ANRS VIRAL HEPATITIS RESEARCH

Colloque : *Vers un contrôle mondial des hépatites virales*
19 mai 2015, Institut Pasteur, Paris

*Pr Stanislas Pol*
Organisation of biomedical research in France

- Research organisations: Inserm, CNRS, Institut Pasteur, CEA, IRD, … (infrastructure, staff)

- Project Funding for biomedical research:
  - ANR (National Research Agency) 250 M euros
  - PHRC (hospital programme for clinical research) 60 M euros
  - INCa (Cancer Institute) 80 M euros
  - ANRS 48 M Euros
  - Private foundations (Genethon, ARC, FRM, Axa, Total…)

Presentation of the ANRS
Focus on ANRS

- Public Agency aimed at funding and coordinating research in all areas relevant to HIV/AIDS and viral hepatitis
- Before 1st January 2012, an autonomous agency then integrated within Inserm
- Annual budget of research: 48 Millions euros

Supported by:

- Ministry of Research (39M€)
- Ministry of Health
- Ministry of Foreign Affairs
- Public institutions
- Private pharmaceutical companies

80% of the ANRS’ budget
20% of the ANRS’ budget
% Distribution of funds according to research area 2014 (46,3 M €)

- Basic Science HIV 16%
- Vaccine HIV-HCV 1.1%
- Clinical trials and cohorts HIV 31%
- Epidemiology/socio-behavioral science 6%
- Resources limited countries (HIV-Hepatitis) 18%
- Hepatitis B and C 21%

- GLOBAL HEPATITIS 30% : 11 M €
- GLOBAL HIV : 70% : 17 M €
ANRS «Scientific performance »

- 550 publications/year
- Approximately 50% of publications have IF > 5.
- 1% of ANRS publications are in the 10 top international journals
- 6.2% of ANRS publications (HIV/AIDS and hepatitis) are in the 1% group of excellence (number of citations), higher than the national average in the field of biology/health
- France is ranked 2nd or 3rd international position in the field of HIV and 2nd in the field of hepatitis
ANRS Funding Mechanisms

- > 93% of ANRS’ budget dedicated to research
- 2 main calls for proposals/year
- Top-down vaccine research program
- Clinical Trials: committees for approval and funding
- ANRS: essentially only funder for HIV and viral hepatitis research in France
Organisation of ANRS

9 offices:

> Clinical and therapeutic research on HIV/AIDS
> Basic research on HIV/AIDS
> Basic, clinical and therapeutic research on viral hepatitis
> Research in public health and the human and social sciences
> Clinical research safety
> Research in resource-limited settings
> Scientific information and communication
> International affairs and scientific relations
> Quality assurance
> Financial and general affairs
LEADING: the ANRS Coordinated Action (AC) in the field of viral hepatitis

**Basic Research**

- AC 29: Entry and assembly mechanisms of hepatitis viruses in their target cells *(J Dubuisson)*

- AC 33: Resistance to antiretrovirals of Hepatitis B and C viruses *(JM Pawlotsky and F Zoulim)*

**Clinical Research**

- AC 7: Cohorts

- AC 24: Clinical trials in viral hepatitis infection *(M Bourliere)*

- AC 5/24: Clinical trials in HIV-Hepatitis co-infection *(M Bourliere and JM Molina)*
The AC common to hepatitis and to HIV field

AC 12: Resource-limited countries (F Dabis)

AC 23: Dynamics of the HIV, HCV and HBV epidemics (D Costagliola)

AC 25: Research in public health, human and social sciences in the field of viral hepatitis (Pr JC Desenclos)
FUNDING: Two calls each year, with peer review

Specific scientific committees (CSS) in the hepatitis field

**CSS with Hepatitis area of expertise**

**CSS 4:** Basic Research (JM Pawlotsky)

**CSS 7:** Clinical Research (F Zoulim)

**CSS assessing both hepatitis and HIV researchs**

**CSS5:** Research in public health and in human and social sciences (pending appointment)

**CSS6:** Research in low and middle-income countries (A Calmy)
ANRS CLINICAL RESEARCH IN VIRAL HEPATITIS
ANRS Staff support in hepatitis clinical sites

ANRS hepatitis network # 150 centers
More than 65 000 patients
28 Clinical Centers with ANRS funded staff
ANRS Involvement In Resource-Limited Countries

- 20% of the total budget (12M€, salaries not included)
- About 30 new projects per year (2 calls for proposals / year)
  Fellowships, Contrat initiation, projects

- Research Fields
  Clinical Research  Social sciences  Prevention
  Epidemiology     Basic Science

- Networking
  Supporting and organizing working groups meeting
  Organization of seminars

- Evaluation-call for proposals
  Scientific Specific Committee (CSS6)
  Multidisciplinary, community representatives
Partnerships: 8 research sites

- **Brazil**
  Hep/HIV – Viro-Immuno/Economic

- **Burkina Faso**
  Hep/HIV – Viro/PMTCT/ART adults

- **Cambodia**
  Hep/HIV±TB – Adults&ped treat.

- **Cameroun**
  Hep/HIV – Viro/Adults&ped treat.

- **Côte d’Ivoire**
  HIV – Viro/Adults&ped treat

- **Egypte**
  Hep C – Viro/Adults treat.

