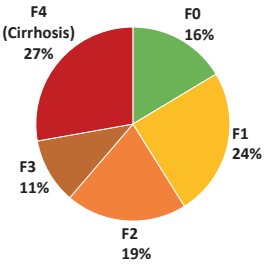


Figure 3: Examples of generic treatments taken by patients

Imported Active Pharmaceutical Ingredients (APIs) from China, compounded and encapsulated in local pharmacies in Australia

Table 2: HCV RNA <25 IU/mL during study

Patients	SOF/RBV N=3	SOF/DCV N=198	SOF/LDV N=237
RVR	2/2 (100%)	95/111 (86%)	82/98 (84%)
EOT	3/3 (100%)	182/184 (99%)	191/193 (99%)
SVR 4	3/3 (100%)	117/100 (85%)	119/130 (92%)
SVR 12	3/3 (100%)	107/132 (81%)	129/148 (87%)

Figure 4: SVR4 responses by genotype

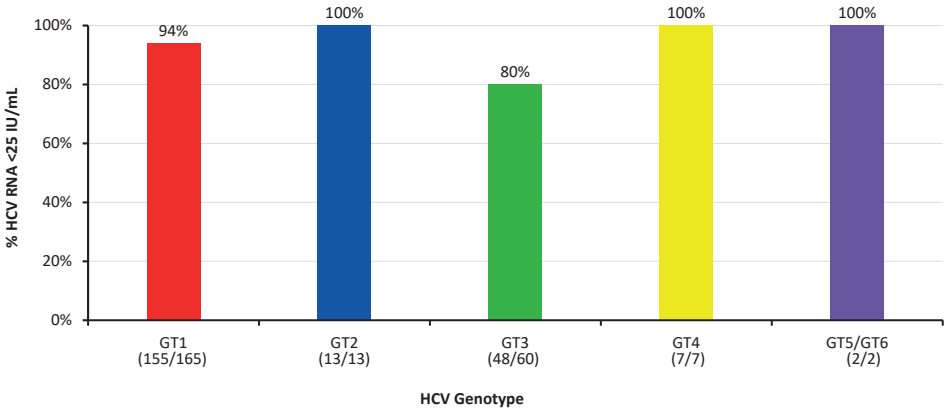
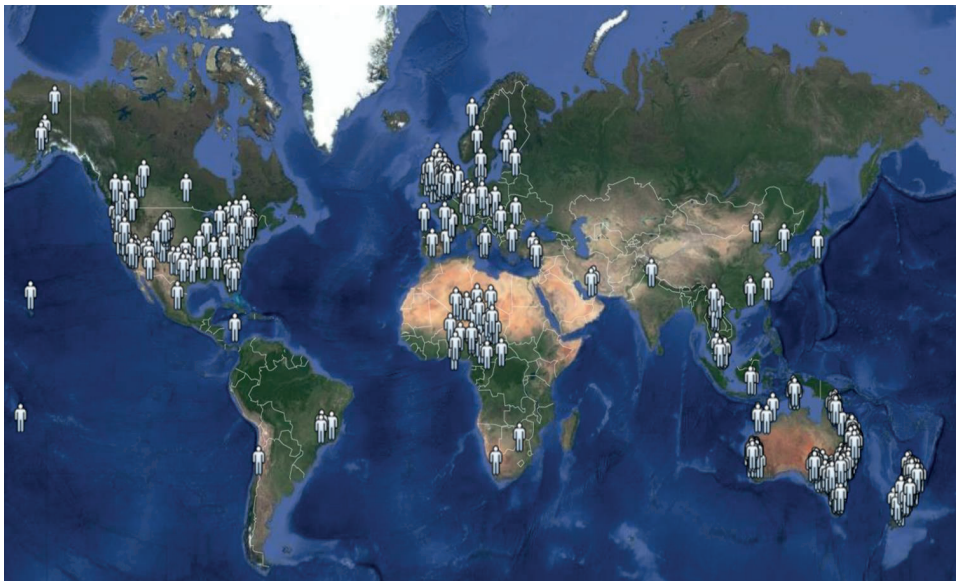


Figure 5: Locations of patients, FixHepC community



Long-Term Virological and Serologic Response of Chronic Hepatitis B Virus Infection to Tenofovir Disoproxil Fumarate-Containing Regimens in HIV-Positive Patients

P-257

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Abstract

Background: Tenofovir disoproxil fumarate (TDF) combined with lamivudine (3TC) or emtricitabine are the recommended nucleos(*t*)ide reverse-transcriptase inhibitors backbone for patients coinfected with HIV and HBV. TDF leads to rapid decline of HBV DNA. However, data regarding the durability of HBV suppression of TDF-containing combination antiretroviral therapy (cART) in HIV/HBV-coinfected patients are scarce in hyperendemic area of chronic HBV infection. We aimed to assess the long-term virological response of HBV to TDF-containing cART in HIV-positive patients in Taiwan where the prevalence of chronic HBV infection was estimated 15-20% in persons born before nationwide neonatal HBV vaccination program was implemented in 1986.

Materials and Methods: Between 2004 and 2016, 405 HIV/HBV-coinfected patients were followed for 5 years or longer. Serial blood samples were collected for determinations of plasma HBV DNA load, HBV serologic markers (HBsAg, anti-HBs, HBeAg, and anti-HBe), and liver and renal functions. Factors associated with undetectable HBV DNA at 5 years of treatment were explored by logistic regression.

Results: Of 405 HIV/HBV-coinfected patients included, 137 received cART which contained 3TC as the only therapy for HBV, 115 received TDF-containing cART as initial anti-HBV therapy, and 153 switched to TDF-containing cART after detection of resistance-associated mutations of HBV to 3TC or an elevation of HBV DNA load. The percentage of HBV viral suppression at year 1 and year 5 were 63.9% and 77.3%, respectively, in patients receiving 3TC monotherapy for HBV, 91.3% and 100%, respectively, in patients receiving TDF-containing regimens as their first cART, and 90.2% and 94%, respectively in patients switching to TDF-containing cART,. In multivariate analysis, the only factor associated with failure to achieve viral suppression at 5 years was higher HBV DNA load at baseline (adjusted odds ratio [AOR], per 1-$\log_{10}$ copies/mL increase, 1.812; 95% confidence interval [CI], 1.269-2.588, p=0.0.1). TDF exposure was of borderline statistical significance (AOR 0.211; 95% CI, 0.004-1.124, p=0.068) in the analysis. During study period, 13 of 59 patients (22.0%) with baseline HBeAg positivity had HBeAg seroconversion and loss of HBsAg was observed in 8 patients (2.0%).

Conclusions: TDF-containing cART achieved durable HBV viral suppression in HIV/HBV-coinfected patients. A higher HBV DNA load at baseline was associated with failure to achieve HBV viral suppression after long-term TDF-containing cART.

Introduction

1. Tenofovir disoproxil fumarate (TDF) leads to rapid decline of HBV DNA, and it is effective for treating chronic hepatitis B in HIV-positive patients failing lamivudine (3TC).
2. For HBV/HIV-coinfected patients, TDF combined with 3TC or emtricitabine (FTC) are the recommended NRTI backbone regimens, and a lifelong treatment duration is suggested.
3. Our study aimed to evaluate the durability of TDF-containing regimens to suppress HBV replication and the change of HBV serology markers in HBV/HIV-coinfected patients receiving long-term TDF-containing regimen. Factors associated with failure to achieve HBV viral suppression after 5 years of treatment will be explored.

Methods

1. A retrospective study was conducted from Jan 2004 to June 2016. HIV/HBV-coinfected adult patients who were regularly followed at NTUH were included.
2. 3 groups were defined: (1) 3TC group: patients who took 3TC-containing cART as the initial and only regimen; (2) TDF group: TDF/3TC (or FTC)-containing cART as the initial regimen; (3) 3TC switch to TDF/3TC (FTC) group: patients who switch from 3TC to TDF/3TC (or FTC)-containing cART .
3. Serial blood samples were collected for determinations of plasma HBV DNA load, HBV serologic markers (HBsAg, anti-HBs, HBe Ag, and anti-HBe), and liver functions after initiation of cART with or without TDF. Undetectable plasma HBV DNA was defined as <128 copies/ml.
4. Factors associated with undetectable HBV DNA at 5 years of treatment were explored by logistic regression.

Results

1. 405 patients were included for analysis: 137 received cART which contained 3TC as the only therapy for HBV, 115 received TDF-containing cART as initial anti-HBV therapy, and 153 switched to TDF-containing cART after detection of resistance-associated mutations of HBV to 3TC or an elevation of HBV DNA load (Table 1).
2. The percentage of HBV viral suppression at year 1 and year 5 were 63.9% and 77.3%, respectively, in patients receiving 3TC monotherapy for HBV, 91.3% and 100%, respectively, in patients receiving TDF-containing regimens as their first cART, and 90.2% and 94%, respectively in patients switching to TDF-containing cART (Figure 2).
3. In multivariate analysis, the only factor associated with failure to achieve viral suppression at 5 years was higher HBV DNA load at baseline (p=0.001) (Table 2).
4. During the study period, 13 of 59 patients (22.0%) with baseline HBeAg positivity had HBeAg seroconversion and loss of HBsAg was observed in 8 patients (2.0%).

Table 1. Baseline clinical characteristics of 405 HBV/HIV-coinfected patients

	3TC (n=137)	TDF/3TC (n=115)	3TC to TDF/3TC (n=153)	p
Age, mean ± SD, years	36.8 ± 8.8	36.9 ± 7.4	41.2 ± 9.0	<0.001
Male sex, n (%)	134 (97.8)	114 (99.1)	147 (96.1)	0.272
Homosexual male, n (%)	113 (82.5)	105 (91.3)	124 (81.0)	0.053
Years since HIV diagnosis, mean ± SD	2.6 ± 3.1	2.7 ± 2.9	7.7 ± 4.6	<0.001
HBV genotype, n (%)	B 71 (51.8) C 21 (15.3) No data 45	B 41 (35.7) C 8 (7.0) No data 66	B 70 (45.8) C 23 (15.0) No data 59	
Prior 3TC use, mean ± SD, years	NA	NA	5.7 ± 4.5	
Document LAM resistance, n (%)	NA	NA	43 (28.1)	
Positive HBeAg at baseline, n/n (%)	10/52 (19.2)	22/85 (25.9)	27/93 (29.0)	0.431
Plasma HBV DNA level at baseline, log10 copies/mL, mean ± SD	4.5 ± 2.6	4.9 ± 2.5	3.6 ± 2.3	<0.001
< 3 $\log_{10}$ copies/mL	50 (36.5)	34 (29.6)	93 (60.8)	
3-5 $\log_{10}$ copies/mL	43 (31.4)	33 (28.7)	28 (18.3)	
>5 $\log_{10}$ copies/mL	44 (32.1)	48 (41.7)	32 (20.9)	
ALT at baseline, IU/L, mean ± SD	99 ± 205	50 ± 60	57 ± 91	0.852
APRI score at baseline, mean ± SD	1.2 ± 2.5	0.9 ± 1.6	0.6 ± 0.6	0.028
Anti-HCV positive at baseline, n (%)	6 (4.4)	10 (8.7)	6 (3.9)	0.186
CD4 cell counts at baseline, mean ± SD, cells/μl	210 ± 173	261 ± 201	514 ± 311	<0.001
Plasma HIV RNA load at baseline, mean ± SD, $\log_{10}$ copies/mL	4.6 ± 1.2	4.7 ± 0.9	1.9 ± 1.0	<0.001
Follow-up duration, mean±SD, years	3.5 ± 1.5	2.6 ± 1.2	3.5 ± 1.5	
HBV DNA <128 copies/mL at year 1, n/n (%)	85/133 (63.9)	105/115(91.3)	138/153 (90.2)	
HBV DNA <128 copies/mL at year 5, n/n (%)	41/53 (77.3)	8/8 (100)	47/50 (94)	

Figure 1. Changes of HBV DNA in HBV/HIV-coinfected patients with 3TC-based cART (n=137), TDF/3TC-containing cART (n=115), or who switched from 3TC-based to TDF/3TC-containing cART (n=153).

