Hepatitis aguda C en pacients VIH

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03/06/2016

- Situación actual de la Hepatitis Aguda C (HAC) en el paciente VIH
- Experiencia en HAC en el paciente VIH en el Hospital Clínic

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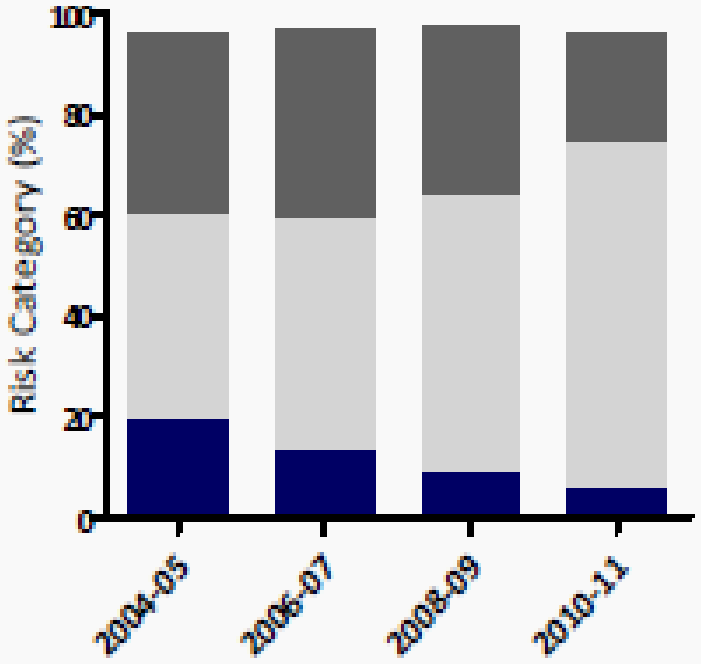
The incidence of HCV superinfection in Icona cohort

Changes in risk behaviors for HIV/HCV acquisition during the study period



Significant decreases in the prevalence of:
* IDU (from 19.2% to 5.6%)
*Heterosexual (from 36.4% to 21.9%)

*Significant increase in MSM (from 40.6% to 68.6%).

Puoti M. Paper #638. CROI '13

Epidemiología

- Un número creciente de casos de hepatitis aguda por el VHC han sido reportados en los últimos 10 años.

Boesecke C. **Diagnosis and Treatment of Acute Hepatitis C Virus Infection** , Infect Dis Clin North Am. 2012 Dec

Epidemiología

- Estudios longitudinales de cohortes han confirmado un aumento en la incidencia de VHC entre los pacientes HSH

van de Laar TJ, J Infect Dis 2007; Gotz HM AIDS 2005 ; Danta M . Curr Pharm Des 2008 ; Serpaggi J AIDS 2006; Luetkemeyer A J Acquir Immune Defic Syndr 2006; Matthews GV . Clin Infect Dis 2009; Giraudon I Sex Transm Infect 2008; van de Laar TJ Gastroenterology 2009;

- Factores relacionados con el aumento de incidencia HAC en el colectivo HSH - VIH
  - Mayor CV VHC en sangre y semen
  - Mayor susceptibilidad mucosa rectal del paciente VIH
  - Presencia de otras ETS ulcerativas
  - HAART disminución de la percepción de riesgo
  - Uso de drogas recreativas: disminución percepción riesgo, mayor número de parejas sexuales, prácticas sexuales más agresivas.
    - Chemsex ?
    - Slamming ?

1. Leruez-Ville Lancet 2000; 2. Pasquier C J Med Virol 2003; 3. Desquilbet L AIDS 2002: 4. Briat A, AIDS 2005; 5. Brenchly JM J Exp Med 2004; 6. Page E Clinical Medicine 2016

Sospecha y evaluación clínica

- Sospecha:
  - Pacientes con clínica sugestiva de hepatitis aguda
  - Aumento inexplicable del valor enzimas hepáticas >1,5 veces limite superior normalidad en control rutinario
  - Proctitis por LUES o LGV

- Evaluación:
  - Estudio serológico y virológico
  - Comportamiento sexual y factores de riesgo clásicos para el contagio

Diagnóstico y Seguimiento

- Diagnóstico HAC:
  - Clínica compatible o elevación de transaminasas
  - Seroconversión de Ac-VHC
  - Presencia ARN-VHC
  - Conductas de riesgo

- Seguimiento: Visita cada 3-4 semanas.
  - Control clínico.
  - Transaminasas.
  - Caída ARN-VHC

Clínica

Período de incubación variable (15-160 días)

- Presentación clínica similar a la de la población monoinfectada

  Características propias de los pacientes coinfectados:

  – inferior presencia de signos y síntomas de hepatitis
  – elevaciones más discreta de ALT sérica

Evolución

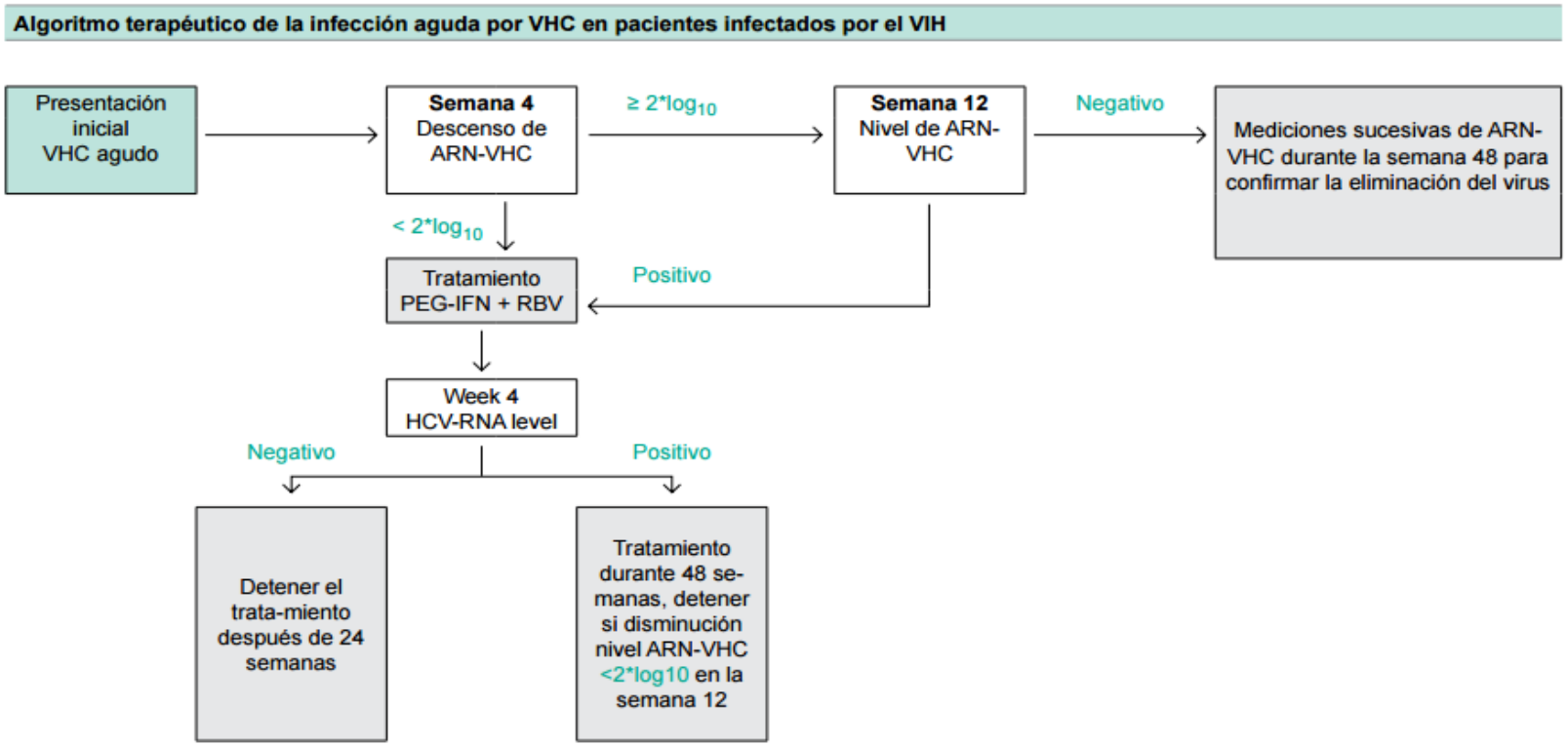
- Evolución a infección crónica hasta en el 85% de los casos.

