Towards HCV control and prevention in Egypt

Advocacy for evidence-based policies

Arnaud Fontanet
Institut Pasteur
Proportion with HCV antibodies among 10-50 years old, national survey, 1996

Mediterranean sea

- Alexandria: 6%
- Middle Egypt: 28%
- Lower Egypt: 8%
- Upper Egypt: 26%
- Red Sea: 19%

Genotype 4

(Frank C et al, Lancet, 2000)
HCV antibody prevalence (%) by age and sex
Zwyat Razin, 2002 (n = 4020) (ANRS 1211).

HCV antibody prevalence (%) by age and sex

Zwyat Razin, 2002 (n = 4020) (ANRS 1211).

(Arafa et al, J Hepatol, 2005)
HCV antibody prevalence (%) by age and sex
Zwyat Razin, 2002 (n = 4020).

HCV antibody prevalence (%)

Past ttt for schistosomiasis + injections
No risk factors!

(Arafa et al, J Hepatol, 2005)
HCV antibody prevalence (%) by age and sex
Zwyat Razin, 2002 (n = 4020) (ANRS 1211).

HCV antibody prevalence (%)

Past ttt for schistosomiasis

(Arafa et al, J Hepatol, 2005)
Egypt ANRS HCV research site

- **In Egypt:**
  - Ain Shams University: epidemiology (Mostafa Kamal Mohamed, Mohsen Gadallah & Wagida Anwar) and immunology (Mona Rafik).
  - Cairo University: clinical expertise (Gamal Esmat),
  - Minia University: virology (Mohamed Abdel Hamid),
  - University of Mansoura: pathology (Khaled Zalata).

- **In France:**
  - Institut Pasteur, Paris: epidemiology (A Fontanet); immunology (M Albert),
  - Tenon Hospital, Paris: clinical expertise (P Bonnard)
  - INSERM, IAME, UMR 1137: cost-effectiveness studies (Y Yazdanpanah).
  - INSERM U550, Paris: genetic epidemiology (L Abel),
  - Beaujon Hospital, Paris: pathology (P Bedossa),
  - Purpan hospital, Toulouse: virology (J Izopet).

SAB:
- Maged El-Sherbiny
- Imam Waked
- Maha Rabat
- C Rice
- JM Pawlotsky
- S Pol

http://www.hepnile.org/
What is the current HCV prevalence in Egypt?
HCV infection prevalence, 15-59 yrs old
DHS Egypt, 2008 (n=11,126)

Overall HCV Ab prevalence:
14.7% (95% CI = 13.9% -15.5%)

Overall HCV viremia:
9.94% (95% CI = 9.40% -10.5%)

→ Estimated 6 million HCV chronic infections in Egypt

Guerra et al., J Viral Hepatitis, 2012
Estimation of HCV incidence at national level

HCV incidence estimated at 2‰ / year at national level, corresponding to 150,000 new infections per year.

(Breban et al., J Viral Hepat, 2012)
Predicted mortality by HCC and liver cirrhosis, Egypt, 1980-2070

Deuffic-Burban et al, J Hepatol, 2006
How is HCV transmitted in Egypt today?
HCV transmission: contact with blood

- Blood transfusion
- Injections: medical, illicit drug use
- Invasive procedures: surgery, fibroscopy, …
- Tattooing, acupuncture, body-piercing, shaving,…
- Mother-to-infant
- Sexual
Results between 2002 and 2012, Abassaia and Imbaba FH, Cairo

3,226 patients

- 365 patients (11.3%) IgM HAV positive
- 213 co-infected (6.6%) (at least 2 infections HAV, HBV, HCV, toxo, CMV, or EBV)
- 1,015 patients (31.5%) IgM HBc positive
- 593 (18.4%) PCR HCV positive
- 1,014 (31.4%) PCR HCV negative
- 26 (0.8%) PCR HCV missing
- 91 (2.8%) Acute C
- 311 (9.7%) Probable
- 67 (2.1%) Maj exp
- 33 (1.0%) Undefined
- 91 (2.8%) Chronic*
- 19 (0.6%) Acute E
- 20 (0.6%) EBV
- 14 (0.4%) CMV
- 6 (0.2%) Toxo
- 955 (29.6%) Others **