Figure 2. Percentage of patients who achieved undetectable HBV DNA in each group (3TC-based cART, TDF/3TC-containing cART, or switched from 3TC-based to TDF/3TC-containing cART)

Figure 1

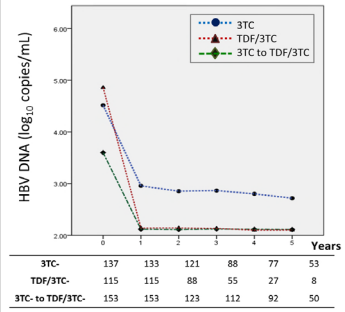

Figure 2

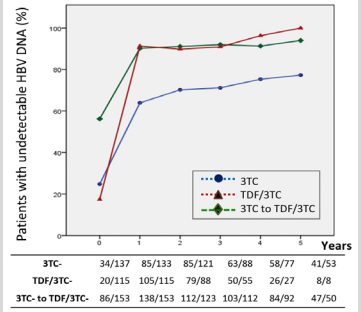

Table 2. Multivariate logistic analysis of the factors associated with failure to achieve viral suppression of hepatitis B virus after 5 years of antiretroviral therapy

Variable	Achieve viral suppression at 5 year (n=96)	Failure to achieve viral suppression at 5 year (n=13)	Logistic Regression			
			OR (95% CI)	Univariate p=	OR (95% CI)	Multivariate p=
Age, years	39.1 ± 8.6	35.9 ± 10.3	0.951 (0.880-1.029)	0.210		
cART duration, years	8.9 ± 4.0	7.7 ± 2.0	0.911 (0.759-1.094)	0.318		
HBV genotype B	50/65 (76.9)	11/13 (84.6)	1.650 (0.329-8.282)	0.543		
Lamivudine resistance of HBV	23/96 (24.0)	3/13 (23.1)	0.952 (0.241-3.757)	0.944		
CD4 count at baseline, cells/μl	388 ± 354	260 ± 222	0.998 (0.996-1.001)	0.205		
Plasma HIV RNA load at baseline, $\log_{10}$ copies/mL	3.3 ± 1.7	4.4 ± 1.7	1.472 (1.012-2.142)	0.043		
Plasma HBV DNA load at baseline, $\log_{10}$ copies/mL	4.1 ± 2.3	6.8 ± 2.6	1.459 (1.152-1.849)	0.002	1.812 (1.269-2.588)	0.001
Tenofovir exposure	55 (57.3)	3 (23.1)	0.224 (0.058-0.864)	0.030	0.211 (0.04-1.124)	0.068
APRI at baseline	0.6 ± 0.6	1.4 ± 2.7	1.511 (0.936-2.440)	0.091	1.625 (0.967-2.73)	0.067
Positive HBeAg at baseline[a]	22/63 (34.9)	5/5 (100)	NA	NA		

Results are *n* (%), or mean ± standard deviation
[a] Five patients who failed to achieve viral suppression and had available baseline HBeAg all had positive HBeAg at baseline and, therefore, the factor was not included in the logistic regression

Conclusions

1. TDF-containing cART achieved durable HBV viral suppression in HIV/HBV co-infected patients.
2. A higher HBV DNA load at baseline and HBeAg positivity at baseline were associated with failure to achieve HBV viral suppression after long-term antiretroviral therapy.
3. The HBsAg loss rate of Taiwanese HBV/HIV-coinfected patient during the 5-year follow-up period is low.

THE EMERGENCE OF HEPATITIS C VIRUS GENOTYPE 4D INFECTION IN MEN WHO HAVE SEX WITH MEN

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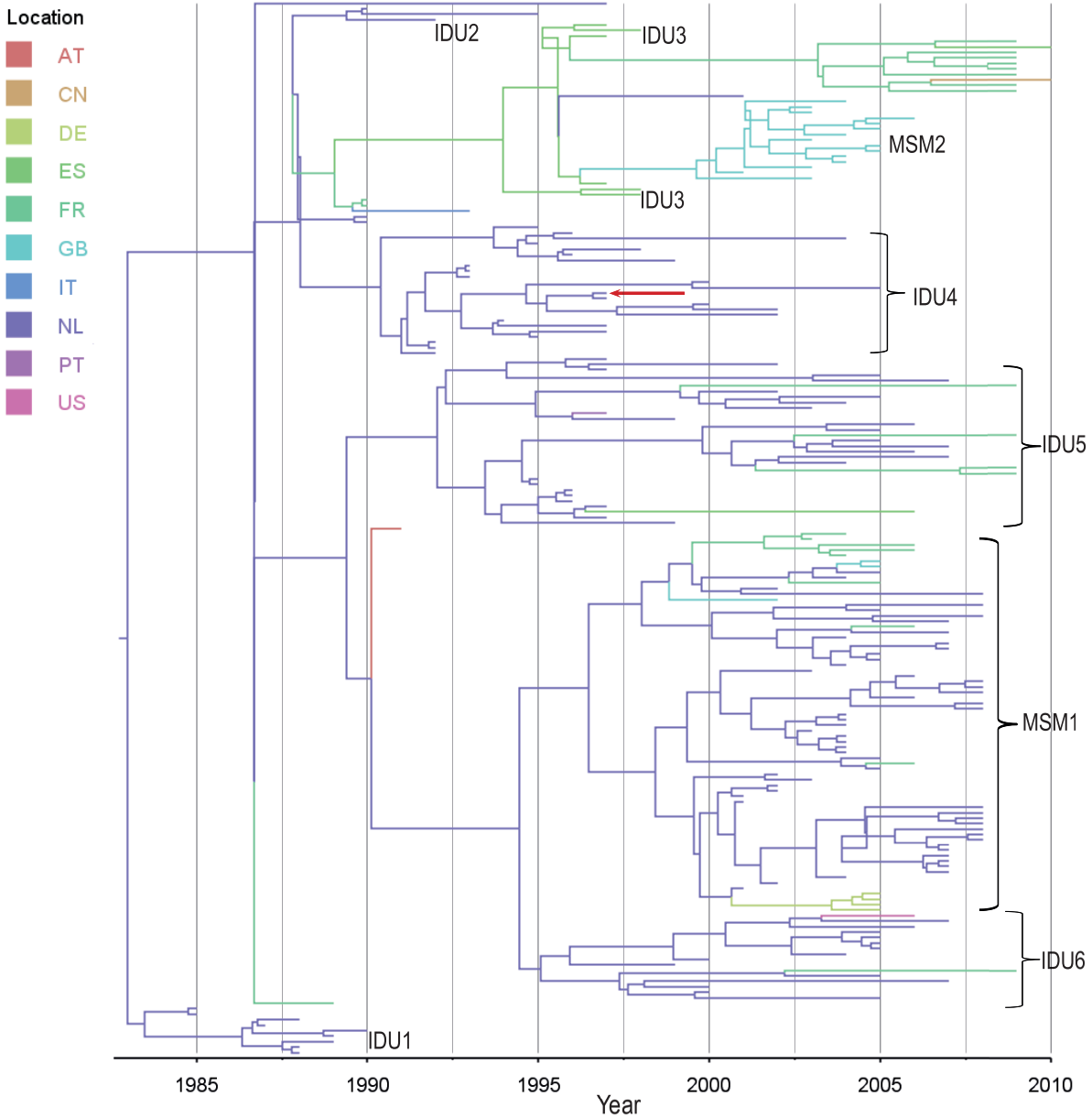

Figure 1: Molecular clock analysis of the 193 sequences using a Bayesian Markov Chain Monte Carlo (MCMC) approach. Branches are coloured by location; AT – Austria, CN – China, DE – Germany, ES – Spain, FR – France, GB – United Kingdom, IT – Italy, NL – Netherlands, PT – Portugal, US – United States of America. The MSM and IDU clusters identified from this analysis are labelled on the figure. The sequence obtained from a Dutch MSM who also reports IDU is indicated by a red arrow.

BACKGROUND

Since 2000, there have been numerous reported cases of acute Hepatitis C virus (HCV) in HIV-positive men who have sex with men (MSM) in developed countries [1]. The majority of these men deny any history of injecting drug use (IDU), making sexual transmission the most likely route of transmission. HCV genotype 4 is increasing in prevalence amongst the MSM population [2], but is subject to less research than other HCV genotypes. This study aims to use a variety of phylogenetic approaches and evolutionary analysis to determine the origins, spread and changing epidemiology of HCV genotype 4d (HCV-4d).

METHOD

NS5B region sequences from patients with HCV-4d were obtained using the Los Alamos HCV Sequence Database and NCBI GenBank. Whole genome sequences were also available from the Acute HCV UK Study using a metagenomic next generation sequencing approach. For each sequence the sample collection date, country and most likely route of HCV infection were recorded. Sequences were aligned and maximum likelihood phylogenetic trees were created with 1000 bootstrap replicates using MEGA software version 6.0.6. Molecular clock analysis was performed using the Bayesian Markov chain Monte Carlo (MCMC) approach on BEAST software version 1.8.2.

RESULTS

193 sequences were used in the final analysis ($n = 193$). Using a maximum likelihood phylogenetic approach, several MSM-specific clusters were seen. In order to attach a timeline to the most recent common ancestors of these clusters, a phylogenetic tree was created using molecular clock methodology on BEAST. Molecular clock analysis (Figure 1) identified 6 HCV-4d clusters comprising of mostly IDU sequences, and 2 MSM-specific clusters. The estimated year of origin of the IDU clusters ranged from 1982-1994, whilst the MSM clusters were estimated to have originated in 1995 and 1999. In the IDU clusters, 65% of lineage splits occurred before 1996. In the MSM clusters, 83% of lineage splits occurred after 2000. The UK-specific MSM cluster (MSM2) appears to originate following a lineage split in 1995 from a strain of HCV-4d circulating in IDUs in Southern Europe.

CONCLUSION

Incidental transfer of HCV-4d strains from IDUs, and rising viral transmission in highly connected MSM populations, have led to the formation of international MSM-specific HCV-4d transmission networks. Increased investment in public health interventions is required to slow this expanding epidemic.

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[1] - van de Laar TJ, Pybus O and Danta M. (2009) Evidence of a large, international network of international hepatitis C virus transmission in HIV-positive men who have sex with men. Gastroenterology. **136**(5), 1609-1617.
[2] - de Bruijne J, Schinel J, van de Laar TJ et al. (2009) Emergence of hepatitis C virus genotype 4: phylogenetic analysis reveals three distinct epidemiological profiles. J Clin Microbiol. **47**(12), 3832-3838.

Poster number

P259

Passcode: P259

Sofosbuvir/Velpatasvir Single Tablet Regimen in HCV Monoinfected and HIV/HCV Coinfected Patients: Comparison of Efficacy and Safety Data from Phase 3 Clinical Trials

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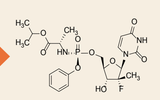
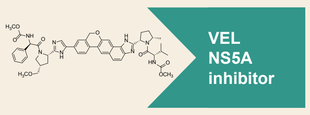
Background and Aim

SOF Nucleotide polymerase inhibitor



- **Sofosbuvir (SOF)[1,2]**
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet



VEL NS5A inhibitor

- **Velpatasvir (VEL)[3]**
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile

SOF + VEL

- **SOF/VEL FDC[4-6]**
  - Once daily, oral, FDC (400/100 mg)
  - Treatment with SOF/VEL for 12 weeks in Phase 3 studies resulted in high SVR in patients with HCV GT 1–6

FDC, fixed-dose combination.

- Liver-related disease remains a major cause of morbidity and mortality in patients coinfected with HCV and HIV-1[7]
- Accelerated progression of liver disease
- Higher rates of cirrhosis, end-stage liver disease, and hepatocellular cancer
- Direct-acting antiviral (DAA) therapy that is effective across all HCV genotypes with limited drug-drug interactions with antiretroviral therapy (ART) is needed
- The aim of this descriptive analysis is to compare efficacy and safety of SOF/VEL in mono-infected HCV patients (ASTRAL 1-3) with HIV/HCV co-infected patients (ASTRAL 5)

Methods

Study Design
The ASTRAL Phase 3 Program (N=1408)

- Primary endpoints
  - SVR12
  - Discontinuations due to AEs

Results

Demographics and Baseline Characteristics

	HIV/HCV n=106	HCV N=1035
Mean age, y (range)	54 (25–72)	53 (18-82)
Male, n (%)	91 (86)	630 (61)
Black, n (%)	48 (45)	61 (6)
Mean BMI, kg/m^2 (range)	27 (19–43)	27 (17-57)
Cirrhosis, n (%)	19 (18)	220 (21)
Treatment experienced,* n (%)	31 (29)	291 (28)
IL28B CC, n (%)	24 (23)	346 (33)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.3 (5.0–7.4)	6.3 (5.5-7.3)
HCV genotype, n (%)		
1	78 (74)	328 (32)
2	11 (10)	238 (23)
3	12 (11)	277 (27)
4	5 (5)	116 (11)
5-6	-	76 (7)

*Includes PEG + RBV failures and PI + PEG + RBV failures.