- La eliminación espontánea del virus (15% de pacientes) suele ocurrir dentro de las 12 semanas después del diagnostico

  - Factores favorables para la eliminación vírica
    - HAC sintomática
    - ALT basal elevada
    - Descenso rápido de ARN-VHC
    - IL28B C/C

  - Factores de riesgo para la persistencia
    - Infección asintomática
    - VIH+
    - Sexo masculino
    - Raza negra

Tratamiento



EACS Treatment Guidelines updated
Version 8 - November 2015

Tratamiento con pINF/RBV en HAC en pacientes HIV/HSH

HIV+ MSM: Hypothesis

Study	Rx	Duration (wk)	SVR rate
Gilleece 2005, London	pIFN+RBV	24	16/27 (59%)
Vogel 2006, Germany	pIFN+RBV	24-48	22/36 (61%)
Dominguez 2006, France	pIFN+RBV	24	10/14 (71%)
Matthews 2009, Australia	pIFN+RBV	24	16/22 (73%)
Piroth 2010, France	pIFN+RBV	24-48	32/39 (82%)
Lambers 2011, Amsterdam	pIFN+RBV	24-48	38/50 (76%)
Obermeier 2011, Germany	pIFN+RBV	24-48	93/175 (53%)
Fierer 2013, (unpublished) New York City	pIFN+RBV	24-48	29/46 (63%)
TOTAL:	**pIFN+RBV**	**24-48**	**256/409 (63%)**

Telaprevir in the Treatment of Acute Hepatitis C Virus Infection in HIV-Infected Men

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(See the Editorial Commentary by Zeremski et al on pages 880–2.)

Background. There is an international epidemic of hepatitis C virus (HCV) infection among human immunodeficiency virus (HIV)–infected men who have sex with men. Sustained virologic response (SVR) rates with pegylated interferon and ribavirin treatment are higher in these men during acute HCV than during chronic HCV, but treatment is still lengthy and SVR rates are suboptimal.

Methods. We performed a pilot study of combination therapy with telaprevir, pegylated interferon, and ribavirin in acute genotype 1 HCV infection in HIV-infected men. Men who were treated prior to the availability of, or ineligible for, telaprevir were the comparator group. The primary endpoint was SVR12, defined as an HCV viral load <5 IU/mL at least 12 weeks after completing treatment.

Results. In the telaprevir group, 84% (16/19) of men achieved SVR12 vs 63% (30/48) in the comparator group. Among men with SVR, median time to undetectable viral load was week 2 in the telaprevir group vs week 4 in the comparator group, and 94% vs 53% had undetectable viral loads at week 4. Most patients (81%) who achieved SVR in the telaprevir group received ≤12 weeks of treatment and there were no relapses after treatment. The overall safety profile was similar to that known for telaprevir-based regimens.

Conclusions. Incorporating telaprevir into treatment of acute genotype 1 HCV in HIV-infected men halved the treatment duration and increased the SVR rate. Larger studies should be done to confirm these findings. Clinicians should be alert to detect acute HCV infection of HIV-infected men to take advantage of this effective therapy and decrease further transmission in this epidemic.

Keywords. acute HCV; treatment; HIV infection; men who have sex with men; telaprevir.

SVR12 Results after 12w Boceprevir+ P/R in the Dutch Acute Hepatitis C in HIV Study

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Poster number: 669

Background

The international epidemic of acute hepatitis C virus (AHCV) continues to spread within HIV+ MSM, with incidence rates between .08 and 1.75%. 24wks of peginterferon(P) (+/- ribavirin(R)) cures 60-70% of them.

The addition of a direct-acting anti-viral drug (DAA) may increase cure rates and allow a shorter treatment. The efficacy and role of the old and new DAA in the treatment of AHCV has not been studied. Furthermore, given the costs of new DAA, almost all European countries currently restrict the use of newer DAA to patients with severe fibrosis or cirrhosis.

This Dutch nationwide study evaluates the efficacy and tolerability of 12w boceprevir+P+R in acute HCV genotype-1 HIV-infected patients.

Methods

- HIV positive MSM were tested for HCV RNA if they presented with an ALAT > upper limit of normal

- Infection date was calculated by retesting stored plasma samples. (CAP/CTM V2, Roche diagnostics)

- HCV genotype 1 infected patients were included and treatment started within 26 weeks after infection

- Boceprevir +P+R were given for 12 weeks, without P/R lead-in

- Virological response was defined as HCV RNA < 15 copies/target not detected

Baseline characteristics (n=57)

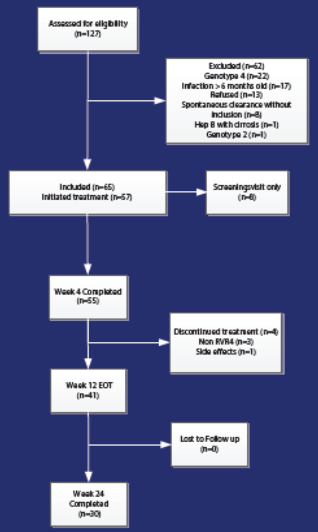
Gender	Male	100 %	
Race	Caucasian	93 %	
	non-Caucasian	7 %	
Genotype	1 a	95 %	
	b	5 %	
IL28B *RS1297*	CC	42,5 %	
	CT	50 %	
	TT	7,5 %	
Age	median	40 years	(IQR 34-47)
CD4 count	median	0,66 E9/l	(IQR 0,45-0,79)
Interval infection-treatment	median	22 weeks	(IQR 16,5-25)
Baseline HCV Load	median	200.000 IU/ml	(IQR 8.375-3.230.000)

Primary endpoint:

Sustained virological response (SVR) 12 weeks after the end of therapy in the RVR4 population

Secondary endpoint:

SVR12 in the intention to treat (ITT) population



Incidence of AHCV in 2014 in the study centers

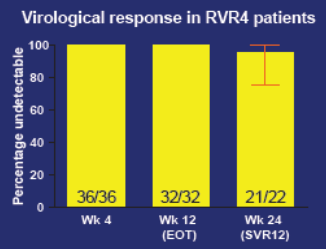
8304 HIV+ and HCV- MSM were in care
91 AHCV infections were diagnosed

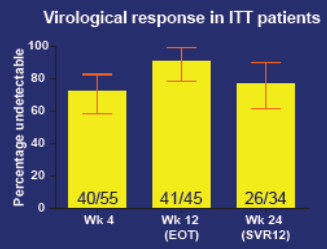
The estimated minimum incidence was therefore 91/8304=11/1000 PYFU (95% CI 8.9-14)

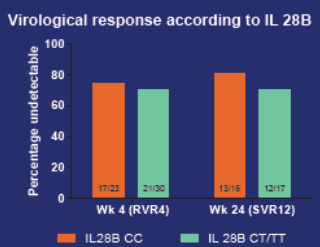
Results

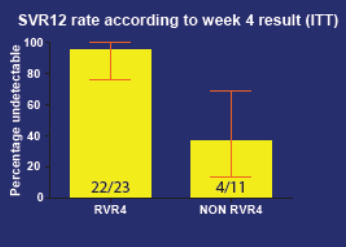
The study is ongoing but fully enrolled with 65 patients included of which 8 cleared HCV spontanuously and 57 started therapy. 34 patients have reached the SVR12 evaluation endpoint.

Three SAE have been reported; 1 myocardial infarction (not related); 1 transient ischemic attack (not related), 1 grade 4 anemia (related). Median amount of AE per patient: grade 1=4, grade 2=1.5 and grade 3=1.









Conclusion

- Addition of boceprevir to P/R halves therapy duration of acute HCV to 12 weeks
- 95% SVR in RVR4 patients (95% CI 75%-99%)
- 76% SVR in ITT population (95% CI 58%-89%)
- IL28 RS1297 nor RS809 genotype had impact on SVR12 results
- No unexpected side effects were observed
- The DAHHS network allows for a fast evaluation of DAA for the treatment of AHCV

QR-link to poster

Hullegie S, et al. Abstract 669. CROI'15

Tratamiento con DAAs

Study name	Coordinator	DAAs	HCV genotype	Duration (weeks)	HIV Status
DAHHS	Erasmus MC	BOC + pegIFN + RBV	1	12	pos
CHAT	UKB	TPV + pegIFN + RBV	1	12	pos
SWIFT-C	ACTG	SOF + RBV	all	8 vs. 12	pos
DARE C III	Kirby Institute	SOF + RBV	all	6	neg + pos
SOL	UKB	SOF + LDV	1, 4	6	pos
Hep-Net Acute HCV	MHH	SOF + LDV	1	6	neg