* TMRI classification, based on follow up visits. Not available for new cohort yet

** Non A, B, C, ...
### Factors associated with acute hepatitis C, univariate analysis, Fever Hospitals, Greater Cairo, 2002-7

<table>
<thead>
<tr>
<th></th>
<th>HCV cases</th>
<th>HAV control</th>
<th>Family control</th>
<th>OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=94</td>
<td>N=94</td>
<td>N=94</td>
<td></td>
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<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>N (%)</td>
<td></td>
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</tr>
<tr>
<td>Hospital admission</td>
<td>15 (16.0)</td>
<td>3 (3.2)</td>
<td>5 (5.3)</td>
<td>3.8 (1.6-8.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgery</td>
<td>8 (8.5)</td>
<td>2 (2.1)</td>
<td>1 (1.1)</td>
<td>5.3 (1.4-20.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stitches</td>
<td>21 (22.3)</td>
<td>6 (6.4)</td>
<td>3 (3.2)</td>
<td>5.1 (2.2-11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intravenous injections</td>
<td>9 (9.6)</td>
<td>1 (1.1)</td>
<td>3 (3.2)</td>
<td>4.3 (1.3-14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Intramuscular injections</td>
<td>13 (13.8)</td>
<td>12 (12.8)</td>
<td>18 (19.1)</td>
<td>0.8 (0.4-1.7)</td>
<td>0.63</td>
</tr>
<tr>
<td>IV infusions</td>
<td>13 (13.8)</td>
<td>5 (5.3)</td>
<td>4 (4.3)</td>
<td>3.3 (1.3-8.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Delivery</td>
<td>4 (14.3)</td>
<td>1 (3.6)</td>
<td>1 (3.6)</td>
<td>6.6 (0.7-60.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cesarian section</td>
<td>3 (10.7)</td>
<td>0</td>
<td>0</td>
<td>---</td>
<td>0.05</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>12 (12.8)</td>
<td>11 (11.7)</td>
<td>5 (5.3)</td>
<td>1.5 (0.7-3.4)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

(Paez A et al, PLoS One 2009)
## Factors independently associated with acute hepatitis C, multivariate analysis, Greater Cairo, 2002-7

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=275</td>
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<tr>
<td>Intravenous injections</td>
<td>5.0 (1.2 – 20.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stitches</td>
<td>4.2 (1.6 – 11.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sniffing</td>
<td>4.4 ( 1.6 – 12.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Injections</td>
<td>7.9 ( 1.4 – 43.5)</td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>3.9 (1.8 - 8.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

(Paez A et al, PLoS One, 2009)
Intra-familial transmission of HCV

Family acute C patients (n = 100)

Families with anti-HCV Ab (n = 31)

Families with HCV RNA + (n =18)

Families with sequences* (n = 12)

Identical sequences* (n = 3)
Married couples
Index patients without RF

*330 nucleotides NS5b

*>99% homology

(Paez et al, Gut, 2010)
Main findings of transmission studies

• Iatrogenic procedures +++
  – Medical injections: intravenous and IV infusions.
  – Stitches and surgery.
  – Obstetrics.

• Illicit drug use in Cairo

Arafa et coll., J Hepatol, 2005
Paez et coll. Gut, 2010
Mostafa et coll., Liver Int, 2010
Intra-familial transmission of HCV

- Limited: \(\approx 10\%\) of incident cases

- Unknown transmission modes (may be related to health care)

- May be partially related to a genetic factor, particularly for children infections

- No argument for a change in current recommendations for prevention of intra-familial transmission among families with HCV+

Mohammed et al, Hepatology, 2005
Plancoulaine et al, Gut, 2008
Laouénan et al, Hum Genetics, 2009
Paez et al, Gut, 2010
How to improve patient’s management?
The treatment

- Pegylated interferon and ribavirin
- Long: six months to one year
- Painful: fatigue, flu-like syndrome, depression
- Expensive: >20000 euros
- Not always effective: cure rate between 40% and 80% depending on the genotype.
- Not so many data about genotype 4
Efficacy of pegylated interferon and ribavirin in genotype 4 chronic hepatitis C (ANRS 1211)

- Cure rate (SVR) estimated at 61.0% (95% CI = 50.7% - 70.6%) for genotype 4 infected patients.