HIV Baseline Characteristics
ASTRAL-5 HIV/HCV Coinfection Study

	SOF/VEL n=106
Mean CD4 count, cells/μL (range)	598 (183–1513)
NRTI backbone	
TDF-based with boosted agent (RTV or COBI)	56 (53)
TDF-based without boosted agent	35 (33)
ABC/3TC-base	15 (14)
ART use at baseline	
PI (DRV, LPV or ATV)	50 (47)
NNRTI (RPV)	13 (12)
Integrase inhibitor (RAL or EVG)	36 (34)
Other (>1 of the above classes)	7 (7)

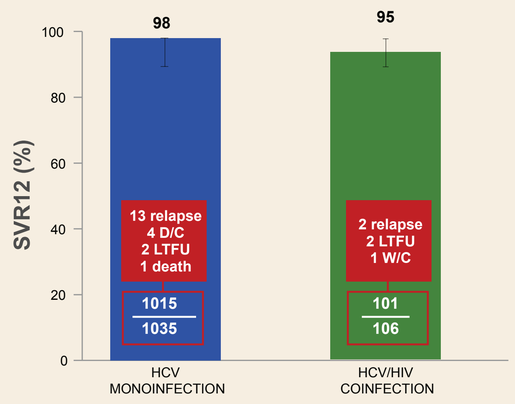
NRTI, nucleoside-analog reverse-transcriptase inhibitor; 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; COBI, cobicistat; DRV, darunavir; EVG, elvitegravir; LPV, lopinavir; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir.

Results (cont'd)

HIV Baseline Characteristics
ASTRAL-5 HIV/HCV Coinfection Study

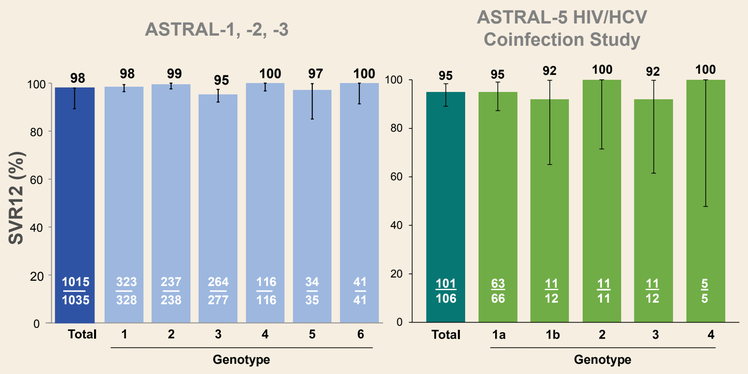
- There were a wide variety of concomitant ART regimens included

Integrated Efficacy: SVR12
ASTRAL-1, -2, -3 vs. ASTRAL 5



- HCV treatment with SOF/VEL results in high SVR rates in both HCV monoinfected and HIV/HCV coinfected patients

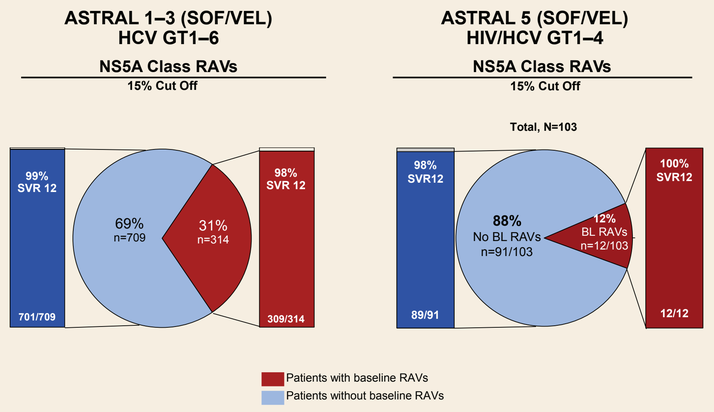
SVR by Genotype



Error bars represent 95% confidence intervals.

- SOF/VEL is highly effective across genotypes

Resistance Analysis
ASTRAL-1, -2, -3 and -5



Safety Analysis of SOF/VEL for 12 Weeks in Mono- and Coinfected Patients

Retrospective integrated analysis of data from 1,141 SOF/VEL patients and control/placebo patients in ASTRAL-1, -2, -3 and -5

Patients, n (%)	SOF/VEL HCV N=1035	SOF/VEL HCV/HIV N=106	Placebo 12 Week N=116	SOF+RBV 12 Week N=132	SOF+RBV 24 Week N=275
AE	821 (79)	75 (71)	89 (77)	101 (77)	260 (95)
Grade 3 or 4 AE	33 (3)	9 (8)	1 (<1)	3 (2)	24 (9)
SAE	23 (2)*	2 (2)*	0	2 (2)	15 (5)
AE leading to treatment D/C	2 (<1)^	2 (2)	2 (2)	0	9 (3)
Death	3 (<1)**	0	0	0	3 (1)*

*No SAE was assessed as related to SOF/VEL
**None were assessed as related to study treatment
^Two subjects D/C SOF/VEL for AEs; (1 D/C day 1 due to difficulty concentrating, headache, and anxiety and 1 D/C day 13 of due to anxiety)

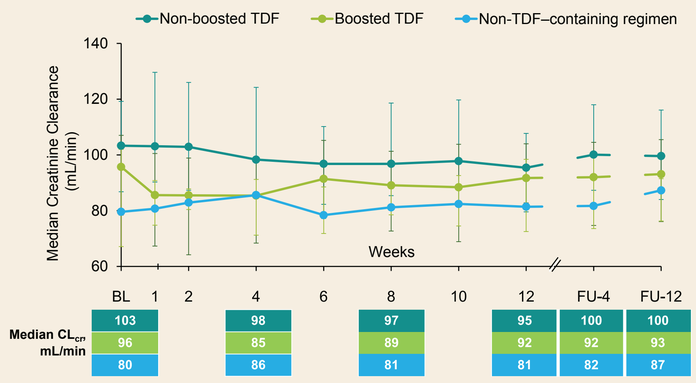
- No patient with confirmed on-treatment HIV virologic rebound
- SAEs: Acute radial nerve palsy and left toe infection/sepsis/UTI
- Most common laboratory abnormality was elevated bilirubin in patients receiving atazanavir/ritonavir

- SOF/VEL is safe and well tolerated

Most common AEs in ASTRAL 1,2 ,3 and 5

Patients, n (%)	SOF/VEL HCV N=1035	SOF/VEL HCV/HIV N=106	Placebo 12 Week N=116	SOF+RBV 12 Week N=132	SOF+RBV 24 Week N=275
Headache	296 (29)	14 (13)	33 (28)	29 (22)	89 (32)
Fatigue	217 (21)	26 (25)	23 (20)	47 (36)	105 (38)
Nausea	135 (13)	7 (7)	13 (11)	19 (14)	58 (21)
Insomnia	87 (8)	7 (7)	11 (9)	18 (14)	74 (27)
Nasopharyngitis	121 (12)	9 (8)	12 (10)	2 (2)	33 (12)
Cough	57 (6)		4 (3)	6 (5)	35 (13)
Irritability	49 (5)		4 (3)	9 (7)	40 (15)
Pruritus	33 (3)		5 (4)	7 (5)	35 (13)
Dyspepsia	33 (2)		4 (3)	5 (4)	30 (11)

Renal Function
ASTRAL-5 HIV/HCV Coinfection Study



FU-4/12, follow-up Week 4/12; Creatinine Clearance calculated using the Cockroft-Gault method; errors bars represent Q1, Q3.

- SOF/VEL did not adversely impact renal function in patients on various ART regimens, including TDF based regimens

Conclusions

- **SOF/VEL treatment for 12 weeks resulted in 98% SVR12 in mono-infected patients and 95% in HCV/HIV co-infected patients**
- **Presence of baseline NS5A RAVs did not impact SVR12 in both patient population**
- **Treatment with SOF/VEL for 12 weeks was safe and well tolerated, including with NRTI, NNRT, integrase inhibitors, and boosted protease inhibitor regimens**
- **SOF/VEL provides a simple STR that can cure the majority of mono and HIV/HCV co-infected patients across all genotypes**

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Poster #P260 HIV/Hepatitis C Co-Infected Patients Are Significantly more Complex to Manage than HIV Mono-Infected Patients in a Large Cohort of Treatment-Naive, HIV-Positive Individuals

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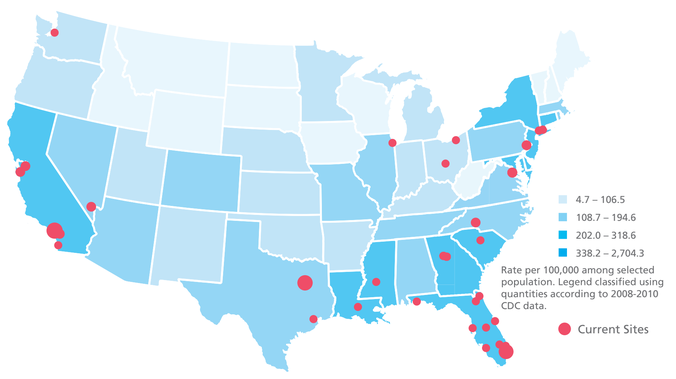
BACKGROUND

Hepatitis C virus (HCV) co-infection is common in patients with HIV due to shared modes of transmission.[1] Understanding differences between HIV mono-infected and HIV/HCV co-infected patient populations may lead to earlier identification of HCV co-infection, more effective management, and better clinical outcomes.

OBJECTIVE:
To evaluate differences between HIV mono-infected and HIV/HCV co-infected patient populations.

METHODS

Figure 1: U.S. Map of OPERA HIV+ Population & CDC (2010) State-by-State Estimates



- The Observational Pharmaco-Epidemiology Research & Analysis (OPERA) database follows 67,500 HIV+ patients through their electronic health records from 79 US community-based outpatient clinics in 15 states. [Figure 1]
- The OPERA population represents ~7% of all HIV+ patients linked to care in the US. It is the largest continuously operating cohort of HIV+ patients in the US, refreshed daily.
- The analysis included HIV+ individuals initiating HIV antiretroviral therapy (ART) for the first time between 1/1/2007 and 3/31/2015. Patients were followed from HIV treatment initiation to discontinuation of regimen, loss to follow-up, death or study end (3/31/2016).
- Demographics and clinical characteristics were compared between HIV/HCV co-infected and HIV mono-infected patients using Pearson chi-square or Wilcoxon rank-sum tests. Differences in time to HIV viral suppression (<50 copies/mL) with and without HCV co-infection were assessed using multivariable Cox proportional hazards regression.

RESULTS

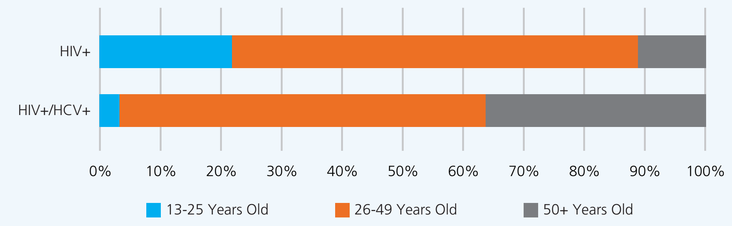
- Of 9,190 HIV+ treatment-naïve patients, 7,837 (85.3%) were HCV antibody negative and 472 (5.1%) were HCV-positive; 881 (9.6%) patients had a history of HCV clearing or no testing prior to baseline and were excluded.
- HIV/HCV co-infected patients were significantly older (median age: 46.7 vs. 34.0 years), less likely to be male (76.9% vs. 86.6%), Hispanic (16.9% vs. 25.5%), or MSM (39.8% vs. 59.8%) than HIV mono-infected patients (p< 0.0001) (Table 1, Figure 2).
- Baseline CD4 cell counts were lower for HIV/HCV co-infected patients (279 vs. 330 cells/μL, p=0.0029) who were also more likely to have an AIDS defining event at baseline (9.7% vs. 6.3%, p=0.0037); there were no differences between groups in baseline HIV viral load.

Characteristic	HIV+ N= 7837	HIV+/HCV+ N= 472	P-value
Age (Median, IQR)	34.0 (26,7, 43.5)	46.7 (38.5, 52.2)	<0.0001
Gender, Male	6782 (86.6%)	363 (76.9%)	<0.0001
Risk of Infection, MSM*	4687 (59.8%)	188 (39.8%)	<0.0001
Race, African American	3065 (39.1%)	182 (38.6%)	0.8120
Ethnicity, Hispanic	1999 (25.5%)	80 (16.9%)	<0.0001
Log^{10} HIV-1 Viral Load, Median (IQR)	4.7 (4.2, 5.1)	4.7 (4.2, 5.1)	0.4079
CD4 Count (Median, IQR)	330 (192, 479)	279 (161, 442)	0.0029
AIDS Defining Event at Baseline	497 (6.3%)	46 (9.7%)	0.0037
History of Syphillis at Baseline	2044 (26.1%)	126 (26.7%)	0.7682

*Only patients with HCV testing were included. Patients with a history of HCV that was resolved at baseline were excluded from this analysis. MSM=men who have sex with men

- Patients 50 or more years of age made up a significantly larger proportion of the HIV/HCV co-infected population than the HIV mono-infected population (36.2% vs. 11.2%, p<0.0001). Few adolescents or young adults (13-25 years old) were co-infected (n=16, 3.4%). (Figure 2)

Figure 2: Age by HCV Co-Infection Status



- HIV/HCV co-infected patients had significantly (p<0.05) more comorbid conditions (e.g., cardiovascular, cancer, endocrine, liver and renal disease; neuropathy; hypertension) and higher pill burden for their non-HIV medications (Table 2, Figures 3 and 4).
- Co-infected patients were twice as likely to present with mental illness (25.6% vs. 13.4%, p<0.0001) and a third had documented substance abuse (32.0% vs. 13.7%, p<0.0001).