Boesecke C, Curr Opi HIV AIDS 2015

SWIFT-C (ACTG 5327): SOF + RBV for 12 wks in AHC coinfection

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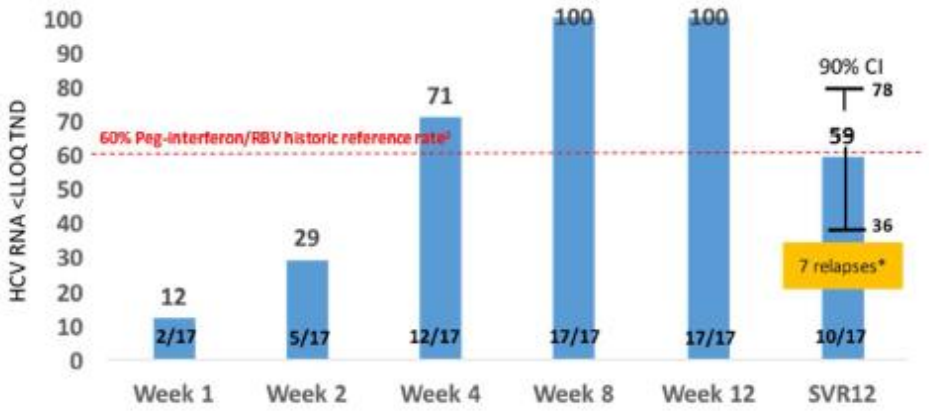
	SOF/RBV 12 weeks N=17
Median age, y (quartiles)	45 (41, 47)
Male, n (%)	17 (100)
White, n (%)	6 (35)
Hispanic or Latino, n (%)	11 (65)
IV Drug Use Ever, n (%)	4 (24)
IL28B CC, n (%)	4 (24)
GT 1, n (%)	15 (88)
First HCV infection, n (%)	17 (100)
Mean HCV RNA, $\log_{10}$ IU/mL ± SD	5.63 ± 1.76
Median time (days) from first evidence of infection (quartiles)	140 (121, 151)
Median CD4, cells/µL (quartiles)	498 (387, 612)
HIV RNA <50 copies/mL, n (%)	15 (88)
Median ALT, mg/dL (quartiles)	181 (165, 284)
Median AST, mg/dL (quartiles)	106 (69, 159)
Median Tbili, mg/dL (quartiles)	0.70 (0.60, 0.80)

Naggie et al, AASLD 2015 #1094

SWIFT-C (ACTG 5327): SOF + RBV for 12 wks in AHC coinfection

universitäts klinikumbonn

Results: Viral Suppression Rates



Naggie et al, AASLD 2015 #1094

DARE-C II:
SOF + RBV for 6 wks in AHC mono- and coinfection

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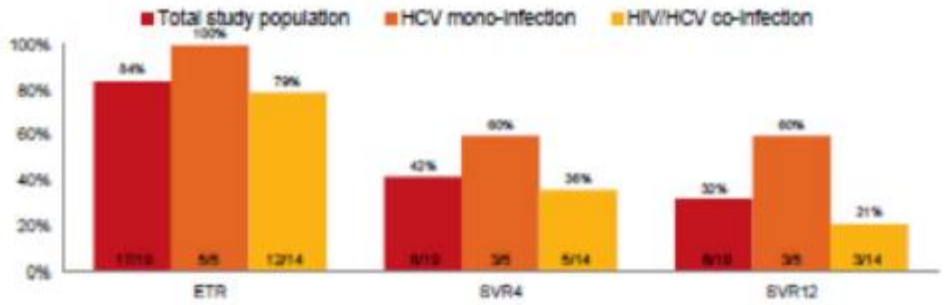
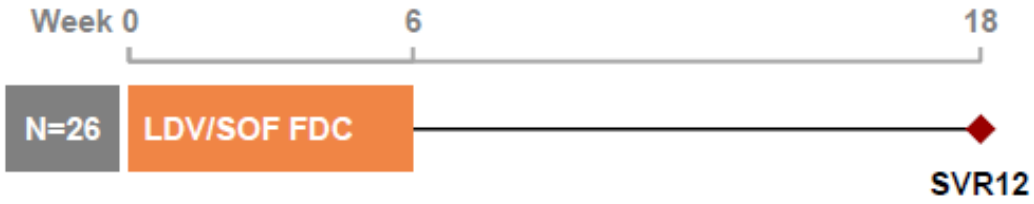
- Mean age 42 years, 89% male (n=17), 74% HIV positive
- 68% GT1a (n=13), 26% GT3a infection (n=5)
- Injecting drug use (n=10, 53%), sexual exposure with a partner of the same sex (n=8, 42%)
- Median HCV RNA at screening 5.7 log10 IU/mL (IQR 5.0-6.3)



Martinello et al, AASLD 2015 #1083

Ledipasvir/Sofosbuvir for 6 Weeks in HIV-Infected Patients with Acute HCV Infection



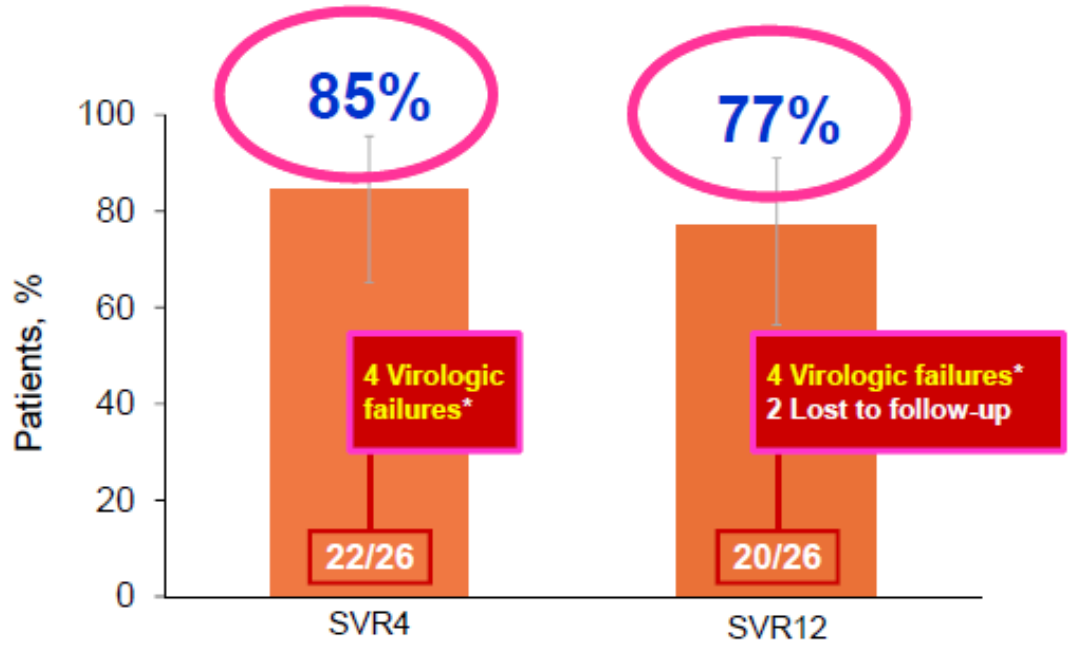
- Patients with chronic HIV and acute HCV infection
  - **HCV GT 1 or 4 N=19 GT1a; N=7 GT4**
  - ART consistent with LDV/SOF co-administration with HIV <200 copies/mL or not receiving ART with no plans to start
- Acute HCV infection with detectable HCV RNA (Roche COBAS® AmpliPrep/COBAS® TaqMan® version 2.0, LLOQ=15 IU/mL) for <24 weeks, defined by
  - HCV RNA-positive and negative anti-HCV antibody/HCV RNA test within last 6 months or
  - Elevated ALT/AST >2.5 x ULN in past 6 months with normal LFTs in past year, and other causes excluded
- **5 sites in Germany and UK**

ART, antiretroviral therapy

CROI '16

#154LB

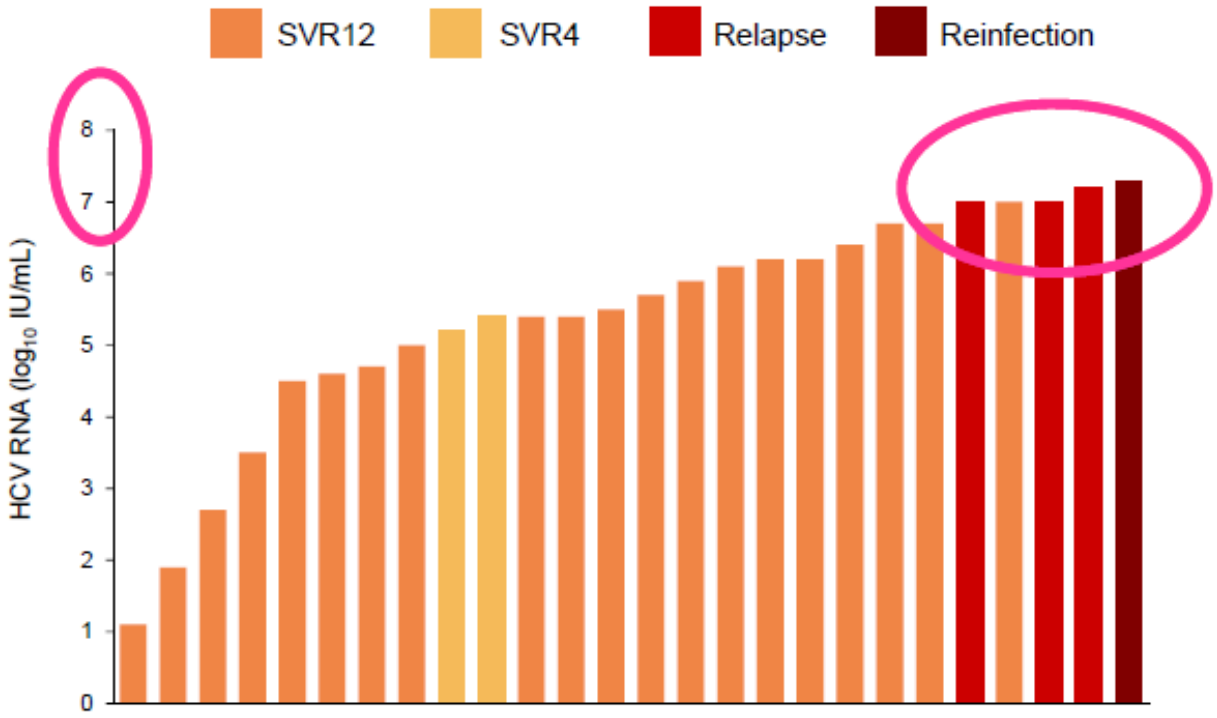
Results: SVR4 and SVR12 (ITT)



*3 patients relapsed, 1 was reinfected (GT 1a at baseline, 4d in post-treatment).
Error bars represent 95% confidence intervals.

