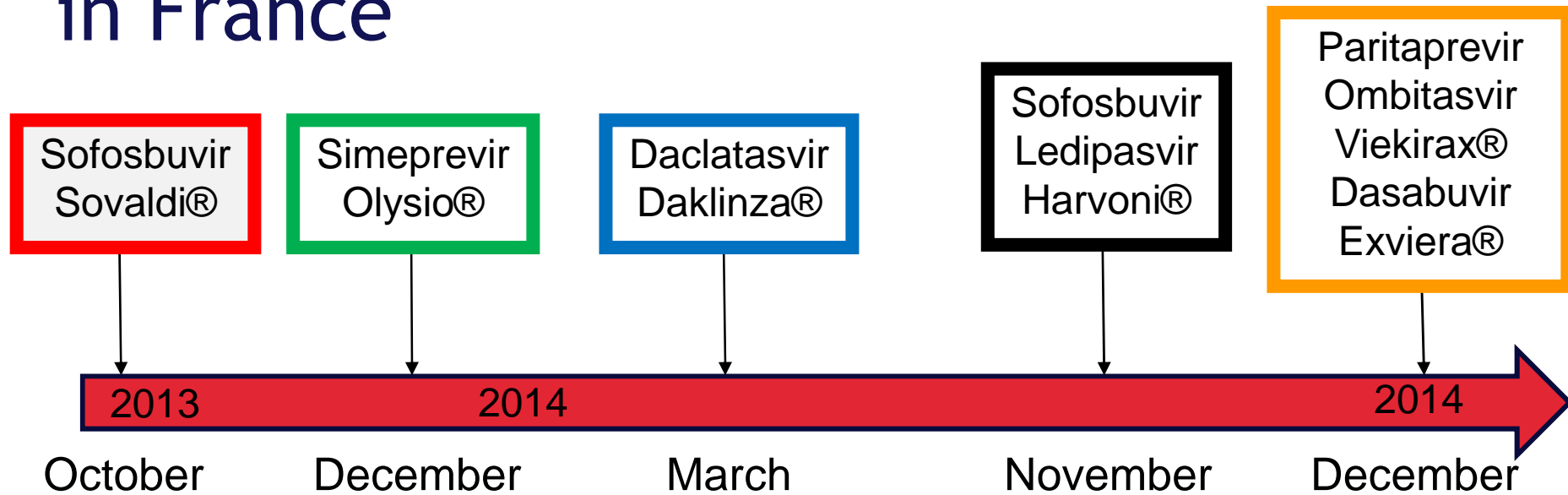


The ANRS CO22 HEPATHER Cohort: Lessons and future prospects

Fabrice CARRAT,
UMR-S 1136, Pierre-Louis Institute of Epidemiology and
Public Health, PARIS - FR

Flow of ATU (early access program) in France



**Restricted to
« priority » patients**

- ☐ F3F4
- ☐ Symptomatic cryoglobulinemic vasculitis
- ☐ Waiting for liver or renal transplantation
- ☐ After liver transplantation

Clinical benefit of universal hepatitis C treatment remains uncertain

BMJ 2015;350:g7809

Is widespread screening for hepatitis C justified?

Several organisations have recommended greatly expanded screening for hepatitis C infection. **Ronald Koretz and colleagues** are concerned that no study has tested whether this will lead to net clinical benefit or harm in screened populations

Ronald L Koretz *emeritus professor of clinical medicine*¹, Kenneth W Lin *associate professor of family medicine*², John P A Ioannidis *professor of medicine*³, Jeanne Lenzer *medical investigative journalist*⁴

Key messages

The CDC and other major organisations are recommending birth cohort population screening for hepatitis C infection

Only a minority of patients with chronic hepatitis C infection will ever develop end stage liver disease