- High alfa-fetoprotein (AFP) associated with treatment failure (SVR = 40.8% versus 80.4% for high vs low AFP, respectively)

Males S. et al., Antiviral Hepatitis, 2007
Opening of 23 national treatment centres, 2006-2012

- Total number of patients treated with PEG-IFN (2006-2012): 220,000
- Annual number of new patients treated: 45,000
- Annual budget for the Ministry of Health: 90 million $
Comparison of treatment efficacy among PEG-IFN available in Egypt (n≈1500)
Cost of pegylated interferon in Resource-limited countries

(Pegylated Interferon (Roche & Merck)
48-weeks
Price (USD))

(Source: MSF, 2012)
New drugs in the pipeline

DAA combinations (17)

Others (6)

Cyclophilin. I (2)

NS5A inhibitors (13)

NS3/4A Protease inhibitors (19)

Nucleotide NS5B Polymerase Inhibitors (1)

Nucleoside NS5B Polymerase Inhibitors (11)

Non Nuc NS5B Polymerase inhibitors (12)

Bourlière M et al. Ther Adv Infect 2013
Non invasive markers of liver fibrosis (ANRS 12184) (n=273)

(Bonnard et al, submitted)
Who should be treated in priority?

- If you have unlimited resources, treating HCV in Egypt at any stage of infection is cost-effective
  
  (Obach et al., Clin Infect Dis, 2014)

- If you can treat only 50,000 patients per year, treating the most advanced forms of disease (F3, compensated F4) is the most cost-effective
Can treatment impact HCV spread?

Zwyat Razin, 2002, n=4020

5% of the population accounts for >50% of all injections
→ First ones to be infected
→ First ones to transmit
Conclusion of the modeling exercise

• Treatment may impact HCV spread if:
  – Applied early in the course of infection
  – Efficacy >80%
  – Patients contributing most to HCV spread, the so-called « surperinjectors », are targeted preferentially (for treatment, and prevention!)
Conclusions & recommendations

• Surveillance:
  – Burden of disease in the next DHS survey
  – Maintain surveillance of acute hepatitis C (risk factors)
  – Implement surveillance of chronic hepatitis C (sentinel groups)
  – Strengthen HCC registry (e.g., Tanta – IARC)

• Prevention:
  – Reduce unsafe injections (unnecessary, and re-use)
  – Strengthen infection control and blood safety
  – Illicit drug use

• Treatment:
  – Bring oral IFN-free regimens
  – Prioritize treatment to advanced forms of disease
  – Simplify monitoring: Fib4 & HCV viral load/core Ag test
  – Do not forget decompensated cirrhosis and HCC!
Acknowledgments

Paris

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Stéphanie Thomas, Darragh Duffy, Matthew Albert

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François Rimlinger, Valérie Thiers

INSERM, IAME, UMR 1137
Dorothée Obach, Sylvie Deuffic-Burban, Yazdan Yazdanpanah

Hôpitaux: Cochin (Stanislas Pol), Tenon (Philippe Bonnard), et Beaujon (Pierre Bedossa)

Cairo

National Committee against viral hepatitis
Wahid Doss, Gamal Esmat, Manal El-Sayed, Magdy Serafy

Ministry of Health
Nasr El Ayed, Amr Khandeel, Sahar El Shourbagy

Fever Hospitals
Hisham El Dakhsh, Hassan Kamel, Salah Abdel Monem, Abdelhak Abdel Rahman

Tropical Medicine and Research Institute
Clinical team, virology team, Mohammed Abdel-Hamid

Ain Shams University
Amira Mohsen, Maha El Gaafary, Mostafa El Hoseiny, Noha Sharaf, Aya Mostafa, Mohsen Gadallah, Rasha Saleh, Wagida Anwar, Mona Rafik, Mostafa K Mohamed
MASTÈRE SPÉCIALISÉ
Pasteur – Cnam - EHESP

TRONC COMMUN
Ethique
Epidémiologie
Biostatistique
Economie santé
Politiques santé
Santé mondiale
Risque sanitaire

INTRO

SPECIALISATION
RISQUE INFECTIEUX
SURVEILLANCE
RECHERCHE CLINIQUE
VACCINOLOGIE
ENTOMOLOGIE
MICROBIOLOGIE MEDICALE

STAGE

EXPERTISE:
-Agences sanitaires
-Industrie
-Services Etat
-Org. internationales
-ONG
-…