#154LB

Results: Baseline HCV RNA and Treatment Outcome (SVR)



- **The 3 relapses had BL VL >7 log10 IU/mL**: GT 1a (2) and 4 (1). No new NS5A or NS5B RAVs were observed

#154LB

XVI Congrés de la Societat Catalano-Balear de Medicina Interna
2 i 3 de juny de 2016

Six weeks of sofosbuvir/ledipasvir (SOF/LDV) are sufficient to treat acute hepatitis C virus genotype 1 monoinfection:

The HepNet Acute HCV IV Study

Katja Deterding, Christoph Spinner, Eckart Schott, Tania Welzel, Guido Gerken, Hartwig Klinker, Ulrich Spengler, Johannes Wiegand, Julian Schulze zur Wiesch, Anita Pathil, Markus Cornberg, Andreas Umgelter, Caroline Zöllner, Stefan Zeuzem, Heiko von der Leyen, Dorothee von Witzendorff, Michael P. Manns, Heiner Wedemeyer

for the HepNet Acute HCV IV Study Group

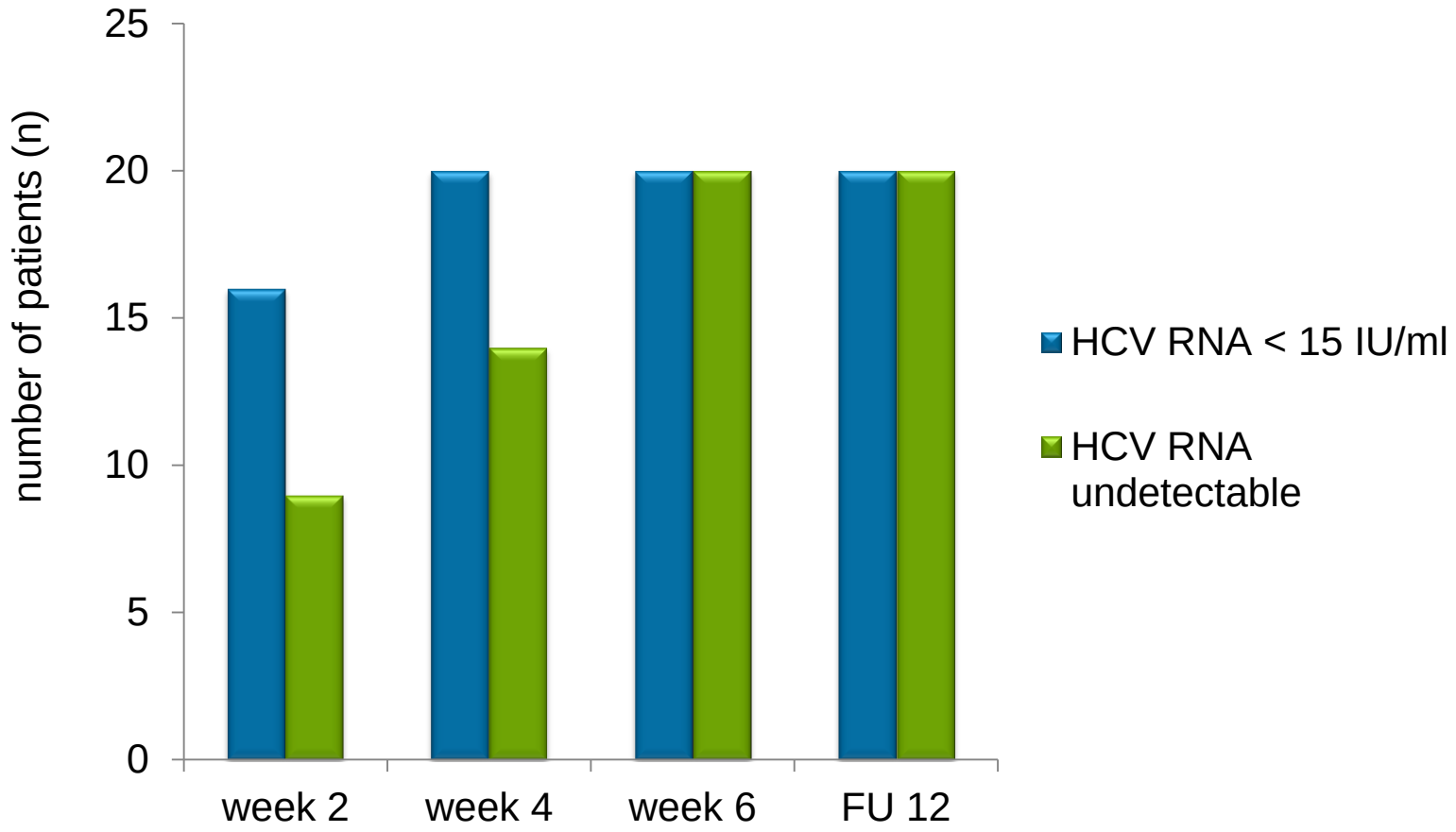
DZIF

Baseline characteristics

	Study cohort
Patients (n)	20
Male, n (%)	12 (60%)
Age (years), mean (range)	46 (23 – 63)
HCV - Genotype	
- Genotype 1a, n (%)	11 (55%)
- Genotype 1b, n (%)	9 (45%)
Risk factors for infection	
- Sexual transmission, n (%)	11 (55%); including 5 men having sex with men
- Medical procedures/needle stick injury, n (%)	5 (25%)
- Nail treatment, n (%)	1 (5%)
- Unspecified, n (%)	2 (10%)
ALT (U/l), mean (range)	463 (32 – 2716)
Bilirubin (mg/dl), mean (range)	24 (5.13 – 111)

DZIF

Virological response



Acute HCV IV Study, EASL 2016

SLAM C:
SOF + LDV or SMP in AHC monoinfection

universitäts klinikum bonn

- Group A (n=14): SOF 400 mg + LDV 90 mg (once daily) for 4 weeks
- Group B (n=15): SOF 400 mg + SIM 150 mg (once daily) for 8 weeks
- All patients GT 1 infection (7/7 GT1a/1b in group A and 7/8 GT1a/GT1b in group B, respectively)
- Mean viral load was 1,200 k in the SOF + LDV group and 1,600 k in the SOF + SIM group

Undetectable	Group A SOF + LDV N=14	Group SOF + SIM N=15
Day 7, n, %	13/14, 92.9%	13/15, 86.67%
4 Weeks, n %	14/14, 100% (ETVR)	14/15, 93.3% (1 dropped started IV drug use)
8 Weeks, n, %	14/14, 100%	14/15, 93.3% (ETVR)
16 Weeks, n, %	14/14, 100%, SVR12	14/15, 93.3%
20 Weeks, n, % (per protocol)	(1 dropped, transferred to the prison)	13/13, 100%, SVR12 (one was lost to follow-up-homeless)
Retention	13/14, 92.9%	13/15, 86.67%

Basu et al, AASLD 2015 #1074

- Poques dades AAD en HAC monoinfectats i coinfectats per VIH

- Periode de tratactament més curt en HAC?

- Situación actual de la Hepatitis Aguda C (HAC) en el paciente VIH
- Experiencia en HAC en el paciente VIH en el Hospital Clínic

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 28, Number 10, 2012

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Low Rate of Sustained Virological Response in an Outbreak of Acute Hepatitis C in HIV-Infected Patients

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Abstract

Recent reports have suggested an increased risk of acute hepatitis C (AHC) infection in homosexual HIV-infected men and that early treatment with interferon-alfa, alone or associated with ribavirin, significantly reduces the risk of chronic evolution. A retrospective analysis of 38 HIV-infected patients who were consecutively diagnosed as developing AHC, defined by both seroconversion of anti-hepatitis C virus (HCV) antibodies and detection of serum HCV-RNA in those with previous negative results.

Thirty-six patients were men with history of unprotected sexual intercourse with men and two were women with sexual and nosocomial risk factors. AHC infection was asymptomatic in 26 patients; asthenia and jaundice were the most frequent symptoms. HCV genotype 1 was present in 19 patients and genotype 4 in 14 patients. Thirty-five patients received early antiviral treatment with pegylated interferon-alfa associated with ribavirin; 15 of the 32 patients who completed the follow-up (47%) achieved a sustained virological response, as defined by undetectable HCV-RNA 6 months after the end of therapy. There is a risk of sexual transmission of HCV in HIV-infected men who have sex with men. In our experience, early treatment of AHC with pegylated interferon-alfa plus ribavirin in HIV patients achieves poor results.

