Viral hepatitis, HIV and TB in injecting drug users: how to manage co-infections?

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Accelerating the implementation of collaborative TB/HIV activities in the WHO European Region
16-17 July 2010, Vienna, Austria
GEORGIA
სიძველეთის დროის
Estimated number of people living with HIV, TB, HCV, HBV: World

- HIV: 33.4 million
- TB: 11.1 million
- MDR TB: 440 thousand
- HBV: 350 million
- HCV: 180 million
- HIV/TB*: 1.4 million
- HIV/HBV: 2-4 million
- HIV/HCV: 4-5 million

* Number of incident TB cases that are HIV-positive

WHO 2009; 2010. UNAIDS 2009
Estimated number of people living with HIV, TB, HCV, HBV: Europe

- **HIV**: 2.3 million
- **TB**: 0.4 million
- **MDR TB**: 81 thousand
- **HBV**: 18 million
- **HCV**: 5-10 million
- **HIV/TB***: 25 thousand
- **HIV/HBV**: 0.15-0.25 million
- **HIV/HCV**: 0.5-1 million

* Number of incident TB cases that are HIV-positive

Estimated number of people living with HIV, TB, HCV, HBV: Georgia

- HIV: 3,500
- TB: 3,640
- MDR TB: 360
- HBV: 45,000
- HCV: 200,000
- HIV/TB*: 120
- HIV/HBV: 320
- HIV/HCV: 1700

* Number of incident TB cases that are HIV-positive

WHO 2009; 2010. National AIDS Center
MDR TB in Georgia

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR among new TB cases</td>
<td>6.8%</td>
</tr>
<tr>
<td>MDR among previously treated TB</td>
<td>27.4%</td>
</tr>
<tr>
<td>MDR among TB/HIV co-infected patients</td>
<td>23.8%</td>
</tr>
</tbody>
</table>
TB/Hepatitis co-infection among HIV patients in Georgia

- HIV/TB: 8.2%
- HIV/HCV: 24.2%
- HIV/HBV: 10.2%
- HIV/TB/HCV: 20.1%
- HIV/TB/HBV: 2.2%
- HIV/TB/HCV/HBV: 1.2%

Non IDU □ IDU

0% 10% 20% 30% 40% 50% 60% 70% 80%
HIV/HCV/HBV/TB/IDU Collaborating Network in Georgia

Infectious Diseases, AIDS and Clinical Immunology Research Center

Georgian Research Institute on Drug Addiction

National Center for TB and Lung Diseases
Prevalence of HIV Among People Who Inject Drugs

Estimated number of IDUs: 15.9 million

Estimated number of HIV positive IDUs: 3 million

The overlap between TB, HIV and injecting drug use

GUIDELINES

1. WHO EURO Clinical protocols 2007
   ✓ Management of hepatitis B and HIV co infection
   ✓ Management of hepatitis C and HIV co infection
   ✓ Management of TB/HIV co infection
   ✓ Care of HIV positive IDUs

2. DHHS 2009
   ✓ Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

3. EACS 2009
   ✓ Clinical management and treatment of chronic hepatitis B and C co-infection in HIV-infected adults
   ✓ Clinical management and treatment of HIV infected adults in Europe

4. WHO 2010 revision
   ✓ Antiretroviral therapy for HIV infection in adults and adolescents
Recommendations for HIV infected IDUs

- HCV, HBV and TB co infection very common in HIV infected IDU-s
- All HIV positive IDUs should be screened for HCV, HBV and TB
- HIV positive IDUs should be vaccinated against HAV and HBV if not immune
- Opioid substitution therapy (OST) is critical in HIV positive IDUs
- Decreased adherence and low access to the health care system should be managed
- Nevirapine, efavirevz, ritonavir and rifampicin decrease methadone concentration and produce withdrawal symptoms
- Active hepatitis may be exacerbated more by Nevirapine
- In alcohol users the potential for pancreatitis is increased with ddI and peripheral neuropathy is increased with d4T
- Intolerance of NNRTI due to liver diseases (HBV, HCV) or psychiatric disorders may require the use of a PI in a first line
WHO 2008: The Three 'I's

The Three I’s to reduce the burden of TB disease among people living with HIV

- **I**ntensified case finding (ICS)
- **I**soniazid preventive therapy (IPT)
- **I**nfection control for people living with HIV (IC)
Management of HIV/TB co-infected patients
Algorithm for assessing TB risk and disease in an HIV-positive person

Recent TB exposure or TB symptoms

Yes

Exclusion or confirmation of active TB
(clinical examination, sputum-smear microscopy, sputum culture, X-ray, trial with a broad-spectrum antibiotic)

Active TB

Drug susceptibility test

TB treatment

Active TB excluded

No

TST, T-SPOT.TB, or QTF-Gold

Positive

TB preventive treatment

Negative

WHO EURO 2007
Recommendations for HIV infected IDUs with Active TB

- Interaction of TB drugs and ARV increased hepatotoxicity in IDUs on OST
- Pyrazinamide, rifampicin, Isoniazid are associated with drug-induced hepatitis
- In the presence of TB treatment is preferable EFV
- Rifampicin for TB treatment should not be administered to patients receiving protease inhibitors, however Rifabutin can be used
- Co-trimoxazole prophylaxis therapy is important in TB patients