We cannot reliably identify those who will develop end stage liver disease

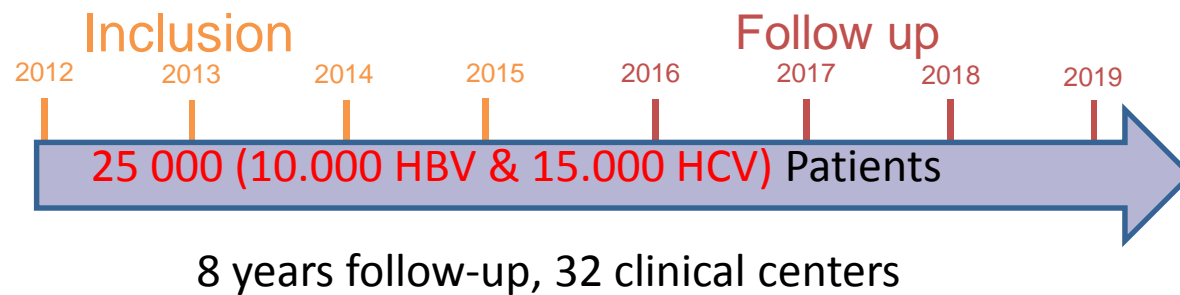
Drug trials rely on surrogate markers such as sustained virological response, which is not a cure

Physicians should resist screening until we have strong evidence that antiviral therapy is clinically effective and the benefits outweigh the harms

ANRS CO22 HEPATHER COHORT SUMMARY

OBJECTIVES

- To describe progression of chronic HCV and HBV infections on the long term and to identify associated **prognosis factors** (including biomarkers).
- To compare the **clinical and cost effectiveness and safety** of treatments in « real life »
- To provide resources for researches in **tailored HCV or HBV subpopulations**