Enferm Infecc Microbiol Clin. 2015;33(1):3–8

ELSEVIER DOYMA

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Original

Brote epidémico de hepatitis aguda C en pacientes infectados por el virus de la inmunodeficiencia humana

Maria Martínez-Rebollar*, Josep Mallolas, Iñaki Pérez, Ana González-Cordón, Montserrat Loncà, Berta Torres, Jhon-Fredy Rojas, Polyana Monteiro, José-Luis Blanco, Esteban Martínez, José-María Gatell y Montserrat Laguno

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INFORMACIÓN DEL ARTÍCULO

Historia del artículo:
Recibido el 7 de noviembre de 2013
Aceptado el 29 de mayo de 2014
On-line el 12 de agosto de 2014

Palabras clave:
Hepatitis aguda C
Coinfección por virus de la inmunodeficiencia humana
Incidencia
Enfermedades de transmisión sexual

RESUMEN

Introducción: Estudios recientes confirman un aumento de la incidencia de infección aguda por el virus de la hepatitis C (HAC) en hombres que tienen sexo con hombres (HSH) infectados o no por el VIH. El tratamiento temprano con interferón-alfa, solo o asociado a ribavirina, reduce significativamente el riesgo de evolución a la cronicidad.

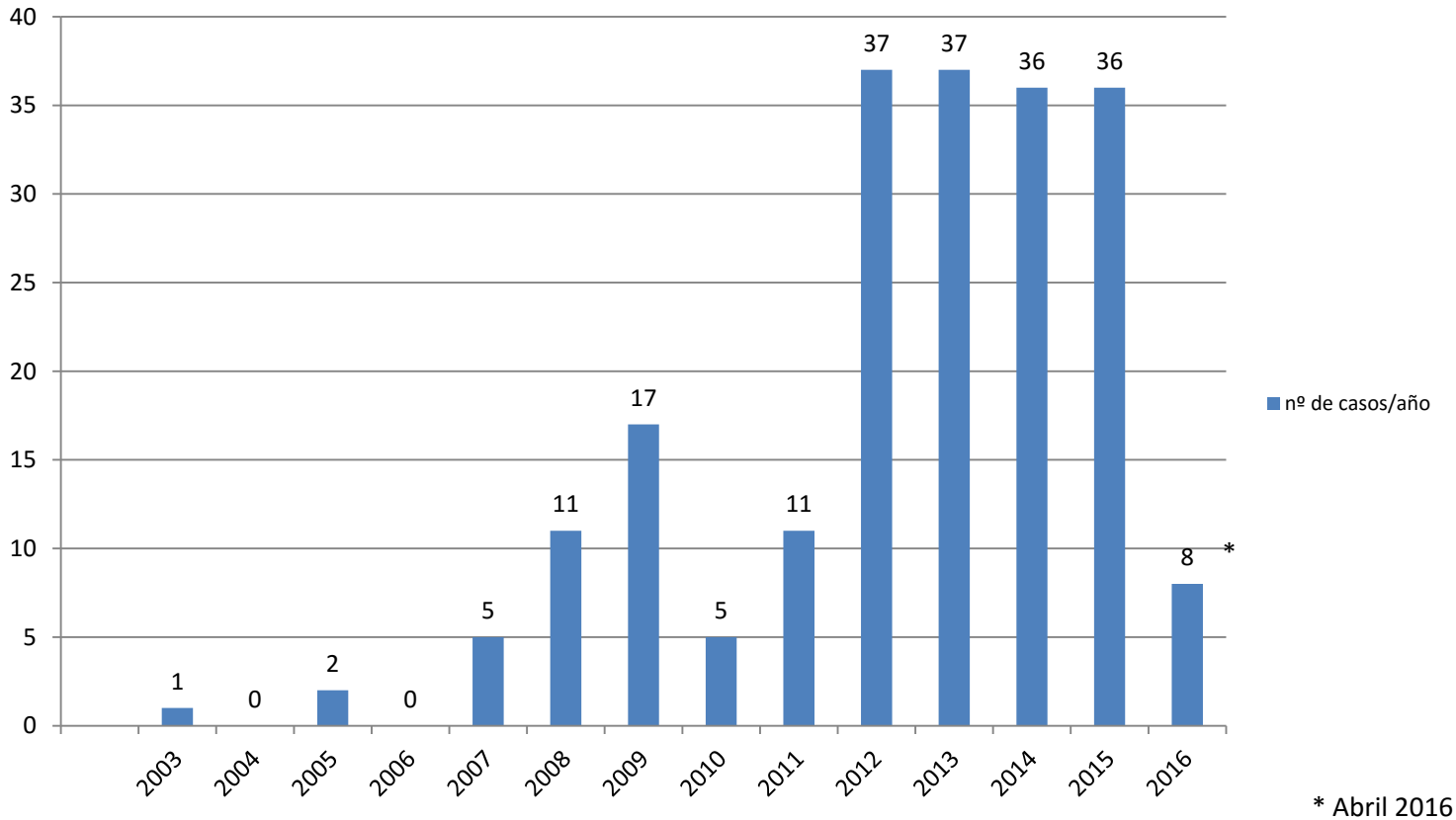
Métodos: Estudio retrospectivo que incluye todos los pacientes VIH diagnosticados de HAC en nuestro centro desde junio del 2003 a marzo del 2013, definida la HAC por la seroconversión de anticuerpos contra el VHC y la detección de ARN-VHC sérico.

Resultados: Se diagnosticaron 93 episodios de HAC en 89 pacientes. Excepto en 3 casos todos eran HSH con antecedentes de prácticas sexuales de riesgo. Treinta y 7 (40%) pacientes presentaban otra enfermedad de transmisión sexual asociada. El 29% (27) presentaron algún síntoma sugestivo de HAC. El genotipo 4 del VHC fue el más frecuente (41%), seguido del genotipo 1. En 70 casos se inició tratamiento con interferón-alfa y ribavirina ajustada a peso. En la actualidad 46 han finalizado el tratamiento y el seguimiento, alcanzando 26 de ellos (56,5%) una respuesta viral sostenida.

Conclusiones: La incidencia de HAC en los pacientes VIH HSH de nuestro centro ha aumentado de forma exponencial en los últimos años, siendo la transmisión sexual la vía principal de infección. El tratamiento precoz con interferón-alfa y ribavirina consigue una respuesta moderada en estos pacientes.

Enero ’03-Marzo ‘13: N= 93 casos en 89 pacientes

Incidencia de Hepatitis aguda C en el Hospital Clínico de Barcelona: nº casos /año



* Abril 2016

Características Clínicas

Enero 2003-abril 2016

- n: **206 casos** en **186 pacientes**
  - 182H (HSH)
  - 1 H (ADVP)
  - 3 M (1 het, 1 nos, 1 ADVP)
- Edad media 39 años (DS 7)
- IL28B (n: 105 pac)
  - CC: 40%
  - CT: 49%
  - TT: 11%