- **Sénégal**
  HIV – Viro/Adults ped treat/IDU

- **Vietnam**
  Hep C/HIV – Viro/Adults treat/IDU
24 countries
17 Sub-saharian Africa
5 Asia
2 South America

100 ongoing projects
80% in 8 countries
ANRS Research Sites
ANRS’ global research priorities

- New tools for prevention / key populations
- HBV Cure
- Strategic evaluation of new molecules anti HCV
- Study reservoirs with the objective of eradication or functional cure
- Test and treat / treatment as prevention
- Develop new vaccine strategies
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
Flow of ATU (early access program) in France

- Sofosbuvir Sovaldi® (October 2013)
- Simeprevir Olysio® (December 2013)
- Daclatasvir Daklinza® (March 2014)
- Sofosbuvir Ledipasvir Harvoni® (November 2014)
- Paritaprevir Ombitasvir Viekirax® Dasabuvir Exviera® (December 2014)

Restricted to « priority » patients
- F3F4
- Symptomatic cryoglobulinemic vasculitis
- Waiting for liver or renal transplantation
- After liver transplantation

Cohort ANRS CO22 HEPATHER
# SVR results in Genotype 1-infected patients

<table>
<thead>
<tr>
<th></th>
<th>SOF/DCV</th>
<th>SOF/DCV/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 w.</td>
<td>24 w.</td>
</tr>
<tr>
<td>% SVR4</td>
<td>85.2</td>
<td>95.1</td>
</tr>
<tr>
<td>% SVR12</td>
<td>84.9</td>
<td>93.4</td>
</tr>
<tr>
<td>% SVR4 cirrhotic</td>
<td>76.5</td>
<td>94.0</td>
</tr>
<tr>
<td>% SVR4 non cirrhotic</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>% SVR4 naïve</td>
<td>87.1</td>
<td>88.7</td>
</tr>
<tr>
<td>% SVR4 experienced</td>
<td>82.6</td>
<td>96.7</td>
</tr>
</tbody>
</table>

(n= 317) (n = 92)

Cohort ANRS CO22 HEPATHER

Pol S et al. ILC 2015
SOF+DCV or SIM+/-RBV in Genotype 4

<table>
<thead>
<tr>
<th></th>
<th>SOF/DCV (n = 33)</th>
<th>SOF/DCV/RBV (n = 15)</th>
<th>SOF/SIM (n = 27)</th>
<th>SOF/SIM /RBV (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx duration (weeks)</td>
<td>12 w. 24 w.</td>
<td>12 w. 24 w.</td>
<td>12 w. 24 w.</td>
<td>12 w. 24 w.</td>
</tr>
<tr>
<td>% SVR4</td>
<td>88.9 95.2</td>
<td>100.0 100.0</td>
<td>78.3 100.0</td>
<td>100.0 100.0</td>
</tr>
<tr>
<td>% SVR12</td>
<td>100.0 90.9</td>
<td>100.0 100.0</td>
<td>88.9 100.0</td>
<td>100.0 100.0</td>
</tr>
<tr>
<td>% SVR4 cirrhotic</td>
<td>85.7 93.3</td>
<td>100.0 100.0</td>
<td>69.2 100.0</td>
<td>100.0 100.0</td>
</tr>
<tr>
<td>%SVR4 non-cirrhotic</td>
<td>100.0 100.0</td>
<td>- 100.0</td>
<td>100.0 -</td>
<td>- -</td>
</tr>
<tr>
<td>%SVR4 naïve</td>
<td>100.0 100.0</td>
<td>- 100.0</td>
<td>66.7 100.0</td>
<td>100.0 -</td>
</tr>
<tr>
<td>%SVR4 experienced</td>
<td>87.5 94.4</td>
<td>100.0 100.0</td>
<td>84.6 100.0</td>
<td>100.0 100.0</td>
</tr>
</tbody>
</table>

Conclusion: The 12 week combination of sofosbuvir-daclatasvir or sofosbuvir-simeprevir is associated with a high rate of SVR4 in genotype 4-infected patients. The addition of ribavirin increases the SVR rate in cirrhotic or experienced patients at 12 weeks without additive effect of the treatment extension to 24 weeks.

Fontaine H et al. ILC 2015, #LP20
Among >1500 patients included in the ANRS HEPAVIH cohort until March 2015, 142 cirrhotic HIV-HCV coinfected patients were analyzed

- 29% treatment naive
- 58% PR failures
- 9% First generation protease inhibitor/PR failures
- 4% failures with other treatment

### Patients included:

<table>
<thead>
<tr>
<th></th>
<th>N=142</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years), med [IQR]</td>
<td>51 [51-56]</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>112 (79)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>53 (37)</td>
</tr>
<tr>
<td>1b</td>
<td>18 (13)</td>
</tr>
<tr>
<td>1 others</td>
<td>11 (8)</td>
</tr>
<tr>
<td>2</td>
<td>4 (3)</td>
</tr>
<tr>
<td>3</td>
<td>29 (20)</td>
</tr>
<tr>
<td>4</td>
<td>27 (19)</td>
</tr>
<tr>
<td>CDC stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>43 (31)</td>
</tr>
<tr>
<td>B</td>
<td>50 (37)</td>
</tr>
<tr>
<td>C</td>
<td>44 (32)</td>
</tr>
<tr>
<td>Child Pugh, n (%)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>101 (89)</td>
</tr>
<tr>
<td>B</td>
<td>9 (8)</td>
</tr>
<tr>
<td>C</td>
<td>3 (3)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/mL, n (%)</td>
<td>122 (87)</td>
</tr>
<tr>
<td>Median CD4 (/mm3), med [IQR]</td>
<td>529 (336-691)</td>
</tr>
</tbody>
</table>

Adapted from: Sogni P. ILC 2015, #LP20
Treatments were prematurely stopped in 3 patients: 1 for intolerance and 2 for other causes.

Treatments were dose-adjusted in 13 patients (adjustment of daclatasvir dose in 8 and ribavirin dose in 5)