Sept 1st, 2015

18,965 enrolled

- 11,619 HCV

- 5636 HBV

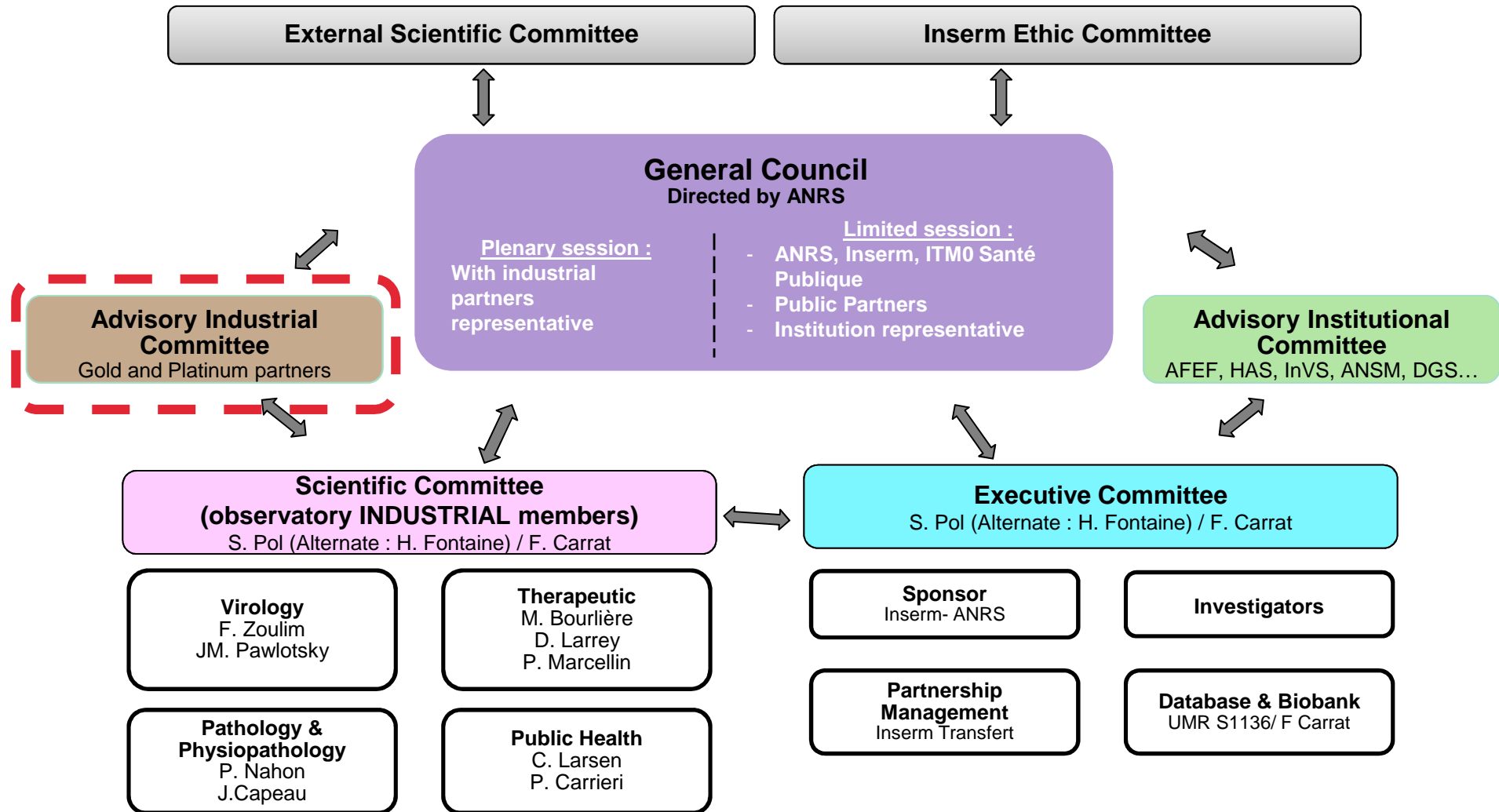
- 1710 HCV/HBV markers

GENERAL APPROACH TO DATA COLLECTION AND FOLLOW-UP

- Electronic data capture on a **dedicated information system**
- Centralized **Biobank** (blood, urine) at inclusion
- Clinical follow-up by **interval**: 1 to 2 yearly visits according to the status
- « **A la carte** » clinical follow-up : Treatment initiation, Clinical event
- Follow-up by individual matching on **medico-administrative database** (SNIIRAM , CEPI-DC)

ANRS CO22 HEPATHER COHORT ORGANIZATION

Governance



SAFETY AND EFFICACY OF THE COMBINATION DACLATASVIR-SOFOSBUVIR IN HCV GENOTYPE 1-MONO-INFECTED PATIENTS FROM THE FRENCH OBSERVATIONAL COHORT ANRS CO22 HEPATHER.

Stanislas POL, Marc BOURLIERE, Sandy LUCIER, Victor DE LEDINGHEN, Fabien ZOULIM, Céline DORIVAL-MOULY, Sophie METIVIER, Dominique LARREY, Albert TRAN, Christophe HEZODE, Jean-Pierre BRONOWICKI, Didier SAMUEL, Patrick MARCELLIN, Jean-Pierre ZARSKI, Anne MINELLO, Laurent ALRIC, Jean-Claude TRINCHET, Pierre NAHON, Dominique GUYADER, Olivier CHAZOILLERES, Ghassan RIACHI, Véronique LOUSTAUD-RATTI, Xavier CAUSSE, Philippe MATHURIN, Isabelle HUBERT-FOUCHARD, Isabelle ROSA, Yves BENHAMOU, Jérôme GOURNAY, Jean-Jacques RAABE, François RAFFI, Ventzislava PETROV-SANCHEZ, Alpha DIALLO, Hélène FONTAINE, Fabrice CARRAT on the behalf of the ANRS/AFEF HEPATHER study group

The ANRS CO22 Hepather cohort is conducted in collaboration with AFEF and supported by MSD, Janssen, Gilead, BMS, Roche, Abbvie.

Background and aims

Real-life results of the Sofosbuvir/Simeprevir combination have been extensively reported but there are few data regarding the Sofosbuvir/Daclatasvir combination (Ally-studies) in GT1 patients.