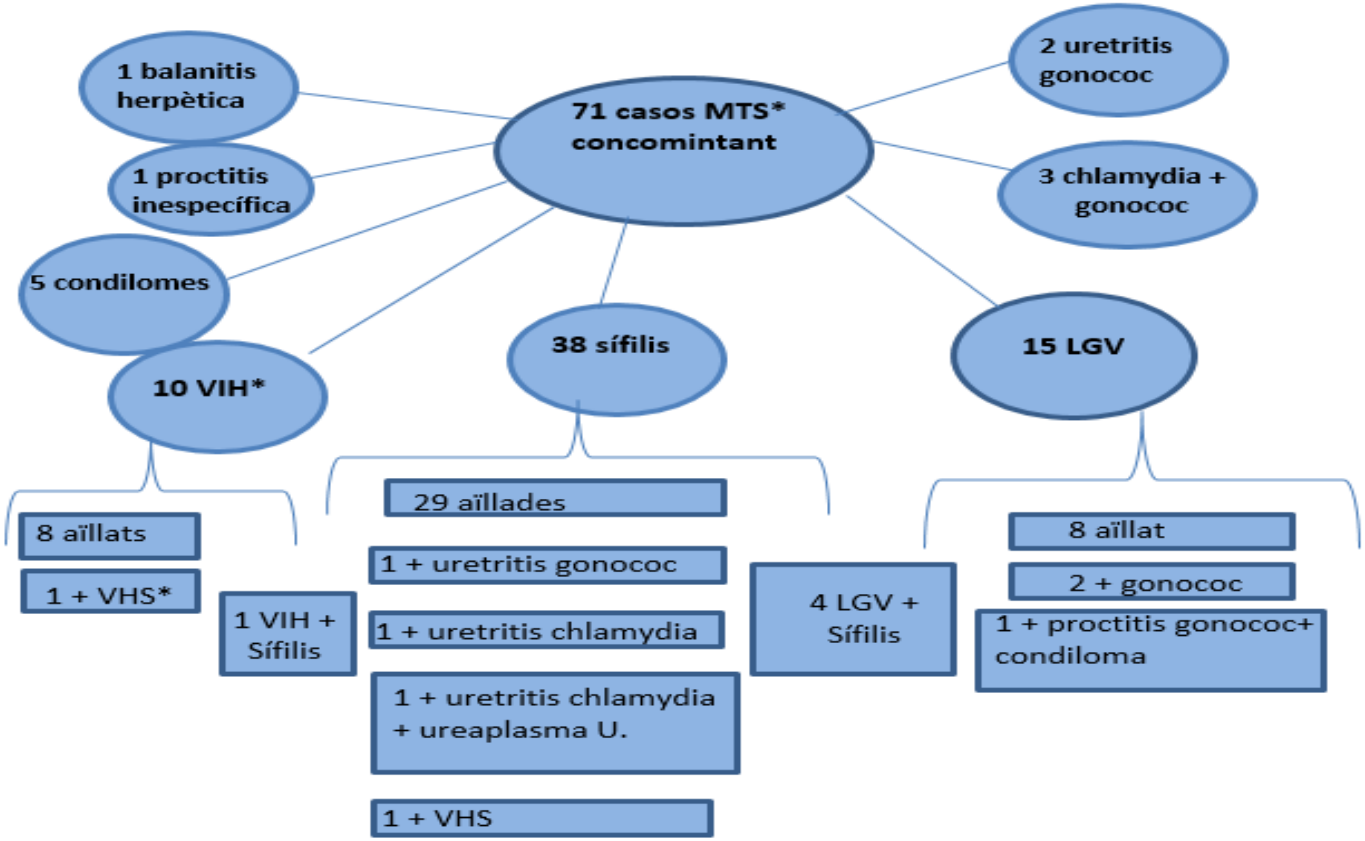
Características Clínicas

- Hepatitis aguda sintomática: 31% síntomas:
  - 15 MEG+Colúria
  - 8 Astenia
  - 5 Molestias Digestivas/Dolor en HD/Nauseas
  - 7 Fiebre
  - 5 Ictericia
- H. asintomática 69%: ↑ GOT/GPT
- 12 casos **aclaramiento espontáneo** (6.1%)
- 19 pacientes reinfectados

  Tasa de reinfección: 9,2%

Características Clínicas

- Co-infección con otras ETS (45%): (N: 161 episodios. Enero 2003-Nov 2014)



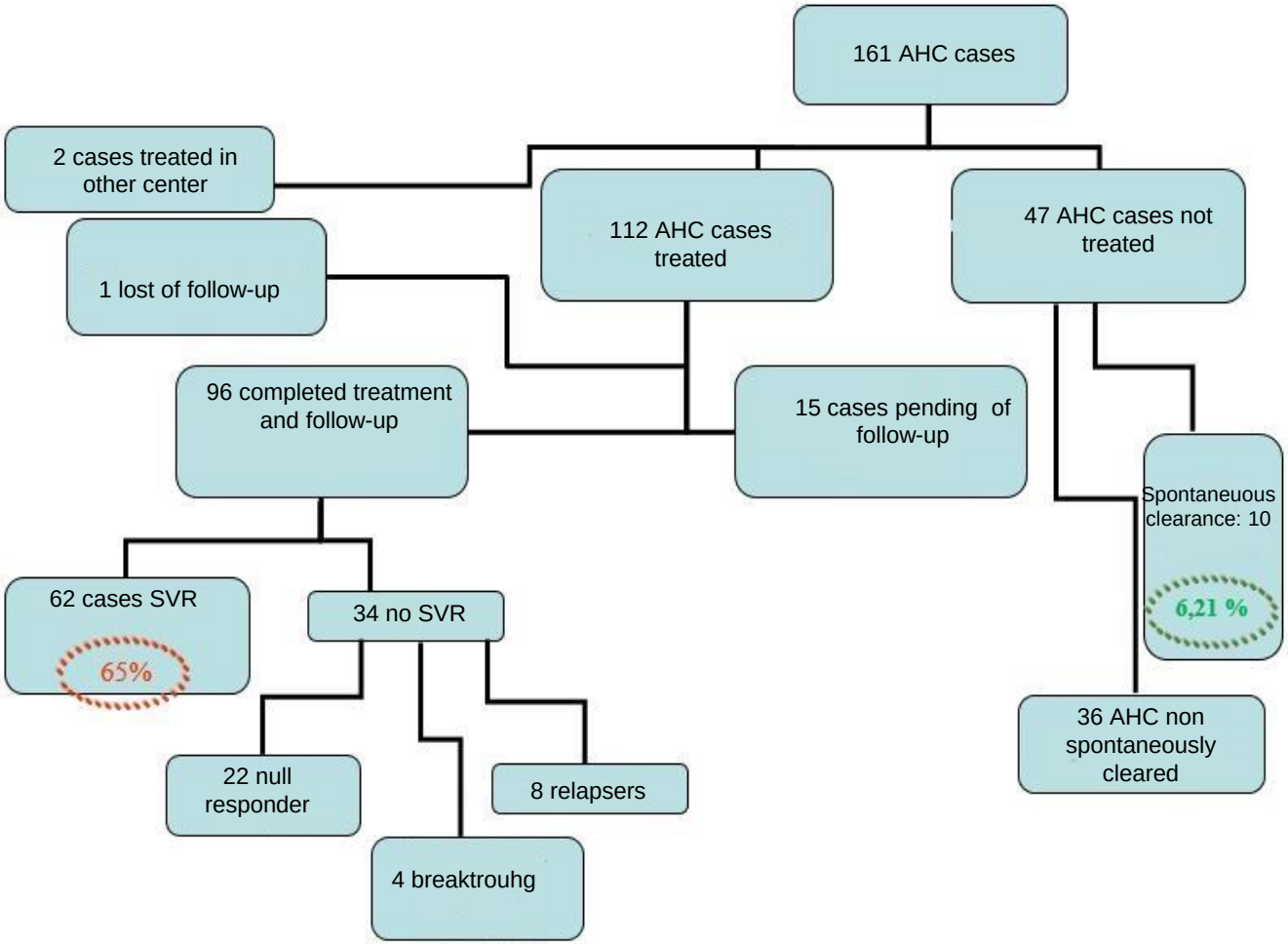
Martínez-Rebollar M, et al. PE 13/17. EACS'15

Características Víricas

- Genotipo VHC:
  - Gen 4: 52%
  - Gen 1: 43%
    - 1a: 29%
    - 1b: 14%
  - Gen 2: 1 pac
  - Gen 3: 3 pac
  - Gen 1 y 4: 1 paci
  - No tipables: 2 pac

Martínez-Rebollar M, et al. PE 13/17. EACS'15

Evolución y tratamiento



Martínez-Rebollar M, et al. PE 13/17. EACS'15

Respuesta al tto

- RVS: 65%
- Factores asociados a la RVS:
  - Variables basales: RNA-VHC pre-tto bajo y ALT alta ($p< 0.0234$ i $p< 0.0464$)
  - Variables de respuesta al tto: RVR, RVP ($p < 0.05$).
    - Analisis de regresión múltiple: RVR y RNA-VHC pre-tto

Martínez-Rebollar M, et al. PE 13/17. EACS'15

Filogenia y HAC

GASTROENTEROLOGY 2009;136:1609–1617

Evidence of a Large, International Network of HCV Transmission in HIV-Positive Men Who Have Sex With Men

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CLINICAL ADVANCES

Liver INTERNATIONAL
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Liver International ISSN 1478-3223

CLINICAL STUDIES

Phylogenetic analysis of acute hepatitis C virus genotype 4 infections among human immunodeficiency virus-positive men who have sex with men in Germany

Martin Vogel[1]*, Thijs van de Laar[2]*, Bernd Kupfer[3], Hans-Jürgen Stellbrink[4], Tim Kümmerle[5], Stefan Mauss[6], Gaby Knecht[7], Annemarie Berger[8], Sylvia Bruisten[2] and Jürgen K. Rockstroh[1]

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7 Infektiologikum Frankfurt/Main, Frankfurt, Germany
8 Institute for Medical Virology, University of Frankfurt, Frankfurt, Germany

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2009, p. 3832–3838 Vol. 47, No. 12
0095-1137/09/$12.00 doi:10.1128/JCM.01146-09

Emergence of Hepatitis C Virus Genotype 4: Phylogenetic Analysis Reveals Three Distinct Epidemiological Profiles▽

Joep de Bruijne,[1]* Janke Schinkel,[2] Maria Prins,[3,4] Sylvie M. Koekkoek,[2] Sem J. Aronson,[1] Marijn W. van Ballegooijen,[5] Hendrik W. Reesink,[1] Richard Molenkamp,[2] and Thijs J. W. van de Laar[3]

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Received 11 June 2009/Returned for modification 19 August 2009/Accepted 24 September 2009

JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2014, **21**, e19–e28 doi:10.1111/jvh.12254

Hepatitis C virus NS3/4A quasispecies diversity in acute hepatitis C infection in HIV-1 co-infected patients

M. Nevot,[1] C. Boesecke,[2] M. Parera,[1] C. Andrés,[1] S. Franco,[1] B. Revollo,[3] P. Ingiliz,[4] C. Tural,[3] B. Clotet,[1,3] J. K. Rockstroh,[2] M. A. Martinez[1] and the NEAT study group [1]*Fundació irsiCaixa, Hospital Universitari Germans Trias i Pujol, Universitat Autonoma de Barcelona, Badalona, Spain; [2]Bonn University Hospital, Bonn, Germany; [3]Fundació Lluita contra la SIDA, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; and [4]Medical Center for Infectious Diseases (MIB), Berlin, Germany*

Received April 2013; accepted for publication February 2014

- El análisis filogenético de las cepas del VHC, demostró la aparición de casos agrupados conforme a la transmisión dentro de una red social y sexual de pacientes HSH coinfectados por el VIH que se extiende a nivel nacional e internacional

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T van de Laar T· Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology. 2009

XVI Congres de la Societat Catalano-Balear de Medicina Interna

2 i 3 de juny de 2016

Phylogenetic analysis of an epidemic outbreak of acute hepatitis C in HIV-infected patients by massive sequencing.

