Management of Hepatitis co-infections in large outpatient cohorts: from screening to liver transplantation
Outline

• Screening for hepatitis coinfection in PLHIV: is it the rule?
• How many PLHIV are coinfected with hepatitis viruses? Which are the characteristics of hepatitis coinfections? What about epidemiological trends?
• How many of coinfected pts are cirrhotics?
• Anti HCV treatment: how many patients are treated and which are the results in the real life?
• Liver transplantation: the Italian experience
Data Source

- **Department of Infectious Diseases** – AO Spedali Civili – University of Brescia. Brescia; Italy. Referral Population: Province of Brescia, about 1.200.000 inhabitants
  - 5151 PLHIV from 1985:
    - Lost at FU 999
    - Death 760
    - On active follow up 3392

- **MASTER Project observational database**:
  - Observational data base based on electronic clinical charts from 7 Italian department of Infectious Diseases (Brescia, Bergamo, Cremona, Ferrara, Firenze, Roma, Bari) including 14.452 pts → 9098 on active follow up

- **OPERA study, observational database**
  - Observational cohort of 1523 HIV/HC coinfected patients enrolled in 95 Italian centres → anti HCV treatment from 2005 to 2009.
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Rate of screening for hepatitis co-infections in the real life:
Data from the MASTER database and OPERA cohort

<table>
<thead>
<tr>
<th>Screening</th>
<th>Study population</th>
<th>% of pts tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti HCV</td>
<td>All HIV+MASTER DB : 9098</td>
<td>94,9%</td>
</tr>
<tr>
<td>HBsAg</td>
<td>All HIV+MASTER DB: 9098</td>
<td>94,2%</td>
</tr>
<tr>
<td>HCV RNA in anti HCV+</td>
<td>All anti HCV+ MASTER DB 3453</td>
<td>92%</td>
</tr>
<tr>
<td>HCV Genotype in HCV RNA+</td>
<td>All HCV RNA+ MASTER DB: 2257</td>
<td>100%</td>
</tr>
<tr>
<td>HBeAg in HBsAg+</td>
<td>All HBsAg+ MASTER DB : 563</td>
<td>74,8%</td>
</tr>
<tr>
<td>HBVDNA in HBsAg+ (once in the last year)</td>
<td>All HBsAgMASTER DB+: 563</td>
<td>61,4%</td>
</tr>
<tr>
<td>Anti HD in HBsAg+</td>
<td>All HBsAg+ MASTER DB: 563</td>
<td>61,3%</td>
</tr>
<tr>
<td>Anti HAV (Opera database)</td>
<td>All anti HCV treated pts: 1523</td>
<td>42,4%</td>
</tr>
</tbody>
</table>
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In summary:

• Accurate screening for HBsAg and anti HCV and definition of HCV infection.
• Unsatisfactory definition of HBV infection status and anti HD screening.
• Insufficient screening (and vaccination?) for HAV in hepatitis coinfected patients (higher risk for severe acute HAV).
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Prevalence of hepatitis markers in the MASTER observational database (9098 pts)

- HBsAg- and HCVAb-: 53.4%
- HCVAb+: 40%
- HBsAg+: 6.6%
Prevalence of HBV and HCV co-infection in 3536 HIV+ persons from MASTER database stratified according to the date of 1st HIVAb+.

HCV Ab reactivity: multivariate logistic regression analysis:
- IDU: OR 21.07 (95% CI 17.2-26)
- Period of 1st HIVAb+ for each 5 years: OR 0.51 (95% 0.46-0.57)
Incidence of HBV and HCV seroconversion from MASTER database

- **Study population** patients with at least 2 HCVAb and/or HBsAg test (last test >2003)
- **Seroconversions (1st test negative → 2nd test positive)** after 1st HIVAb+ tests

  - **Anti-HCV:** 216 out of 2571 HCV infections: 8%
    - All: 86 x 100.000 pyfu.
    - Heterosexual: 48 x 100.000 pyfu
    - MSM: 41 x 100.000 pyfu
    - IDU: 489 x 100.000 pyfu (p<0.01 vs Hetero and MSM)

  - **HBsAg:** 173 out of 480 HBV infections: 36%
    - 18% of all HBV infection acquired in HIV/HCV co-infected
    - Incidence of HBsAg seroconversion: 400 x 100.000 pyfu.
      - Italian general population: 3 x 100.000 PYFU (SEIEVA 2004 [www.iss.it](http://www.iss.it))
      - US HIV+: 1200 x 100.000 PYFU → 3 x Italy (Kellerman CID, 2003)
Presented at the 7th International Workshop on HIV & Hepatitis Co-infection, Milan, Italy, 1 - 3 June 2011

Prevalence of HCV Genotypes in 2257 HIV/HCV+ persons from MASTER database stratified according to the date of 1st HIVAb+.