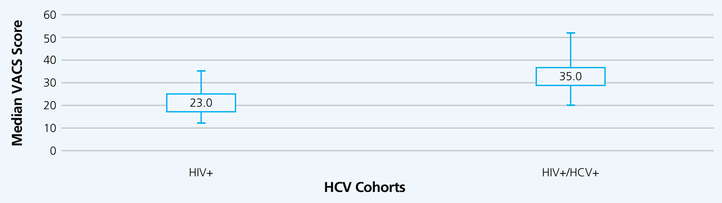
Table 2: Comorbid Conditions with Significant Differences between HIV+ and HIV+/HCV+

	HIV+ N= 7837	HIV+/HCV+ N= 472	P-value
Any Comorbidity at Baseline	3374 (43.1%)	472 (100.0%)	<0.0001
Substance Abuse	1074 (13.7%)	151 (32.0%)	<0.0001
Mental Health Conditions	1048 (13.4%)	121 (25.6%)	<0.0001
Hypertension	1028 (13.1%)	106 (22.5%)	<0.0001
Endocrine Disorders	1002 (12.8%)	80 (16.9%)	0.0090
Liver Diseases	290 (3.7%)	472 (100.0%)	<0.0001
Peripheral Neuropathy	185 (2.4%)	30 (6.4%)	<0.0001
Invasive Cancer	132 (1.7%)	15 (3.2%)	0.0168
Cardiovascular Disease	111 (1.4%)	22 (4.7%)	<0.0001
Renal Disease	35 (0.4%)	9 (1.9%)	<0.0001

* Only patients with HCV testing were included. Patients with a history of HCV that was resolved at baseline were excluded from this analysis

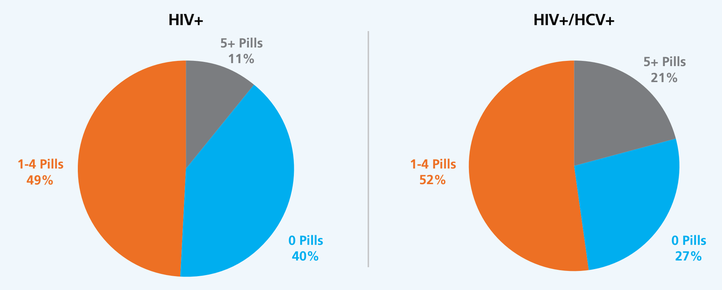
- Co-infected patients had median VACS Index scores 12 points higher than HIV mono-infected patients (p<0.0001). The impact of a 5-point change in the VACS index on 5-year mortality has been estimated at 30%.[2]

Figure 3: Median (IQR) VACS Index by HCV Co-Infection Status



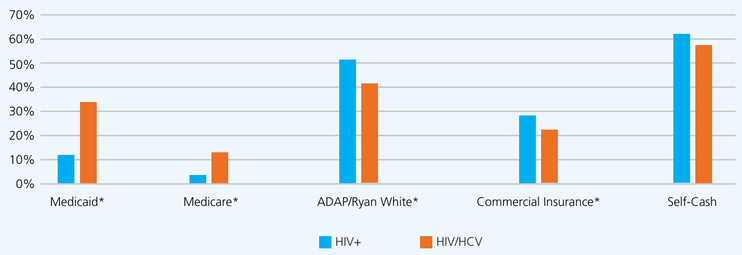
* The Veterans Aging Cohort Study (VACS) Index predicts all-cause mortality, cause-specific mortality and other outcomes through a score of including age, CD4 count, HIV-1 RNA levels, indices of organ system dysfunction and HCV infection. It was developed in veterans with HIV and has been validated in other populations including non-veterans, non-HIV, and other countries.[2]

Figure 4: Non-HIV Pills Per Day by HCV Co-Infection Status



- HIV/HCV co-infected patients were more likely to receive Medicaid and Medicare and less likely to have ADAP/Ryan White or commercial insurance than HIV mono-infected patients (Figure 5).

Figure 5: Healthcare Payers at Baseline



Patients had multiple payers at baseline.
*Payers that were significantly (p<.05) different between HIV mono-infected and HIV/HCV co-infected groups.

- HIV treatment was less successful in HIV/HCV co-infected patients, both in achieving suppression (HIV/HCV: 55.5% vs. HIV: 65.4%, p<0.0001) and avoiding rebound (HIV/HCV: 22.1% vs. HIV: 14.4%, p<0.0001) during initial treatment. In crude and adjusted models, those with HIV/HCV co-infection were significantly less likely to suppress their HIV VL to undetectable during their initial regimen (cHR=0.78 (95% CI=0.69, 0.89) aHR=0.80 (0.70, 0.91)). (Table 3)
- HIV mono-infected patients were less likely to virologically rebound once suppressed in both crude and adjusted models. HIV/HCV co-infected patients were significantly more likely to rebound (cHR=1.67 (1.30, 2.22) aHR=1.56 (1.18, 2.07)).

Table 3: Virologic Outcomes of Patients Initiating ART by HCV Co-Infection Status

	HIV+	HIV+/HCV+
Achieved Virologic Supression[1]	65.4%	55.5%
Unadjusted HR (95% CI)	0.78 (0.69,0.89)	
Adjusted HR (95% CI)[2,3]	0.80 (0.70, 0.91)	
Experienced Rebound[4]	14.4%	22.1%
Unadjusted HR (95% CI)	1.67 (1.30, 2.22)	
Adjusted HR (95% CI) [4,5,6]	1.56 (1.18, 2.07)	

[1] Suppression Defined as VL<50 copies/mL
[2] Referent= HIV+; HR > 1.0 indicates increased likelihood of suppression
[3] Cox regression adjusted for age at baseline, sex, African American race, , baseline VL, baseline CD4, AIDS, syphilis, substance abuse, mental illness, and total comorbid conditions at baseline
[4] Only among patients who first achieved suppression; rebound defined as 1 VL >200 copies/mL followed by discontinuation or 2 VL's >200 copies/mL
[5] Referent =HIV+; HR <1.0 indicates decreased risk of rebound after suppression
[6] Cox regression adjusted for age at baseline, sex, African American race, Hispanic ethnicity, baseline VL, baseline CD4, AIDS, syphilis, substance abuse, mental illness, and total comorbid conditions at baseline

DISCUSSION

- HIV/HCV co-infected patients tend to be older, have more comorbid conditions, receive more medications, and be more medically frail (higher mortality risk) than HIV mono-infected patients.
- Co-infected patients present with more advanced HIV disease (lower CD4 counts and more AIDS defining Illness) and are less likely to suppress and more likely to rebound virologically while receiving their initial HIV antiretroviral therapy.
- Psychologically, HIV/HCV patients suffer disproportionately from mental illness and substance abuse.
- HIV/HCV co-infected patients tend to be socioeconomically disadvantaged relying on Medicaid significantly more than HIV mono-infected patients.
- Strategies to simplify HIV treatment in HIV/HCV co-infected patients by optimizing pill count (lower pill burden) and limiting or avoiding complex drug interactions will be particularly important as more HIV/HCV co-infected patients are offered interferon (IFN) free, direct acting antiviral (DAA) treatment for their HCV infection. Moreover, during HCV treatment, continued management of multiple co-morbid conditions will also be necessary and reinforces the importance of simplification of HIV treatment in co-infected individuals.

KEY FINDINGS

HIV/HCV co-infected patients differ significantly from HIV mono-infected patients. Co-infected patients are more complex and pose unique treatment challenges for clinicians. Strategies to simplify co-infected patients' HIV care and avoid complications will be particularly important for this population as clinicians begin HCV treatment with DAA-based therapies while continuing to simultaneously manage the treatment of multiple co-morbid conditions.

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SPONSORSHIP

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P261

Efficacy of generic Direct Acting Antiviral Treatment for Hepatitis C, imported into Russia and Eastern Europe.

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Introduction:

Prices of branded Direct Acting Antivirals for Hepatitis C (HCV) are very high in Russia and most of Eastern Europe. Sofosbuvir is now registered in Russia but is not available through the government treatment programmes.

A 12-week course of original SOF is offered privately for around $9,500, which is unaffordable for most people. An increasing number of people in this region are treating their HCV infection with generic drugs produced in India, China or Egypt and legally imported.
This analysis assessed the efficacy of these generic DAAs.

Methods:

Generic versions of sofosbuvir (SOF), ledipasvir (LDV) and daclatasvir (DCV) were sourced from generic suppliers in India and Egypt, costing $700 to $900 per treatment course.
The choice of DAAs and length of treatment were determined based on baseline HCV Genotype and stage of fibrosis. Online patient Facebook groups such as the Gepatitka group provided patient support.

Patients taking generic DAAs were evaluated pre-treatment, at week 4 (RVR), at the end of treatment (EOT, typically week 12) and then for SVR 4, 12, and 24.
This analysis includes available data from 213 patients being monitored in hospitals, private doctors and AIDS clinics in Russia, Belarus, Ukraine, Spain, Colombia, Israel and Estonia.

Results:

213 patients were treated; 156 received SOF/DCV, 47 SOF/LDV, and 10 received SOF/RBV. The median length of treatment was 12 weeks.
The SOF, LDV and DCV were mainly from Indian generic companies (see Table 2).
Overall, the patients were 56% male with a mean age of 36.4 years; 41% were Genotype 1 and mean baseline HCV RNA was 6.37 $\log_{10}$ IU/mL.
Rapid virological response (RVR) was observed in 85% (141/165) of the patients (see Table 1 for results by treatment). Based on currently available data, 100% (81/81) reached HCV RNA<LLOQ at the end of treatment (EOT) and 100% (85/85) at SVR 4.

Conclusions:

In this programme, treatment with legally imported generic DAAs achieved high rates of SVR in Russia and Eastern Europe.

The price of a 12 week treatment starts from $435 for SOF/RBV and £495 for SOF/DCV via this treatment access programme, versus over $15,000 if bought commercially.

Mass treatment with generic DAAs is a feasible and economical alternative route of accessing curative DAAs, where the high-prices for branded DAA's prevent access to treatment.

Acknowledgements:

We would like to thank all of the authors and their institutions for collaborating on this work, and all of the patients from the ITPC EECA Gepatitka community for pioneering this style of treatment and data collection.