RECHERCHE:
-Université
-Instituts
-…

Cnam ou EHESP
Oct-Déc
Institut Pasteur
Jan-Avr
Ouvert
Mai-Nov

Total : 75 ECTS
15 étudiants/an spéc. infectieux

Promotion 2010-11
mastère santé publique

Stages:
- Histoplasmosose en Guyane
- Hépatites à l’InVS
- VIH au Cameroun
- Paludisme au Bénin
- Leptospirose en Nouvelle-Calédonie
- Susceptibilité génétique dengue (IP Paris)
- Vaccin grippe (IP Paris)
- Infections respiratoires au Cambodge…

Recrutement:
- 50%: médecins, vétérinaires, pharmaciens,…
- 30%: biologie (M2, Post-doc., ENS)
- Et : Sciences-Po, ESSEC, …
Back-up slides
Results between 2002 and 2012, Abassaia and Imbaba FH, Cairo

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IgM HAV positive

1,015 patients (31.5%)
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          - Married couples
          - Index patients without RF

*330 nucleotides NS5b

*>99% homology

(Paez et al, Gut, 2010)
Current treatment indications in Egypt

• Inclusion:
  – Age: 18 to 60 years
  – BMI < 35 mg/kg
  – Liver biopsy:
    • F1 with ALT>1.5 ULN
    • F2-F3
    • No F4, even compensated
  – No co-infection with HBV or HIV
  – No treatment contra-indication

• Monitoring:
  – Quantitative PCR quantitative at W12, W24, W48 and W72:
    • Stop if PCR+ at W12 or W24
  – Side effects
Who should we treat?
- National Committee: All patients with fibrosis stage ≥F2 (or F1 if high ALT).
- MOH: Same without patients with cirrhosis.

Are other treatments cost-effective?
- Reiferon Retard®
- Protease inhibitors (at what cost?)

Treatment cost-effectiveness studies
ANRS 12135 (P.I.: Y. Yazdanpanah & W. Anwar)
## Treatment cost-effectiveness studies

ANRS 12135 (P.I.: Y. Yazdanpanah & W. Anwar)

<table>
<thead>
<tr>
<th></th>
<th>Ministry of Health guidelines</th>
<th>National Committee guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(No treatment of cirrhotic patients)</td>
<td>(Treatment of cirrhotic patients)</td>
</tr>
<tr>
<td>Simulated number of patients treated from 2008 to 2016</td>
<td>514,675</td>
<td>590,784</td>
</tr>
<tr>
<td>Number of live years gained per treatment</td>
<td>0.43</td>
<td>0.64</td>
</tr>
</tbody>
</table>

(Obach et al., EASL 2012)
National Control Strategy for Viral Hepatitis / 2013 - 2017

Success: Burden of infection
Treatment

Not so good: Prevention

Priority: Prevention
C/E treatment

Egyption National Control Strategy for Viral Hepatitis
2008-2012

2013-2017

Arab Republic of Egypt, Ministry of Health and Population
National Committee for the Control of Viral Hepatitis

April 2013
Preparation of the 2013-2017 National Strategy

• Organization of six workshops in Cairo (September-December 2012):
  – Surveillance
  – Blood safety
  – Infection control
  – Hep B immunisation
  – Information and education
  – Patients management

• Involvement of:
  – Egyptian Ministry of Health
  – WHO
  – CDC (Francisco Averhoff & Amy Kolwaite)
  – Institut Pasteur (Adeline Bernier)
  – International experts (TAG members)

→ National Strategy document
  – Needs budgeting
  – Governance workshop
Prevention versus treatment

Zwyat Razin (n=20,000)
Drop in injections and re-use

Targeting the entire population

Targeting the core group

Drop in re-use:
-10%
-20%
-30%

-10% injections
-30% injections
Providing treatment

Targeting the entire population

Targeting the core group

Treating late  Treating early

Ttt efficacy:
-60%
-80%
-95%
Impact of targeting the core group

Treat late

Treat early

Reaching 5%

Reaching 2%
Impact of targeting the core group

Treat late

Treat early

Reaching 5%

Reaching 2%