HCVRNA + 2257 out of 3177 tested: 71%

Distribution of HCV G1 subtypes:
- HCV Genotype 1a 59%
- HCV Genotype 1b 27%
- HCV G1 not subtyped or mixed: 13%
Characteristics of HBV coinfection in 563 HIV /HBV coinfected patients (88% on ART) from MASTER database

Anti HD reactivity in 12% of HBsAg negative/anti HBs + patients tested for anti HD: rate of resolved HD coinfection (with clearance of HBsAg): 53%
Management of Hepatitis co-infections in large outpatient cohorts: from screening to liver transplantation

In summary:

- 40% HCV coinfected
  - Decreasing number of coinfected patients in those with more recent diagnosis of HIV infection
  - Incidence of new HCV infection after HIV diagnosis is very high in IDU. No high incidence in MSM
  - Most HCV are infected by difficult to treat genotypes: HCVG1 is the most prevalent but 60% are subtype a (implication for the usage of DAA anti HCV)
  - No epidemiological trends in HCV genotypes
Management of Hepatitis co-infections in large outpatient cohorts: from screening to liver transplantation

- 6.6% HBsAg + coinfected
  - Stable trend over time
  - High incidence of acute HBV infection in HIV: 13 x HIV uninfected population → failure of vaccination strategies
  - A minority is HBeAg positive
  - Half of HBsAg+ are coinfected by HCV and/or HD
  - There are data suggesting that HD coinfection has a benign outcome (anti HBs seroconversion) in most of the cases
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Prevalence of FIB- 4 > 3.25 in MASTER Observational Database

- 6249 HIV infected persons with complete hepatitis markers

% of pts. with FIB-4 > 3.25
RESULTS –
FIB-4 VALUES DISTRIBUTION IN HIV HCV coinfection patients

3061 HIV/HCV coinfectected patients

Advanced liver disease in 23% (95% CI 21.5-24.5)
Male gender
HIV infection diagnosed after 2001
HCV G 3
Current usage of EFV
Previous usage of drugs
Currently No ART
Current CD4 < 200
Nadir CD4 > 350
AIDS diagnosis
Distribution of Fibrosis stages in 744 HIV+ patients treated for HCV in the OPERA Cohort

Staging according to METAVIR

- 20% F0
- 40% F1
- 17% F2
- 19% F3
- 4% F4

Fibrosis staging by liver biopsy in 547 and by fibroscan in 197
0-7 Kpa: F1; 7,1-11 F2; 11,1-16,5: F3; > 16,5 F4

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Management of Hepatitis co-infections in large outpatient cohorts: from screening to liver transplantation

In summary:

- >20% of HCV coinfected patients have cirrhosis
- The prevalence of cirrhosis is lower in HBsAg+ and higher in HBV+ HCV coinfected subjects
- Immune deficiency, ART exposure, HCV Genotype 3 are related to a diagnosis of cirrhosis
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Survey database OPERA

- Questionnaire sent to 31 Italian HIV outpatients clinic
- Population of HCV coinfected
  - 7017 pts (33% of all HIV+)

Presented at the 7th International Workshop on HIV & Hepatitis Co-infection, Milan, Italy, 1 - 3 June 2011
Database OPERA Survey

Why 84% HCV coinfected patients were not treated?
1818 (31%) pts refused treatment, 4057 (69%) had contraindications

Prevalence of contraindications in 4057 Italian HIV HCV+

- Decompensated cirrhosis: 10%
- Current Opp. Infections or Tumours: 7%
- Haematological contr.: 36%
- Psychiatric contraindications: 8%
- Active IDU: 11%
- Alcohol abuse: 13%
- Comorbidities: 15%
Hepatitis outpatient clinic since from 2003
3 doctors 1 psychologist
HCV RNA+ pts 981
– Treated: 451 (46%)
Percentage of SVR in 1523 HIV/HCV coinfected pts included in the database OPERA and treated with PEGIFN + RBV.
Management of Hepatitis co-infections in large outpatient cohorts: from screening to liver transplantation

In summary:

• Efficacy of PEG IFN + RBV as anti HCV treatment seems to be low in the real life and definitely less than 50%

• However the major limitation is the reduced access to treatment of HIV/HCV coinfected patients. Even if new and more effective treatment will be available patients’ eligibility remains the greatest issue for controlling HCV coinfection in HIV infected persons.

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Liver transplantation in HIV-infected recipients in HAART era in Italy:

“Eligible” subjects:
- No history of an AIDS defining illness in the previous two years
- CD4 >200 or >100 if intolerant to ARVs
- HIV RNA undetectable, or
- intolerant to ARVs but post-transplant HIV suppression is expected

“Ineligible” subjects:
- Did not meet 1 or more criteria above

From 1/1/2002 to 31/3/2011:
116 liver transplantation:
- 4 combined Liver + Kidney
- 4 re-transplantation
Highest number in 2007: 22
Liver transplantation in Italy
Data in 2008 on the first 60 liver transplantations

Most (53) were men, with a mean age of 43 years (range 34-58)

Results
The median waiting time for a liver transplant was 74 days (range 2-850 days).
Liver transplantation was secondary to:
- hepatitis C virus (HCV): 39 patients;
- hepatitis B virus (HBV): 5 patients
  both HCV and HBV: 5 patients;
- HBV and hepatitis delta virus (HDV): 2 patients;
- HBV, HBV, and HDV: 5 patients;
- cryptogenic (cause unknown) (HCC): 1 patient
- Rendu-Osler syndrome: 1 patient;
- data unavailable: 2 patients.
- 23 patients (39.7%) had concurrent HCC.
- The median CD4 cell count at the time of transplantation was 354 cells/mm3 (range 119-977 cells/mm3).
- HIV RNA was undetectable in 86.4% of the transplant recipients.

Grossi, EASL 2008
Liver transplantation in Italy
Data in 2008 on the first 60 liver transplantations

• Overall survival was 58.3% (41 out of 60 patients) after a median follow-up of 350 days after transplantation (range 4-1720 days).

• All HCV-infected recipients experienced recurrent HCV infection of the donor liver after transplantation

Grossi EASL 2008
Management of Hepatitis co-infections in large outpatient cohorts: from screening to liver transplantation

• Liver transplantation in HIV remains an “elite” procedure limited to a very small number of patients.
• HCV reinfection is the main clinical issue
• A network for the management of advanced liver diseases should probably join transplant centers in order to optimize patients’ selection and timing for liver transplantation