SVR12* was obtained in

- 120 / 126 (95%) patients naïve of treatment
- 40 / 41 (98%) treatment experienced (1st gen PI) patients
- 25 / 167 (15%) patients had cirrhosis

*Sulkowski et al. New Engl J Med 2014;370:211-221

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Patients

All patients with HCV Genotype 1 infection who initiated a combination of Sofosbuvir (400 mg/d) and Daclatasvir (60 mg/d) before July 1st 2014 were included (n=409) :

- with ribavirin (1-1.2 g/d) (n=92) or without (n=317)
- 319 (78%) patients had cirrhosis
- 307 (75%) were previously treated with:
 - Pegylated interferon and Ribavirin (n =134, 43.6%)
 - Pegylated interferon, Ribavirin and a 1st generation PI (n =173, 56.3%)

SVR results

	SOF+ DCV (n=317)		SOF+ DCV+ RBV (n=92)	
	12w	24w	12w	24w
SVR4 N %	46/54 85.2	250/263 95.1	12/12 100	79/80 98.7
SVR 4 in cirrhotics N %	26/34 76.5	203/216 94.0	9/9 100	59/60 98.3
SVR 4 in Non cirrhotics N %	20/20 100	47/47 100	3/3 100	18/18 100
SVR4 in treatment-naïve patients N %	27/31 87.1	47/53 88.7	4/4 100	14/14 100
SVR4 in treatment-experienced patients N %	19/23 82.6	203/210 96.7	8/8 100	65/66 98.5
SVR4 in PI/PEG/RBV-experienced patients N %	4/5 80.0	128/132 97.0	4/4 100	32/32 100
SVR4 in PEG/RBV experienced N %	15/18 83.3	75/78 96.1	4/4 100	33/34 97.1

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PROJET FINANCÉ PAR L'ANR

Predictors of virlogical failure (SVR4) with adjustment on propensity scores

Covariates	OR	95%CI	P-Value	Adj. OR	95%CI	P-Value
Age (<65 vs ≥65 yrs)	1.1	0.4-3.2	0.84			
Sex (F vs M)	1.8	0.7-4.4	0.19			
RBV incl. Regimen (N vs Y)	6.3	0.8-49.2	0.07	6.5	1.0-275.6	0.054
Treatment duration (12 vs 24 weeks)	3.5	1.2-9.8	0.017	3.6	1.1-11.5	0.03
Treatment naïve (N vs Y)	0.2	0.07-0.8	0.023			
Cirrhosis (Y vs N)	9.2	2.0-Infinity	0.008	12.7	2.7-infinity	0.002
Decompensated cirrhosis (Y vs N)	3.3	1.1-10.0	0.03			
HCV viral load (≥800,000 vs < 800,000 IU/mL)	0.6 1	0.4-1.0	0.04			
Total Bilirubin (<21 vs ≥ 21 µmol/L)	0.3	0.1-0.8	0.02			
Propensity score to receive RBV	0.4	0.003-42.3	0.69	1.2	0.7-2.0	0.58
Propensity score to be treated 24 weeks	0.4	0.002-6.2	0.50	0.9	0.4-1.3	0.32

Conclusion

1. The Sofosbuvir/Daclatasvir combination is associated with a high rate of SVR4 in difficult-to-treat patients infected by Genotype 1
2. Cirrhosis was strongly associated with treatment failure: all patients with treatment failure had cirrhosis
3. A 24 weeks regimen and addition of RBV were both associated with response to treatment in those patients

GT1

**Non cirrhotic patients : SOF+DCV 12 w.
Cirrhotic patients : SOF+DCV + RBV 12w.**

ANRS CO22 HEPATHER

Cohort Sept 1st, 2015

- 18,965 patients included, 4836 HCV-infected patients treated by DAAs

Drug combination	Number
Sofosbuvir + RBV	459
Sofosbuvir + PegIFN + RBV	269
Sofosbuvir + Daclatasvir	1420
Sofosbuvir + Daclatasvir + RBV	453
Sofosbuvir + Simeprevir	752
Sofosbuvir + Simeprevir + RBV	84
Sofosbuvir + Ledipasvir	780
Sofosbuvir + Ledipasvir + RBV	337

Future prospects -ongoing studies

- Antiviral resistance in patients with virological treatment failure after DAAs (JM Pawlotsky)
- Comparison of HCC phenotypes between sustained virological responders and chronically infected patients (JC Duclos-Vallée, P Nahon) – collaboration with the ANRS CO12 cohort (1300 patients with cirrhosis)
- Validation of a genetic signature for the prognosis of liver fibrosis in HCV infected patients (A Dessein)
- Clinical response to DAAs HCV therapy in patients with HCV-related vasculitis (P Cacoub)