Noelia Cano-Pérez [1], María Martínez-Rebollar [2], Josep Gregori [3,4], Josep Quer [3], Patricia González [1], Martina Gamboto [1], Hanna Visser [1], Juan I. Esteban [3], Josep Mallolas [1], Xavier Forns [3], Sofía Pérez-del-Pulgar [1], Montse Laguno [1].

Liver Unit, Hospital Clínic, IDIBAPS, CIBERehd, Barcelona, Spain [1]. Infectious Diseases Unit, Hospital Clínic, IDIBAPS [2]. Liver Unit, Vall d'Hebron Institut de Recerca-Hospital Universitari Vall d'Hebron , CIBERehd, Barcelona, [3] Roche Diagnostics SL. , Sant Cugat del Vallès, Barcelona, Spain [4]

BACKGROUND

The incidence of acute hepatitis C among HIV-infected men who have sex with men (MSM) has significantly increased in recent years [1,2]. This increase may be due to factors such as high HCV viral load in blood and semen, sex with risk of mucosal damage, a higher number of sexual partners, presence of concomitant ulcerative sexually transmitted diseases and the use of recreational drugs [3].

OBJECTIVE

To investigate the dynamics of HCV transmission in an outbreak of acute hepatitis C in HIV-positive MSM in Barcelona.

MATERIALS & METHODS

- Between 2008 and 2013, 113 cases of acute hepatitis C in HIV-infected MSM were diagnosed in the Infectious Diseases Unit, Hospital Clínic, Barcelona.
- Phylogenetic analysis of the HCV NS5B gene was performed in a total of 80 patients. Viral RNA was extracted from serum samples collected from each patient at the time of acute hepatitis C diagnosis.
- Massive sequencing was performed using the Roche 454 GS Junior platform, as previously described [4].

  NS5B region → 339-bp fragment
  Positions 8280-8618 (ref. H77)

  Mean coverage → 1236 reads per sample
- To define possible transmission networks, phylogenetic trees were constructed from genetic distance (d_A) matrices. For comparison purposes, we included 37 HCV-infected local controls in the phylogenetic analysis: genotype 4d n=15, genotype 1a n=11, and genotype 1b n=11.

RESULTS

1. Patients Characteristics

Number of patients amplified in the study	80
Age (years)	38 (25-51)
Baseline CD4 (cells/µl)	923
Undetectable HIV viral load	55 (69%)
Antiretroviral therapy	61 (76)%
HCV viral load (Log IU/mL)	6.37 (3.70-6.99)
HCV treatment (pegIFN + RBV)	61 (76%)
SVR	40 (66%)

Quantitative variables are shown as median (range)
Qualitative variables are shown as n (%)

2. Prevalence of genotypes

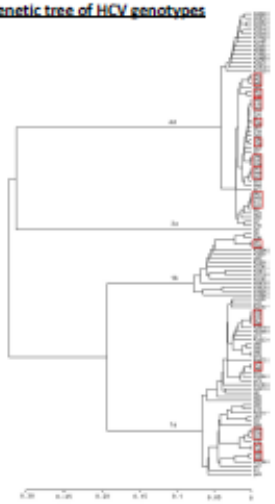
Genotype 4d	51 % (n=41)
Genotype 1a	41 % (n=33)
Genotype 1b	6 % (n=5)
Genotype 3a	1 % (n=1)

The more prevalent genotype is 4d, despite the prevalence of this genotype in our geographic area is 7% [5].

This is consistent with the observations made in other European studies in Amsterdam, London and France[6], several sources suggest that the genotype 4d was introduced through an intravenous drug user belonging to the group [7].

3. Characterization of the transmission of acute hepatitis C in the cohort of patients coinfected with HIV

Phylogenetic tree of HCV genotypes

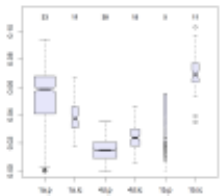


HIV-coinfected patients are identified consecutively from p1 to p84 and local controls as a K followed by a number. We have highlighted in red clusters of patients sharing the dominant haplotype, which indicates HCV transmission.

As shown in the phylogenetic tree, patients are grouped by genotype . We observed that the genetic distances of patients with genotype 4d are shorter than the genetic distances from other genotypes (phylogenetic tree and boxplot).

We have identified 14 clusters: 5 of genotype 1a , 1 of genotype 1b and 8 genotype 4d .

Genetic distance analysis



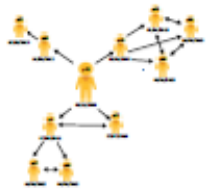
	P
d_A(1a) < d_A(1a-K)	<2e-16
d_A(1a -K) < d_A(1a-K)	0.0002
d_A(1b) < d_A(1b-K)	<2.2e-16
d_A(4d) < d_A(1a)	<2.2e-16
d_A(4d) < d_A(1b)	0.039
d_A(1b) < d_A(1a)	0.0008

d_A = genetic distance
p = patient in our cohort
k = local control

Intrapopulation genetic distances between HIV-coinfected patients and their respective local controls are significantly different. Molecular analysis shows that, in our cohort of HIV-coinfected patients, the genetic distances between genotype 4d viruses are significantly lower than those of the subtypes 1a and 1b. This result may suggest the existence of a single source of infection for genotype 4d and different sources for subtypes 1a and 1b in our study cohort.

Predicted network of infection in genotype 4d patients

By monitoring common mutations in the quasispecies and taking into account the date of acute hepatitis C diagnosis, we can suggest a transmission network for genotype 4d virus. Each dummy represents one patient with an assigned number and the date of HCV infection detection.



CONCLUSIONS

1. HCV infection spreads rapidly among HIV-positive MSM through a local transmission network in Barcelona.
2. The most prevalent HCV genotype in this cohort of HIV-coinfected MSM patients is genotype 4d .
3. We have identified 14 monophyletic groups (5, 1a; 1, 1b and 8, 4d), suggesting a possible direct transmission of HCV infection.
4. The low genetic distance among genotype 4d infected patients suggests a single source of infection for this genotype 4d cohort.

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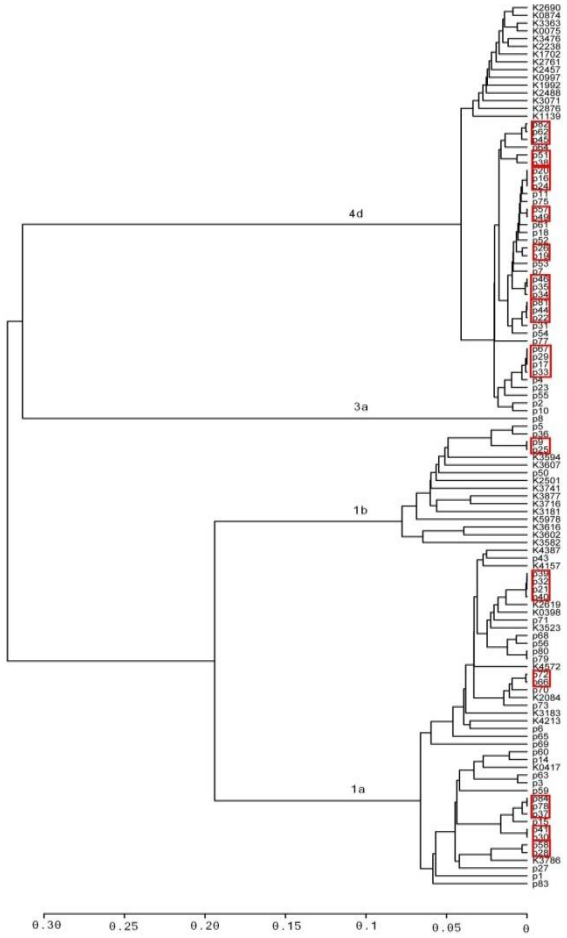
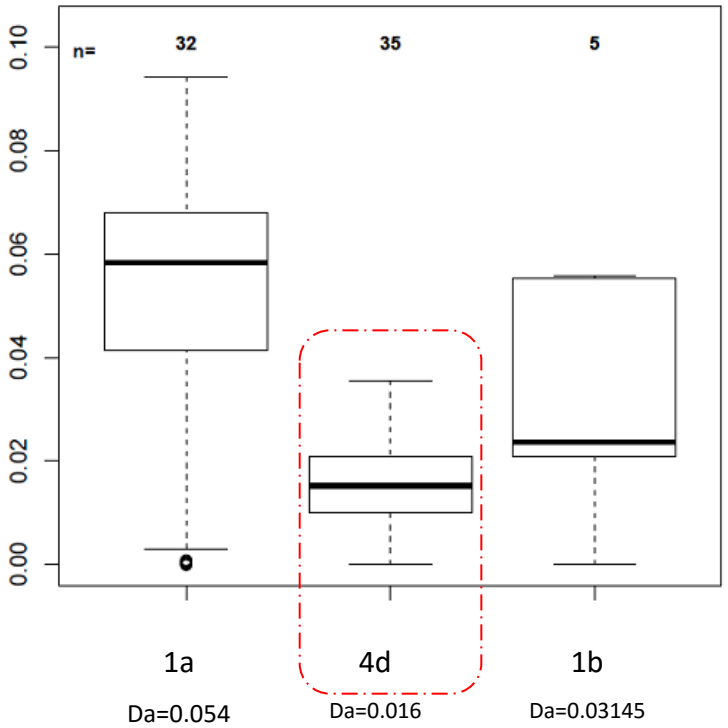
6. Thijs J. W. van de Laar et al. Gastroenterology. 2009
7. Joep de Bruijne et al. J Clin Microbiol, 2009.