Table 1: Baseline Characteristics

Patients	SOF/RBV N=10	SOF/DCV N=156	SOF/LDV N=47
% Male	60 %	56 %	53 %
% Cirrhosis	0 %	11 %	13 %
% GT 1	20 %	25 %	100 %
% GT 3	70 %	69 %	0 %
+ RBV	100 %	20 %	23 %

Figure 1: Patients by genotype

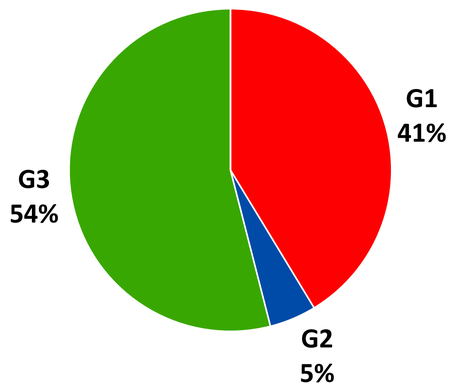

Figure 2: Fibrosis scores of patients

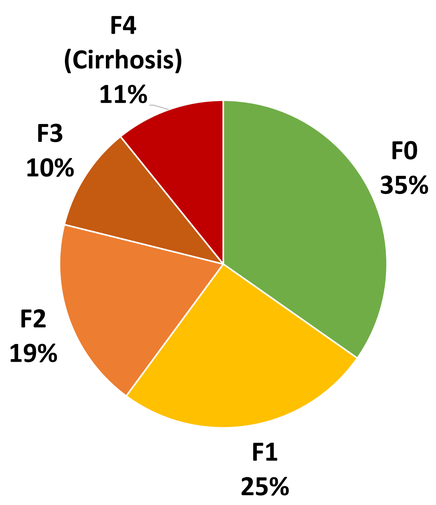

Table 2: Generic manufacturers used

Company	SOF	DCV	LDV
Hetero	119/213 (56%)	87/156 (56%)	31/47 (62%)
Natco	29/213 (14%)	11/156 (7%)	8/47 (16%)
Mylan	16/213 (8%)	2/156 (1%)	0/47 (0%)
Zydus	14/213 (7%)	17/156 (11%)	2/47 (4%)
Strides A.	10/213 (5%)	0/156 (0%)	0/47 (0%)
Marcyrl	7/213 (3%)	5/156 (3%)	1/47 (2%)
Chinese API	0/213 (0%)	25/156 (16%)	1/47 (2%)
Other	12/213 (6%)	8/156 (5%)	4/47 (8%)
No data	6/213(3%)	1/156 (1%)	3/47 (6%)

Figure 3: Generic treatments taken by patients

Pharmed Healthcare | Hetero | Natco | Zydus

Table 3: HCV RNA <25 IU/mL at RVR, EOT and SVR

Patients	SOF/RBV N=10	SOF/DCV N=156	SOF/LDV N=47
RVR	7/8 (88%)	100/120 (83%)	34/37 (92%)
EOT	4/4 (100%)	62/62 (100%)	15/15 (100%)
SVR 4	3/3 (100%)	58/58 (100%)	25/25 (100%)
SVR 12	2/2 (100%)	42/43 (98%)	16/16 (100%)

Figure 4: RVR responses by genotype

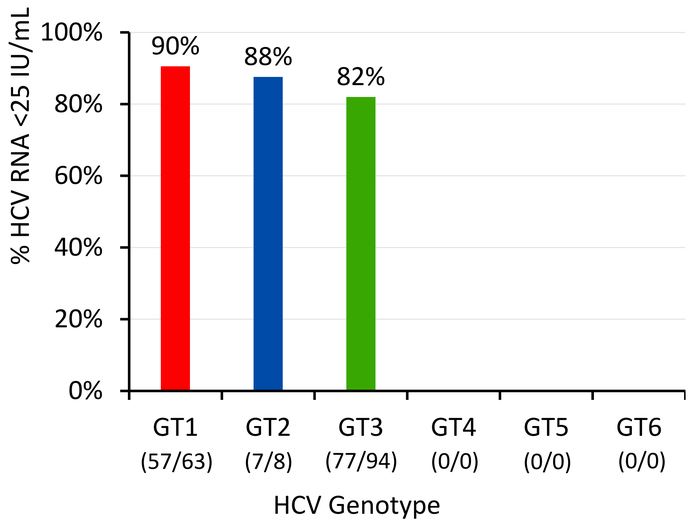

Figure 5: SVR4 responses by genotype

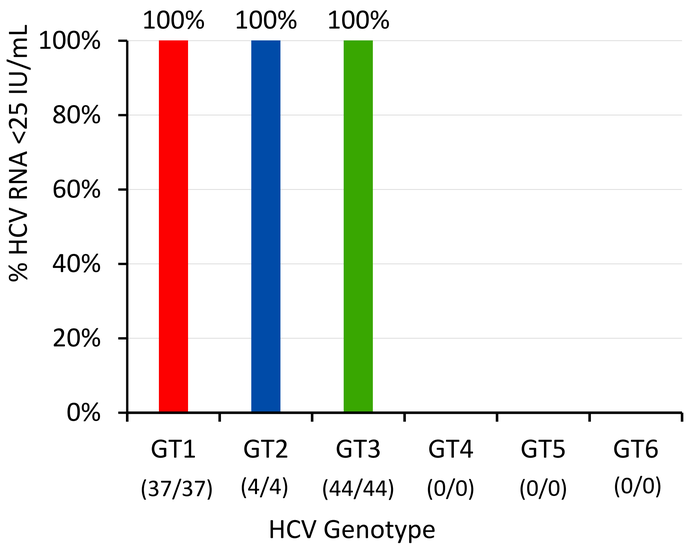

Figure 6: SVR12 responses by genotype

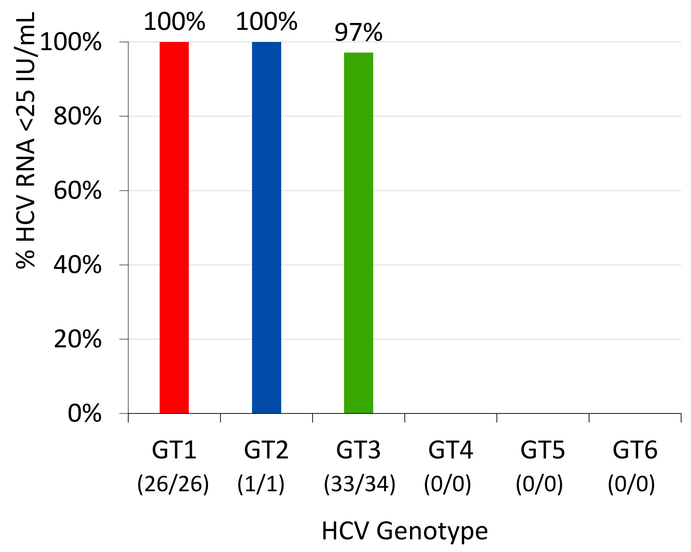

Figure 7: Locations of patients; ITPC EECA, Gepatitka community

P262

Efficacy of generic Direct Acting Antiviral Treatment for Hepatitis C, imported into South-East Asia and China.

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Introduction:

China and several countries in South-East Asia are not included in voluntary license agreements for Direct Acting Antivirals.
Prices of DAAs in Southeast Asia are high. For example, a 12-week course of SOF/DCV in Thailand is over $10,000, versus under $500 in India.
An increasing number of people in Southeast Asia are treating their Hepatitis C infection with generic drugs produced in India or China.
This analysis assessed the efficacy of generic DAAs imported into South-East Asia.

Methods:

Generic versions of sofosbuvir (SOF), ledipasvir (LDV) and daclatasvir (DCV) were sourced from generic suppliers in India.
The choice of DAAs and length of treatment were determined based on baseline HCV Genotype and stage of fibrosis.
Patients taking generic DAAs were evaluated pre-treatment, at week 4 (RVR), at the end of treatment (EOT, typically week 12) and then for SVR 4, 12, and 24.
This analysis includes available data from 237 patients being monitored in hospitals, private doctors and clinics in Singapore, Vietnam, Thailand, Indonesia, China and India.

Results:

237 patients were treated; 77 received SOF/LDV, 91 SOF/DCV, and 69 received SOF/RBV.
The median length of treatment for SOF/LDV and SOF/DCV was 12 weeks, whereas SOF/RBV had a median treatment of 24 weeks.
Overall, the patients were 72% male with a mean age of 43.1 years; 41% were Genotype 1 and the mean baseline HCV RNA was 7.2 $\log_{10}$ IU/mL.
Based on currently available data, 99% (85/86) reached HCV RNA<25 IU/mL at end of treatment (EOT), and 100 % (33/33) at SVR 4.
EOT responses were slightly lower for patients treated with SOF/LDV (97%) than with SOF/DCV (100%).

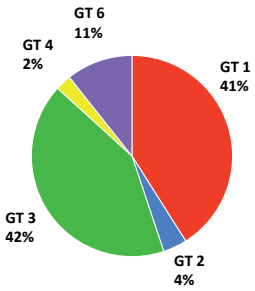
Conclusions:

In this analysis, treatment with legally imported generic DAAs achieved Sustained Virological Response (SVR4) in all patients evaluated so far.
Mass treatment with imported generic DAAs is a feasible and economical alternative route of accessing curative DAA's, where the high-prices for branded DAA's prevent access to treatment.
Mass treatment of Hepatitis C is currently unaffordable at pharmaceutical company prices (e.g. over $10,000 per treatment in Thailand)
Buyers Clubs allow patients to be cured for $700-$900 per person. These prices are falling rapidly.

Acknowledgements:

We would like to thank all of the authors and their institutions for collaborating on this work, and all of the patients from the Chinese and South East Asia buyers club community for pioneering this style of treatment and data collection.

Figure 1: Patients by Genotype



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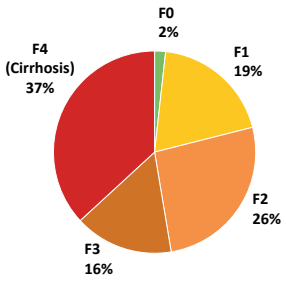

Table 2: Generic manufacturers used for imports

Company	SOF	DCV	LDV
Cipla	190/226 (84%)	78/83 (94%)	67/75 (89%)
Zydus	13/226 (6%)	4/83 (5%)	1/75 (1%)
Hetero	11/226 (5%)	1/83 (1%)	3/75 (4%)
Mylan	9/226 (4%)	0/83 (0%)	4/75 (5%)
Natco	1/226 (1%)	0/83 (0%)	0/86 (0%)
Other	2/226 (3%)	0/83 (0%)	0/86 (0%)

Figure 3: Examples of generic treatments taken

Hetero Cipla Mylan

Table 3: HCV RNA <25 IU/mL during programme

Patients	SOF/RBV N=69	SOF/DCV N=91	SOF/LDV N=77
RVR	39/40 (98%)	23/23 (100%)	38/38 (100%)
EOT	28/28 (100%)	26/26 (100%)	31/32 (97%)
SVR 4	17/17 (100%)	6/6 (100%)	10/10 (100%)
SVR 12	11/13 (85%)	2/2 (100%)	9/9 (100%)

Figure 4: RVR responses by genotype

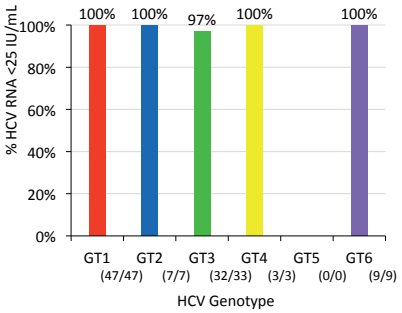

Figure 5: EOT responses by genotype

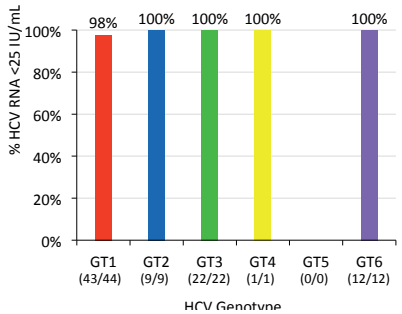

Figure 6: SVR4 responses by genotype

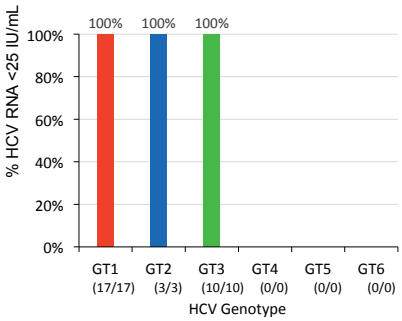

Figure 7: Locations of patients; South East Asian buyers club community

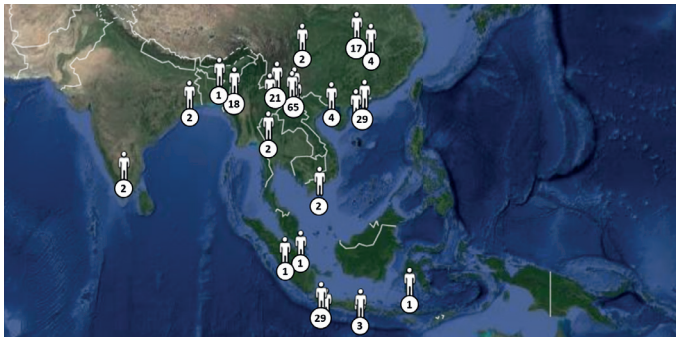

Table 4: Locations of patients

Location	No. Patients
China	154/237 (64%)
India	37/237 (16%)
Indonesia	37/237 (16%)
Singapore	1/237 (<1%)
Thailand	3/237 (1%)
Vietnam	2/237 (1%)
Not Disclosed	3/237 (1%)

Table 1: Baseline Characteristics

Patients	SOF/RBV N=69	SOF/DCV N=91	SOF/LDV N=77
% Male	80%	67%	70%
% Cirrhosis	14%	5%	12%
% GT 1	41%	22%	62%
% GT 3	45%	68%	6%
+ RBV	100%	7%	16%

Is ART use associated with increased risk of ALT elevation in HIV/HCV co-infected patients over and above what is expected in HIV mono-infected: a nested case control study approach

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HIV Drug Therapy 2016 GLASGOW

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Introduction

- Antiretroviral therapy (ART) induced toxicity has been frequently reported in HIV/HCV co-infected individuals. However, there is conflicting evidence on whether HIV/HCV co-infection has a synergistic effect on ART-induced toxicity.
- One way to evaluate this hypothesis is to compare the risk of ALT elevation associated with the use of ART in HIV/HCV co-infected vs HIV mono-infected populations.