The ANRS CO22 HEPATHER Cohort

Acknowledgements

ALL THE PATIENTS

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Eric Saillard, Pointe à Pitre

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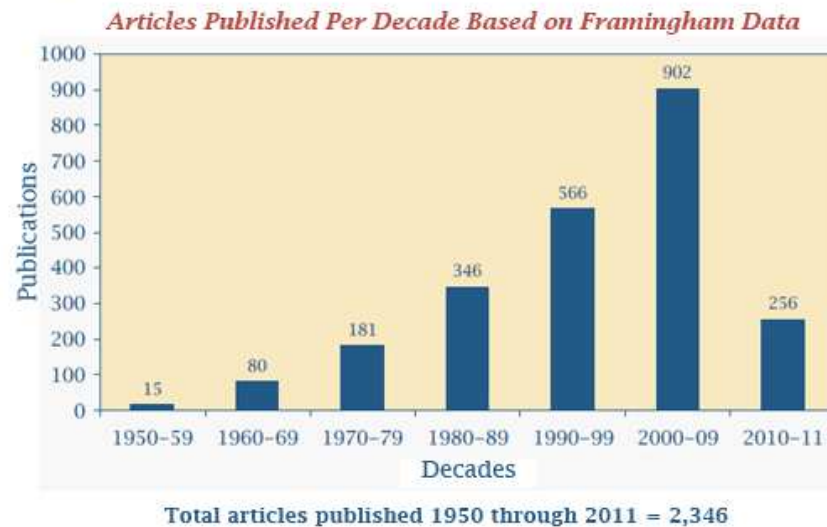
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Scientific production in a cohort

Framingham Heart Study Bibliography

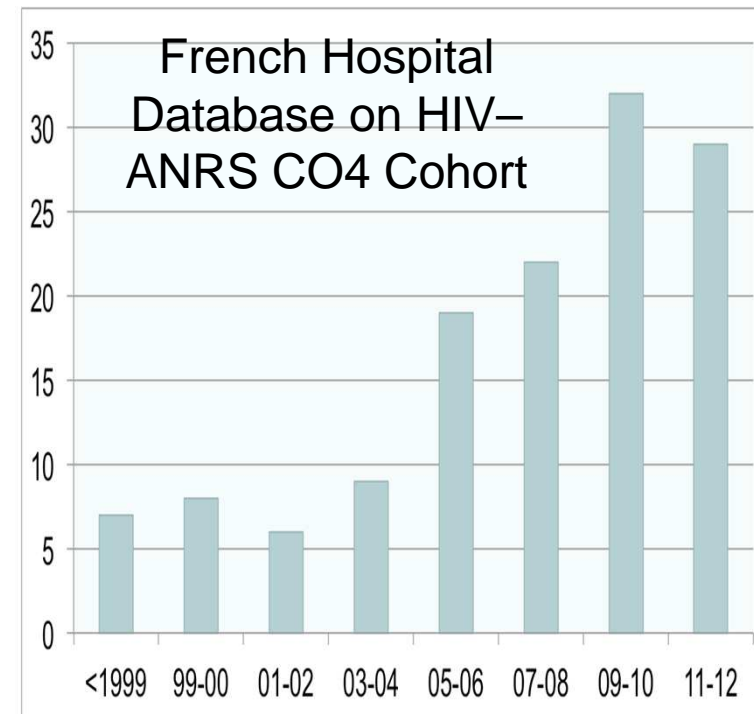
Since 1951 investigators have published research results based on Framingham Heart Study data in peer review medical journals. These articles are listed here in the Framingham Heart Study bibliography in reverse chronological order and are updated annually. Abstracts of many of the articles can be accessed through PubMed via the link at the end of each entry.



1948 : cohort set-up

2011 : 2,436 publications !

(source : <http://www.framinghamheartstudy.org/>)



1989 : Inclusion started

1992 : 1st paper

2012 : 132 publications

(source : D Costagliola – U1136)