Phylogenetic tree of HCV genotype



Genetic distance analysis



14 monophyletic groups (5, 1a; 1, 1b and 8, 4d) have been identified, suggesting a possible direct transmission of HCV infection

XVI Congres de la Societat Catalano-Balear de Medicina Interna
2 i 3 de juny de 2016

Efficacy of GZR/EBR in Early Chronic Hepatitis C in HIV/HCV co-infected patients.

Montserrat Laguno, Maria Martínez-Rebollar, Josep Mallolas

EudraCT number: 2016-001536-36

- HCV NS5A inhibitor, 50 mg
- HCV NS3/4A inhibitor, 100 mg

- Broad genotypic activity[1-3]
- Retains activity against many clinically relevant RAVs[1-3]
- All-oral, once-daily regimen

1. Summa V, et al. Antimicrobial Agent Chemother 2012:56;4161-67
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3. Harper S, et al. ACS Med Chem Lett. 2012 Mar 2;3(4):332-6.

PUBLISHED 09-JULY-15

THE LANCET HIV

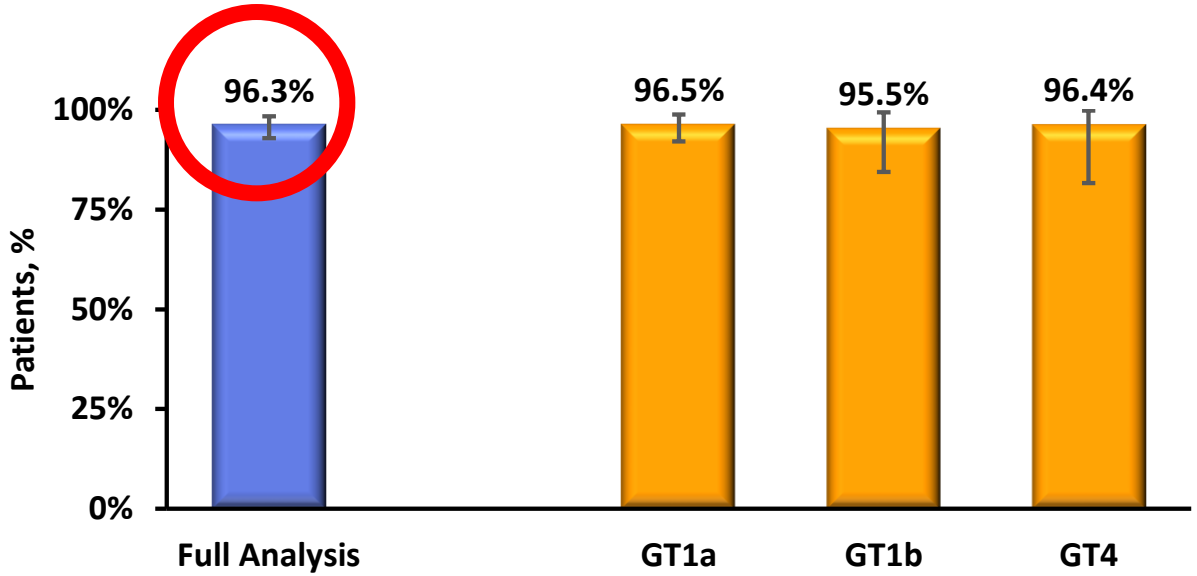
Articles

Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial

Prof Jürgen K Rockstroh, MD, Mark Nelson, MD, Prof Christine Katlama, MD, Jay Lalezari, MD, Josep Mallolas, MD, Mark Bloch, MBBS, Prof Gail V Matthews, MBChB, Prof Michael S Saag, MD, Philippe J Zamor, MD, Chloe Orkin, MBChB, Jacqueline Gress, BA, Stephanie Klopfer, PhD, Melissa Shaughnessy, MS, Janice Wahl, MD, Bach-Yen T Nguyen, MD, Eliav Barr, MD, Heather L Platt, MD, Michael N Robertson, MD, Prof Mark Sulkowski, MD

Published Online: 09 July 2015

SVR12: FULL ANALYSIS SET*



	All GT† 210/21[illegible]		GT1a 139/144	GT1b 42/44	GT4 27/28
SVR12	**96.3%**		**96.5%**	**95.5%**	**96.4%**
Relapse, n (%)	5 (2.3)		4 (2.8)	0 (0)	1 (3.6)
Other Failure Criteria, n (%)	3 (1.4)		1 (0.7)	2 (4.5)	0 (0)
Reinfection, n	2		1	1	0
LTFU or discontinued unrelated to VF, n	1‡		0	1	0

*Full analysis set includes all patients who received ≥1 dose of study medication
†2 patients with GT6 infection were also included; both patients achieved SVR12.
‡Reason for discontinuation: prohibited concomitant medication (nevirapine)

Rationale:

Treat and cure these patients with early chronic hepatitis C has a double interest for us in Spain:

1.- Cure the patient and avoid the liver disease progression and

2.- Avoid new HCV infection from patients with high risk of transmission.

We would like to propose a study in HIV/HCV co-infected individuals with F0-F1 fibrosis to receive a DAA combination therapy for a shortened duration of 8-12 weeks as this particular patient group should be very easy to treat (see study design below).

Early chronic hepatitis C is defined as chronic hepatitis C with known episode of AHC within the last 3 years including those who failed to PEG/RBV or those who never received therapy for AHC

Objectives:

- To evaluate the efficacy of 12 or 8 weeks treatment with Grazoprevir + Elbasvir in Early Chronic Hepatitis C GT1,4 in HIV co-infected patients

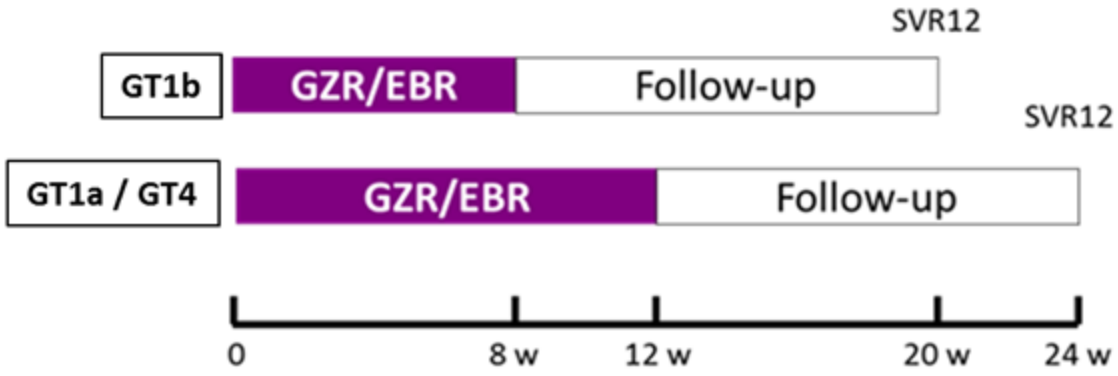
- To evaluate the safety and tolerability of Grazoprevir + Elbasvir in HIV-HCV co-infected patients

Hypotesis:

- The proportion of Early Chronic Hepatitis C GT1,4 HIV co-infected patients achieving SVR 12 weeks after the end of all study therapy will be superior to 90%

Study design/Clinical plan

- Multicenter (2 centers), single arm study according to HCV genotype.
- The trial will enroll approximately 60 non-cirrhotic, Early Chronic Hepatitis C HCV Genotype 1, 4.
- HCV-HIV co-infected patients.



Conclusions

- HAC en VIH HSH es una comorbilitat important. ETS
- Tenir presents factors de risc per fer diagnòstic
- Focus de manteniment de l'epidèmia del VHC
- Tractament efectiu per disminuir la incidència