Objective

- To determine whether use of ART in HIV/HCV co-infected patients is associated with increased hepatoxicity defined as ALT elevations as compared to HIV mono-infected patients.

Methods

- We selected individuals in the ICONA Foundation Study cohort with at least one ALT measurement and known current HCV status. We designed a case-control analysis nested in the cohort.
- Cases were defined as individuals who showed liver enzyme elevation (LEE) >5 x upper limit normal at their last clinical observation; controls were participants who showed normal liver enzyme levels after the same time after enrolment in the cohort.
- Controls were matched by a pre-defined set of potential confounders: age {≤20, 21-25, 26-30 to >65}, CD4 count cells/mmc {≤350, 351 - 500, >501}, HIV-RNA viral load copies/ml {≤1000, 1001 – 5000 to >100,000} and mode of HIV transmission.
- A conditional logistic regression model was used to evaluate the association between ART exposure and risk of LEE in a univariable model adjusted for matching factors and after further controlling for gender, nationality, alcohol use, smoking status and calendar year of enrolment. Interaction between HIV/HCV co-infection status and ART exposure were also formally assessed.

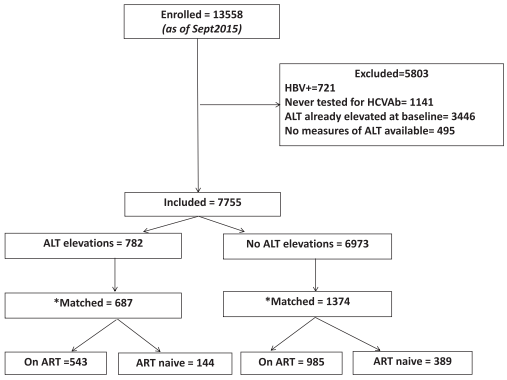
Results

- We included 2061 individuals (1:2 matching) with median calendar year of last clinical visit in 2014 (IQR: 2007 - 2015) [Figure 1].
- Overall, median age was 35 (IQR: 31-40), mode of HIV transmission was reported as follows; PWID (32%), MSM (36%), heterosexual (30%) and other/unknown (3%), median CD4 count 386 (IQR: 188-586) cells/mmc and HIV-RNA viral load log10 copies/ml 4.5 (IQR: 3.8 – 5.1).
- Majority were males (70%). Individuals reporting smoking were less in cases than controls 22% and 26% (p=0.03). Proportion of HIV/HCV co-infected individuals was higher in cases than in controls 39% and 29% respectively (p<0.001). Proportion of ART use was higher in cases than controls 79% and 72% respectively (p<0.001) [Table1].
- In the model without interaction, ART use was associated with an increased risk of LEE [adjusted odds ratio (aOR) 1.87 [95% CI: 1.39-2.53; p<0.001] independently of all factors included [Table 2].
- In the model with the interaction term, the association between co-infection and risk of LEE was 3.76 [95% CI: 1.31 – 10.81] in individuals on ART and 3.17 [95% CI: 2.09 – 4.80] in ART naïve individuals (p=0.69) [Figure 2].

Conclusion

- Our analysis show no evidence that risk of ALT elevation due to HIV/HCV co-infection is exacerbated by the exposure to ART(3-fold increased risk in both strata).
- Further analyses are needed to investigate the possible effect associated with the use of specific drugs/regimens

Figure 1. Patient selection flow diagram



·(Case: Control as 1:2): Matched on age, CD4 cell count HIV-RNA viral load and mode of HIV transmission

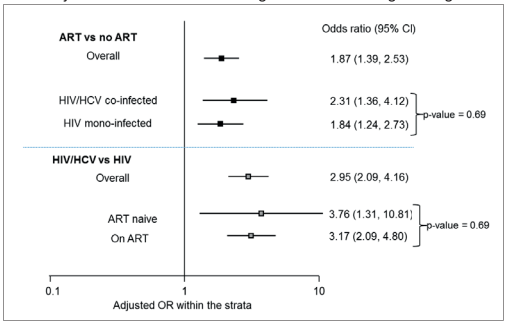
Table 1. Patient characteristics stratified by ALT elevation status (cases/controls)

Patient characteristics	Elevated ALT N= 687 (%)	No elevated ALT N= 1374 (%)	Total N= 2061 (%)	p-value
Gender,				
Female	195 (28.4%)	427 (31.1%)	622 (30.2%)	0.209
Nationality				
Italian	614 (89.4%)	1242 (90.4%)	1856 (90.1%)	0.466
Smoking status				0.032
No	152 (22.1%)	335 (24.4%)	487 (23.6%)	
Yes	151 (22.0%)	354 (25.8%)	505 (24.5%)	
Unknown	384 (55.9%)	685 (49.9%)	1069 (51.9%)	
Alcohol consumption				0.174
Abstaining	157 (22.9%)	336 (24.5%)	493 (23.9%)	
Moderate	61 (8.9%)	158 (11.5%)	219 (10.6%)	
Hazardous	18 (2.6%)	29 (2.1%)	47 (2.3%)	
Unknown	451 (65.6%)	851 (61.9%)	1302 (63.2%)	
HCV status (time-dependent)				<.001
HCV negative	418 (60.8%)	971 (70.7%)	1389 (67.4%)	
HCV positive	269 (39.2%)	403 (29.3%)	672 (32.6%)	
ART status (time-dependent)				<.001
ART naive	144 (21.0%)	389 (28.3%)	533 (25.9%)	
On ART	543 (79.0%)	985 (71.7%)	1528 (74.1%)	

Table 2. Unadjusted and adjusted odds ratio from fitting a conditional logistic regression model

	Unadjusted OR(95% CI)	p-value	Adjusted OR(95%CI)	p-value
HCV status(time-dependent)				
HCV negative	1.00		1.00	
HCV positive	2.89 (2.10, 3.97)	<.001	2.95 (2.09, 4.16)	<.001
ART status(time dependent)				
ART naive	1.00		1.00	
on ART	1.82 (1.39, 2.37)	<.001	1.87 (1.39, 2.53)	<.001
Gender				
Male	1.00		1.00	
Female	0.83 (0.66, 1.06)	0.134	0.85 (0.65, 1.10)	0.204
Italian				
No	1.00		1.00	
Yes	0.88 (0.64, 1.21)	0.444	0.83 (0.58, 1.20)	0.323
Smoking				
No	1.00		1.00	
Yes	0.95 (0.72, 1.26)	0.732	0.96 (0.70, 1.32)	0.814
Unknown	1.26 (0.99, 1.60)	0.060	1.17 (0.85, 1.61)	0.325
Alcohol				
Abstain	1.00		1.00	
Moderate	0.82 (0.57, 1.18)	0.280	0.74 (0.48, 1.12)	0.152
Hazardous	1.33 (0.70, 2.52)	0.380	1.18 (0.57, 2.44)	0.650
Unknown	1.15 (0.91, 1.45)	0.233	0.99 (0.73, 1.33)	0.934
Calendar year	0.98 (0.96, 1.00)	0.066	0.99 (0.97, 1.02)	0.540

Figure 2: Adjusted odds ratio from fitting a conditional Logistic regression model



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Long-term trends in HCV treatment uptake, efficacy and liver disease in the SHCS

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BACKGROUND:

- Interferon-free Hepatitis C virus (HCV) therapies with second-generation direct acting antiviral agents (DAAs) are highly effective and well tolerated.
- DAAs have the potential to substantially increase treatment eligibility and efficacy in HIV-infected patients.
- We assessed the impact of DAAs on treatment uptake, efficacy as well as its impact on liver disease burden in the Swiss HIV Cohort Study (SHCS).

MATERIALS AND METHODS:

- We prospectively collected data on all SHCS participants who started HCV therapy since January 2009.
- HCV treatment uptake and efficacy as well as the stage of liver fibrosis were compared between three different time periods:
  - period 1: 01/2009-08/2011 (prior to the availability of DAAs)
  - period 2: 09/2011-03/2014 (first generation DAAs)
  - period 3: 04/2014-12/2015 (second generation DAAs).

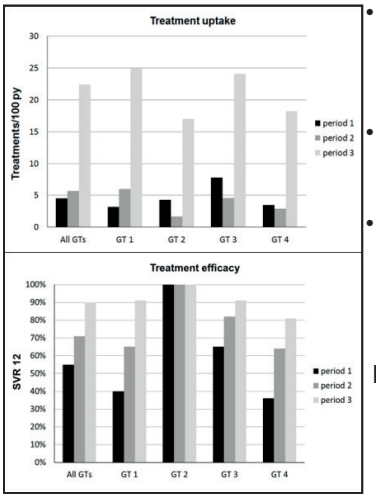
Patients treated with second generation DAAs (period 3) who reached end of follow-up

N	103
Demographic characteristics	
Age, median (IQR)	53 (47-56)
Male (%)	79 (77)
Caucasian (%)	98 (95)
Illicit drug use (%)	12/103 (12)
Depression (%)	33/103 (32)
HIV characteristics	
Controlled HIV RNA<20 copies/ml (%)	99/103 (96)
Patients on ART (%)	99/103 (96)
CDC Stage C (%)	42/103 (41)
Median CD4 in cells/ul (IQR)	509 (400-747)
CD4 cell category (cells/ul) (%)	
1-200	7 (11)
200-350	6 (10)
>350	48 (79)
HIV Transmission group (%)	
MSM	11/103 (11)
IDU	61/103 (59)
HET	23/103 (22)
Other	8/103 (8)
Laboratory values	
Median eGFR in ml/min (IQR)*	96 (73-105)
Median Thrombocytes in G/L (IQR)	131 (90-181)
Liver Enzymes, median (IQR)	
ALT (U/L)	57 (37-94)
AST (U/L)	57 (40-87)
ALT elevation** (%)	54/96 (56)
Hepatitis C characteristics	
HCV viral load (log10 copies/ml), median (IQR)	6.1 (5.4-6.5)
HCV Genotype (%)	
GT 1	61/103 (59)
GT 2	1/103 (1)
GT 3	22/103 (21)
GT 4	19/103 (18)
Liver Fibrosis stage (%)	
F0-1	12/103 (12)
F2	6/103 (6)
F3	14/103 (14)
F4	71/103 (69)
APRI >1.5	35 (34)
APRI >2	29 (28)
Child-score (%)	
A	49/71 (69)
B	5/71 (7)
C	3/71 (4)
missing	14/71 (20)
Treatment	
SOF based (%)	93/103 (90)
SOF LDV	41/103
SOF DCV	24/103
SOF SIM	5/103
SOF INF	14/103
OMV/PTV/RTV + DSV (%)	9/103 (9)
Ribavirin (%)	62/103 (60)
Treatment history (n/total(%))	
Treatment naïve	36/103 (35)
Experienced	67/103 (65)

RESULTS:

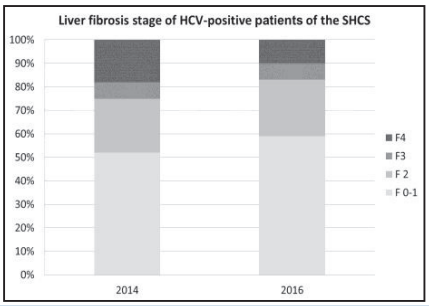
- At the beginning of the third period, 876 SHCS participants had a chronic HCV infection and of those, 186 started HCV therapy with a second generation DAA.
- Ninty three of 103 patients (90%) who reached the end-of follow-up, and from whom complete data was already available achieved an SVR.
- Detailed causes for not reaching SVR in 10 patients:
  - 3 death (2 liver decompensation and 1 sepsis)
  - 4 viral relapses (3 SOF/RBV, 1 SOF/LDV)
  - 1 virological breakthrough (SOF/RBV)
  - 2 lost-to follow-up.

Figure 1: Treatment uptake and efficacy over the 3 periods



- Treatment uptake (4.5/100py, 5.7/100py, 22.4/100py) and efficacy (SVR 12): 54%, 70%, 90%) continuously increased
- Treatment uptake increased across all HCV genotypes in period 3.
- Patients treated for HCV-genotype 1 during period 3 had significantly higher liver fibrosis stages (21/58 (36%) vs 44/61 (72%) with F4) than those treated during period 2.
- The proportion of those remaining to be treated with liver cirrhosis declined by 50% during the last 2 periods (18% vs 10%).

Figure 2: Evolution of liver fibrosis in the SHCS



CONCLUSION:

- The introduction of interferon-free second generation DAA treatments in the SHCS increased treatment uptake and efficacy across all HCV genotypes.
- Because of treatment priorities and limitations in reimbursement, most patients treated with second generation DAAs had advanced fibrosis or cirrhosis.
- The treatment of these patients was made possible because of the favorable safety profile of new drugs, and reduced the number of cirrhotic patients with replicating HCV infection in the SHCS.

ACKNOWLEDGEMENTS

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HIV Drug Therapy Glasgow 2016
Poster # P265

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Effectiveness of all-oral DAAs for HCV Genotype 4 in HIV/HCV-coinfected Subjects with Compensated Liver Disease: Real-world experience from the MADRID-CoRe Study

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Background

- HCV genotype 4 (GT4) is the second most prevalent HCV genotype in HIV/HCV-coinfected patients in Spain[1]
- Treatment with OBV/PTV/r ± RBV for 12 weeks in HCV GT4 monoinfected patients with or without cirrhosis resulted in high SVR rates in the phase IIb PEARL I trial[2]
- Treatment with LDV/SOF ± RBV for 12 weeks resulted in high SVR rates in two phase II trials of HCV GT4 monoinfected patients with or without cirrhosis[3,4]
- Little is known about real life effectiveness of IFN-free regimen combining direct-acting antivirals (DAAs) in coinfected patients
- We evaluated therapeutic outcomes of different all-oral DAAs regimens for GT4 in coinfected patients with compensated liver disease

1) Berenguer J, et al. Open Forum Infect Dis 2016; 3: ofw059. 2) Hezode C, et al. Lancet 2015; 385: 2502. 3) Abergel A, et al. Hepatology 2016; 64: 1049. 4) Kohli A, et al. Lancet Infect Dis 2015; 15: 1049.

Madrid-CoRe

Madrid-CoRe (Madrid Coinfection Registry)
- Prospective registry of HIV/HCV-coinfected adults (≥18 years) undergoing DAA therapy for HCV in the region of Madrid
- Compulsory for all hospitals from the Madrid Regional Health Service (SERMAS)

Patients registered in MADRID-CoRe
- 2,402 patients registered between Nov 2014-May 2016

Eligibility criteria for this study

Key inclusion criteria
- HIV/HCV-coinfection
- HCV Genotype 4
- Scheduled to finish treatment on May 31, 2016

Key exclusion criteria
- Current of previous decompensated liver disease defined as Child-Turcotte-Pugh (CTP) stage B or C, liver decompensation or hepatocellular carcinoma.

Study analysis

Primary endpoint
- Week 12 sustained viral response (SVR_{12}) by intention to treat analysis (ITT)

Secondary endpoints
- Viral relapse
- Viral breakthrough
- Treatment discontinuations (D/C) due to adverse events (AEs)
- Treatment D/C due to reasons other than AEs
- SVR_{12} by modified ITT (m-ITT) analysis, not including in the analysis patients with D/C due to reasons other than AEs

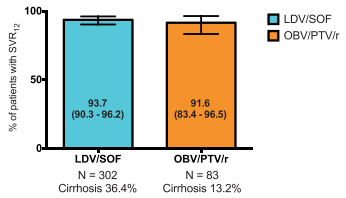
Patients and DAA-regimens

- 406 coinfected individuals met the inclusion criteria.
- Sofosbuvir/Ledipasvir (SOF/LDV) 302 patients
  - 287 without RBV [8wk 2, **12wk 204**, **24wk 81**]
  - 15 with RBV [12wk 13, 24wk 2].
- Ombitasvir/Paritaprevir/Ritonavir (OBV/PTV/r) 83 patients
  - 2 without RBV for 12wk
  - 81 with RBV [**12wk 69**, 24wk 12],
- Simeprevir/Sofosbuvir (SMV/SOF) 10 patients
  - 8 without RBV [12wk 6, 24wk 2]
  - 2 with RBV [12wk 1, 24wk 1].
- Daclatasvir/Sofosbuvir (DCV/SOF) 11 patients
  - 8 without RBV [12wk 1, 24wk 7]
  - 3 with RBV [12wk 2, 24wk 1].

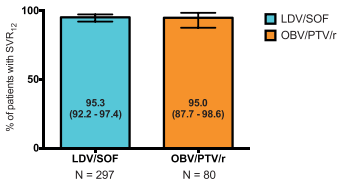
All-oral DAAs for GT4 in Coinfected Subjects with Compensated Liver Disease

	LDV/SOF	OBV/PTV/r	SMV/SOF	DCV/SOF
Baseline variables	N = 302	N = 83	N = 10	N = 11
Age– median (IQR)	51 (48 – 54)	50 (46 – 53)	52 (47 – 54)	51 (49 – 53)
Male – nº (%)	236 (78.1)	61 (73.5)	8 (80.0)	7 (63.6)
cART – nº (%)	293 (97.0)	79 (95.2)	8 (80.0)	9 (81.8)
Log HCV-RNA – median (IQR)	6.2 (5.9 – 6.7)	6.2 (5.8 – 6.6)	6.3 (6.0 – 6.6)	6.0 (5.5 – 6.5)
Cirrhosis – nº (%)	110 (36.4)	11 (13.2)	9 (90.0)	10 (91.0)
Liver stiffness – median (IQR)	10.1 (7.9 – 17.3)	8.5 (6.8 – 10.3)	48.0 (25.7 – 66.4)	27.7 (16.0 – 48.0)
HCV-naïve – nº (%)	186 (61.6)	47 (56.6)	4 (40.0)	7 (63.6)
Outcomes				
SVR_{12} (ITT) – nº (%)	283 (93.7)	76 (91.6)	5 (50.0)	7 (63.6)
% SVR_{12} (ITT) – 95% CI	90.3 – 96.2	83.4 – 96.5	18.7 – 81.3	30.8 – 89.1
Relapse – nº (%)	13 (4.3)	2 (2.4)	5 (50.0)	2 (18.2)
Breakthrough – nº (%)	0	1 (1.2)	0	0
D/C due to AEs – nº (%)	1 (0.3)	1 (1.2)	0	1 (9.1)
D/C other reasons – nº (%)	5 (1.6)	3 (3.6)	0	1 (9.1)
SVR_{12} (m-ITT) – nº (%)	283 (95.3)	76 (95.0)	5 (50.0)	7 (70.0)
% SVR_{12} (m-ITT) – 95% CI	92.2 – 97.4	87.7 – 98.6	18.7 – 81.3	34.8 – 93.3

LDV/SOF and OBV/PTV/r ± RBV for GT4 SVR_{12} by ITT analysis



LDV/SOF and OBV/PTV/r ± RBV for GT4 SVR_{12} by m-ITT analysis*



*m-ITT analysis = not including in the analysis patients with D/C due to reasons other than AEs

Conclusions

- High effectiveness was found with LDV/SOF and OBV/PTV/r for GT4 in coinfected patients with compensated liver disease.
- Small sample size and very high liver stiffness preclude any conclusion about the effectiveness of SMV/SOF and DCV/SOF

adrid CoRe Team

Juan González-García and Juan Berenguer are the senior authors of this communication

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Continued increase of recent hepatitis C virus infections among HIV-positive patients in Taiwan

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Introduction

1. We previously have shown an increasing trend of recent HCV infection in HIV-positive patients seeking HIV care at the National Taiwan University Hospital (NTUH), Taipei, from 1994 to 2010.
2. Patients with recent HCV seroconversion were 7 times more likely to have syphilis than those who did not have HCV seroconversion.
3. This study aimed to follow the trend of recent HCV infection after 2011.

Methods

1. Between 2011 and 2015, consecutive HIV-positive patients at the NTUH were prospectively observed. Antibodies to HCV were determined with a third-generation enzyme immunoassay (Diagnostic Bioprobes, Italy) and the plasma HCV RNA load was determined followed by HCV genotyping.
2. Recent HCV infection was defined when seroconversion occurred within 1 year of previous seronegativity. The date of seroconversion was assigned as the midpoint between the date of the last negative and that of the first positive anti-HCV result.
3. All patients were followed until 30 April 2016.

Results

1. After excluding 29 patients without anti-HCV data and 371 with prevalent HCV infection, 3083 were included (Figure 1).
2. During the study period, 248 had no follow-up serologic tests for HCV and 136 developed incident HCV infections during a total of 9900.51 PYFU, giving an overall incidence rate of 13.74 per 1000 PYFU. The rate was 12.64, 13.81, 13.76, 10.87, and 17.23 per 1000 PYFU in 2011, 2012, 2013, 2014, and 2015, respectively (Figure 2).
3. Compared with 2,699 patients who did not seroconvert for HCV, patients with recent HCV seroconversion were more likely to be male (100.0% vs 96.2%, *P*=0.009), younger (man age, 32.4 vs 35.6 years, *P*=0.0004), and MSM (86.0% vs 78.4%, *P*=0.0065) and to have recent syphilis (64.7% vs 11.2%, *P*<0.0001) (Table 1).
4. The mean plasma HCV RNA load was 5.39 $\log_{10}$ copies/ml. Of the 84 HCV strains, genotype 1 and genotype 2 accounted for 45% and 35%, respectively (Figure 3).

Conclusions

The increasing trends of recent HCV infection continue in HIV-positive patients seeking HIV care at the university hospital in Taiwan from 2011 to 2015.

Figure 1. Study flow diagram

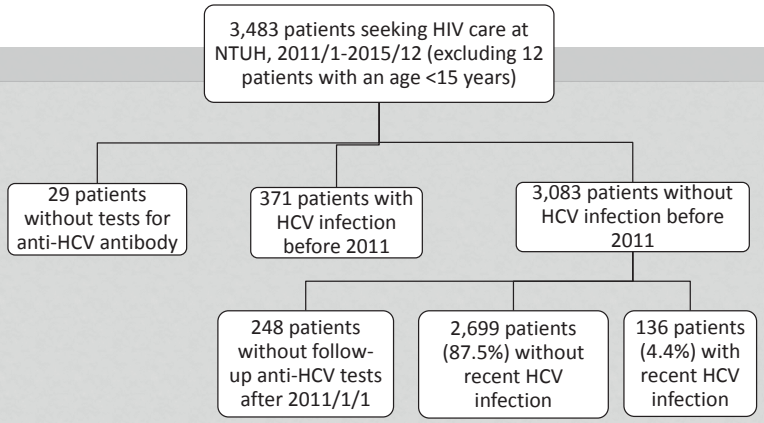
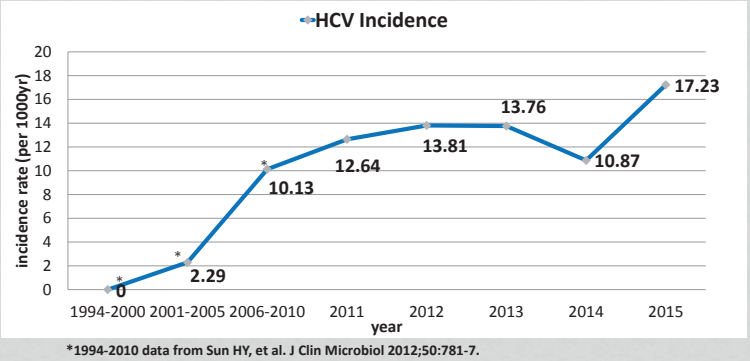


Table 1. Comparisons of characteristics between patients seeking HIV clinical services in NTUH with or without recent HCV infection

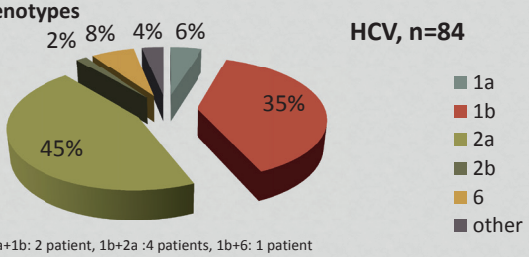
Characteristics	Recent HCV infection	No recent HCV infection	P value
	N=136	N=2699	
Male, n (%)	136 (100.0)	2,595 (96.2)	0.0090*
Age at the study started, mean (SD), years	32.4 (8.1)	35.6 (10.6)	0.0004*
Risk, n (%)			0.0065*
MSM/Bisexual	117 (86.0)	2,116 (78.4)	
Heterosexual	5 (3.7)	282 (10.5)	
IDU	2 (1.5)	8 (0.3)	
Others	12 (8.8)	293 (10.9)	
HBsAg-positive, n (%)	19 (14.0)	379 (14.0)	0.6626
Ever on HARRT, n (%)	133 (97.8)	2514 (93.2)	0.0335*
Prior syphilis (before last visit or seroconversion 6 mo and after 3 mo), n (%)	88 (64.7)	301 (11.2)	<.0001*

Figure 2. HCV infection incidence rate among HIV-positive patients



*1994-2010 data from Sun HY, et al. J Clin Microbiol 2012;50:781-7.

Figure 3. HCV genotypes



*Multi types : 1a+1b: 2 patient, 1b+2a :4 patients, 1b+6: 1 patient

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Treatment failure with DAAs in chronic hepatitis C: a portuguese multi-center report

Valente C[1], Casella MI[2], Faria D3, Aleixo MJ4, Vaz Pinto I5, Mota M6, Mingo A7, Carvalho A8, Roxo F9, Faísca R 10, Proença P7, Poças J2, Prata M1, Marques N4, Saraiva Cunha J1

GEPCOI, Grupo Português de Coinfecção VIH/Hepatites

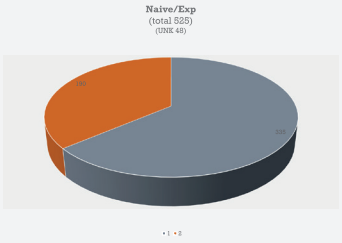
Introduction:

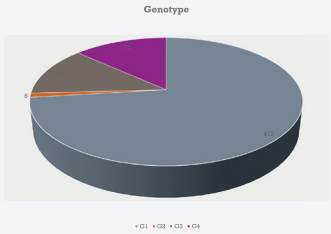
Either in clinical trials or in real-life studies, cure rates with oral-direct acting antiviral (DAAs) in the treatment of chronic hepatitis C are greater than 90%. However, as these drugs become more widely used, clinicians are begining to report ocasional cases of treatment failure.

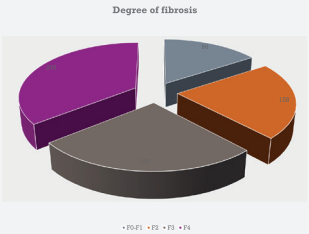
Materials and methods:

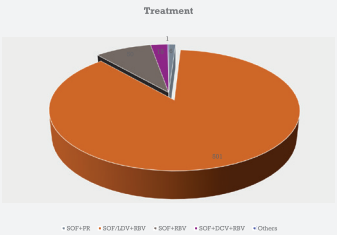
GEPCOI is a multicenter group that envolves several sites in Portugal. For this analysis 10 centers (north-2; center-2; south-6) participated and all cases of DAAs failure were collected. Treatment failure was considered in case of Relapse, virological failure during treatment, discontinuation or death. All co-infected HIV/HCV patients that started DAAs drugs were included in this analysis.

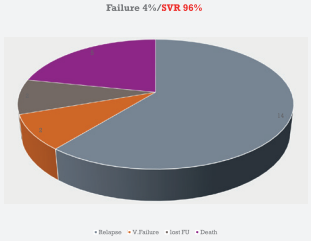
Results: 573 co-infected patients started treatment including DAAs, at beginning of 2015.











23 patients did not achieved SVR
Male sex – 95,6%; average 47 yrs
Naive-65,2%; Null responders-21,7%; Relapsers-4%
(previous treatent with PegIFN+RBV)
All patients were under ART and only 2 had detectable viraemia (28 and 3400 cp/ml)(CD4 ranging from 145-1615 cél/mm3)
Only 3 patients changed ART due to HCV treatment (2 cases changed from NNRTI/PI to II and 1 case switch from TDF/FTC to ABC/3TC)

Relapse/virological failure-16 patients:
G1-10 (62,5%); G2-2 (12,5%); G3-3 (18,7%), G4-1 (6,25%)
All G1/G4 patients were treated with SOF/LDV±RBV 12/24w
All G2/G3 patients (except one*) were treated with SOF+RBV 12,16 or 24w
(* classified initially as G1 and treated with Asunaprevir+Daclatasvir+RBV)
7 patients with F4; 5 with F3; 3 with F2 and 1 with F1
10 patients with G1 (2,4%); 3 patients with G3 (4,2%); 2 patients with G2 and 1 patient with G4 (1,3%)

DEATHS

	Sex/ age	RNA HIV	ART	HCV gen	Fibrosis KPa	Alb g/dL	Plat 10^9/L	MELD	HCV Tx	Death
Case 1	M 45yr	0	TDF/FTC+ RAL*	1a	F4 16	3,3	94	17	SOF/LDV+ RBV 12w	DHD at EOT
Case 2	M 52yr	0	ABC/3TC+ ATV/r	1b	F4 72	3,3	57	9	SOF/ LDV 24w	DHD during Tx (3°M)
Case 3	M 51yr	0	ABC/3TC+ LPV/r	1b	F4 ?	3	45	27	SOF/LDV+ RBV 24w	DHD during Tx (6ªw)
Case 4	M 45yr	0	ABC/3TC+ ATV/r	3a	F4 15	2,4	73	12	SOF/ RBV 24w	Pneum during Tx (2ªw)
Case 5	M 47yr	0	TDF/FTC+ ETV+RAL	1	F4 ?	2,1	43	24	SOF+DCV+ RBV 24w	DHD (SBP) During Tx (8ªw)

DHD-decompensation of hepatic disease; **EOT**-end of treatment; **Tx**-treatment; **SBP**-spontaneous bacterial peritonites; * changed ART when started HCV tx

Conclusions:

In this analysis of 573 patients, SVR was 96%. Failures in this real-life study occured in 4% (G1-3,4%, G3-8,4% and G4-1,4%) with Relapses or Virological failures accounting for 70% of the total. They were mainly individuals with advanced fibrosis (F3/F4-74,9%), Those who died were all cirrhotic and all of them had both low level of albumin (≤3,3 gr/dL) and low level of platelets (≤94 000). HCV drugs had no impact on HIV disease outcome during or at the end of treatment. In these patients with advanced disease concerns regarding drug-drug interactions, renal impairment, haematological impact, should be taken into account. Due to these factors a close monitoring should be done.

Seroepidemiology of Hepatitis A Virus Among HIV-positive Patients in Taiwan in the Setting of Acute Hepatitis A Outbreak in 2015-2016

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Introduction

- Hepatitis A virus (HAV) has been reported to cause clustered infection or outbreaks via unprotected fecal-oral sex among men who have sex with men (MSM). Current guidelines recommend HAV vaccination for all MSM and HIV-infected patients to prevent possible outbreaks.
- Since June 2015, an ongoing outbreak of acute hepatitis A has been occurring among MSM in Taiwan; more then 750 cases were reported to Taiwan CDC as of September, 2016.
- This study aimed to describe the HAV seroprevalence and incidence of acute hepatitis A among HIV-positive men and the rate of HAV vaccination among those who were seronegative for HAV.

Materials and Methods

- We carried out a retrospective cohort study including all HIV-positive men who sought HIV care at our hospital during 1st June 2015 and 30th June 2016. A total of 2029 patients was enrolled.
- Demographic and clinical characteristics of patients from 1st Janurary 2012 to 30th June 2016 was retrospectively collected, including plasma HIV RNA load (PVL), CD4 count and HAV serologies at baseline and during follow-up. Dates of HAV vaccination were also recorded.
- The incidence rate of acute hepatitis A was estimated before and during the outbreak periods in Taiwan.
- A case-control study was conducted. Case patients were those who acquired acute hepatitis A within the study period; and 4 controls were identified that were matched wth case patients by age (± 5 years), HIV risk factor, and similar observation duration.

Results

- In 2029 patients with available HAV serologies, 33.6% were seropositive (682/2029) at their first available serology data (Fig. 1).
- The baseline characteristics between HAV-positive and HAV-negative patients are shown in Table 1.
- 54.3% (731/1347) of seronegative patients were vaccinated against HAV. However, most of these patients (684/731) were vaccinated only after the outbreak of HAV was taking place in Taiwan.
- 35 cases of acute hepatitis A were observed in the study cohort during the designated period. All of those patients were MSM. The incidences of acute hepatitis A before and after outbreak are shown in Table 2.
- In the case-control study (Table 3), acute HAV infection was significaltly associted with recent syphlis that had occurred within 3 months of acute hepatitis A, with an adjusted odds ratio of 10.89 (95% CI, 2.31-51.26).

Summary & Conclusions

- Among our patients, the HAV seroprevalence, while increasing with age, remained low in MSM aged <40 years (Figure 2), suggesting a large number of susceptible persons being at risk for HAV infection during this ongoing outbreak in Taiwan.
- 54.3% of HAV-seronegative patients was vaccinated in our study. However, most of the vaccinaiton occurred only after the outbreak, suggesting a low adherence to the recommendations for HAV vaccination in the high-risk group.
- The incidence rate of acute hepatitis A among HIV-positive MSM was estimated 45.1 per 1000 person-years of follow-up.
- Acquisition of acute hepatitis A in this outbreak was associated with recent syphilis infection, suggesting risky sexual behavior contributing to this acute HAV outbreak in the at-risk group in Taiwan.

Figure 1. Seroprevalence and HAV vaccine coverage of in the study cohort

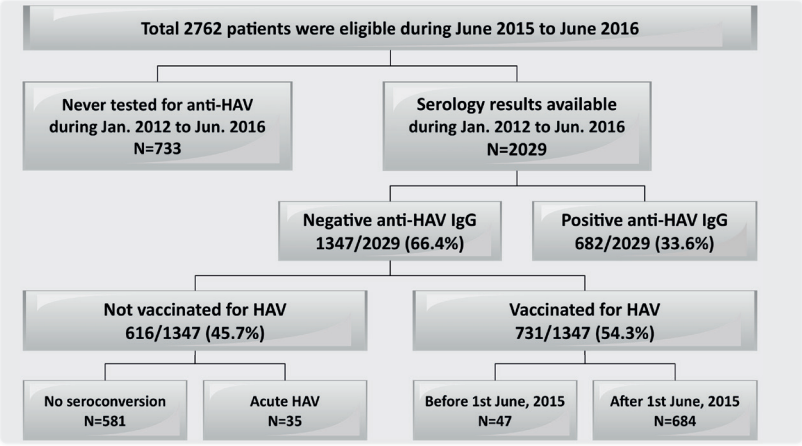

Table 1. Baseline characteristics of HAV-positive and -negative patients

Clinical characteristics at baseline*	Baseline anti-HAV IgG		p-value
	HAV-seropositive (N=682)	HAV-seronegative (N=1347)	
Age (years)	45.1 (11.2)**	34.9 (7.8)	<0.001
MSM Risk factor	537/682 (78.7%)	1154/1347 (85.7%)	
CD4 count (cells/μL)	533.3 (292.5)	475.9 (260.3)	<0.001
Plasma viral load (log)	4.26 (1.42)	4.55 (1.06)	0.002
Previously vaccinated against HAV before year 2012	183/682 (26.8%)	86/1347 (6.4%)	<0.001

* Defined as the date of first available anti-HAV serology after January, 2012
** Mean and standard deviation are shown

Table 2. Estimated incidence rate of acute hepatitis A among HIV-positive MSM

Duration	Length of follow-up (person-year)	HAV vaccination	Acute hepatitis A
Before outbreak*	2534.81	N=28	N=0
	Incidence rate: (per 1000 person-year)		0
Within outbreak*	777.17	N=609	N=35
	Incidence rate: (per 1000 person-year)		45.1

* The duration before outbreak is defined since 01/01/2012 to 05/31/2015.
The duration within outbreak is defined since 06/01/2015 to 06/30/2016.

Table 3. Multivariable analysis of factors associated with recent HAV infection

Clinical Factors	Adjusted OR (95%CI)
CD4 cell counts (per 10 cell/mL increase)	1.00 (0.98-1.03)
Plasma viral load (per 1 log unit increase)	1.06 (0.77-1.46)
Recent Syphilis Infection within 3 months	10.89 (2.31-51.26)*
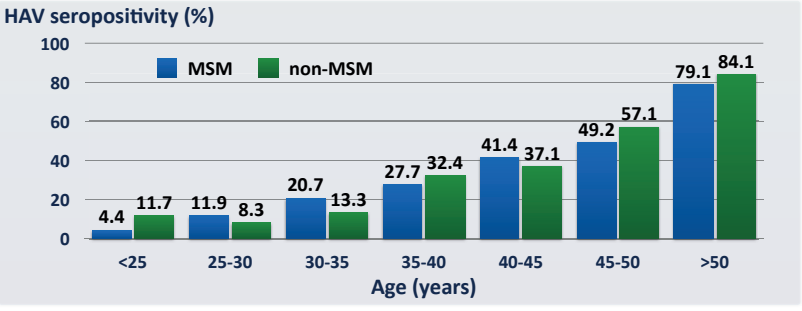
Figure 2. HAV-seroprevalence among HIV-infected patients in different age groups