- Recommended TB regimens in patients with chronic hepatitis or cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Initial phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preffered</td>
<td>SHRE 2 months</td>
<td>HR 6 months</td>
</tr>
<tr>
<td>1st alternative</td>
<td>SHE 2 months</td>
<td>HE 10 months</td>
</tr>
<tr>
<td>2nd alternative</td>
<td>RE 9 months</td>
<td>–</td>
</tr>
</tbody>
</table>

Management of tuberculosis and HIV co infection WHO 2007
### HAART in TB/HIV co-infection

#### When to start

<table>
<thead>
<tr>
<th>CD4 count, cells/mm³</th>
<th>WHO – EURO 2007</th>
<th>DHHS, 2009</th>
<th>EACS, 2009</th>
<th>WHO - 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Start ART as soon as TB treatment is tolerated (2-8 weeks)</td>
<td>Start ART after 2 weeks of TB treatment</td>
<td>As soon as practical</td>
<td>- Irrespective of CD4 cell counts, TB should be started on ART as soon as possible after starting TB treatment.</td>
</tr>
<tr>
<td>100-200</td>
<td>Start ART after completion of initial TB treatment phase (earlier if severely compromised)</td>
<td>Start ART after 8 weeks of TB treatment</td>
<td>As soon as practical, but can wait until after completing 2 months TB treatment especially when there are difficulties with drug interactions, adherence and toxicities</td>
<td></td>
</tr>
<tr>
<td>200-350</td>
<td></td>
<td>Start ART after 8 weeks of TB treatment (on case-by-case basis in clinician’s judgment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;350</td>
<td>Monitor! Consider ART if CD4 drops below 350 cells/mm³</td>
<td>Start ART after 8-24 weeks or after end of TB treatment</td>
<td>As physician discretion</td>
<td></td>
</tr>
</tbody>
</table>
# HAART in TB/HIV co-infection

## What to start

<table>
<thead>
<tr>
<th>What antiretroviral therapy to start</th>
<th>WHO - EURO 2007</th>
<th>WHO – 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred - 2 NRTIs + 1 NNRTI AZT (TDF) +3TC (FTC)+EFV (NVP)</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Alternative - 3 NRTIs AZT+3TC + ABC (TDF)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Recommended second-line antiretroviral therapy

<table>
<thead>
<tr>
<th>2 NRTIs + 2 PIs (one of them boosted)</th>
<th>If rifabutin available (150 mg 3 times/Week)</th>
<th>Same regimens as recommended for adults (without TB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred – ABC (TDF) + ddI + LPV/r + RTV</td>
<td>If rifabutin not available</td>
<td>Same NRTI backbones recommended for adults (without TB) Plus LPV/r or SQV/r with adjusted dose of RTV</td>
</tr>
<tr>
<td>Alternative – ABC (TDF) + ddI + SQV/r +RTV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Clinical management of TB/HIV co-infection**

TB-infection - LTBI (positive tuberculin skin test or IGRA)  
Or contact with active TB

**Isoniazid, 300mg/d + piridoxin 50mg/d 6 months**

<table>
<thead>
<tr>
<th>Type of active TB case</th>
<th>Initial phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>New TB patient</td>
<td>HRZE 2 months</td>
<td>HR 4 months</td>
</tr>
<tr>
<td>Previously TB treated patient, including</td>
<td>HRZES 2 months</td>
<td>HRE 5 months</td>
</tr>
<tr>
<td>• relapse</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td>• treatment after default</td>
<td>HRZE 1 month</td>
<td></td>
</tr>
<tr>
<td>• treatment failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic or MDR-TB cases (sputum positive after supervised re-treatment)</td>
<td>A specially designed regimen, whether standard or ad hoc</td>
<td></td>
</tr>
</tbody>
</table>

WHO, Clinical protocols, 2007
MDR-TB therapy

- Household contact of known MDR-TB patient with new TB;
- History of treatment with second line-drug;
- Probable treatment failure:
  - Smear positive in fifth month of therapy;
  - HIV positive and clinically worsening during category 1 or 2

Patient at risk of MDR-TB
- Send two sputums for culture and drug susceptibility testing (DST).
- Conduct HIV testing if patient’s serostatus unknown

Start Category 4 regimen
- Provide HIV care if necessary

Z - Km - Lfx - Eto - Cs - PAS

<table>
<thead>
<tr>
<th></th>
<th>Duration</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial phase</td>
<td>At least 6 mo and until sputum smears and cultures are negative</td>
<td>Close monitoring for side-effects At least five drugs Includes injectable</td>
</tr>
<tr>
<td>Continuation phase</td>
<td>12-18 months</td>
<td>Fewer side effects Usually only oral drugs</td>
</tr>
</tbody>
</table>

Adjust treatment regimen when DST results are available
Management of HIV/HBV co-infected patients
Recommendations for HIV infected IDU with HBV co infection

- HIV/HBV positive IDUs should be vaccinated against HAV if not immune
- For HIV-positive IDU with HBV co infection 3TC/FTC and TDF are active against both infection
Development of HBV chronic infection is 6 times higher in HIV positive persons.

In HBV/HIV-coinfected patients development of severe fibrosis and cirrhosis is 4.2 times greater.

HBV/HIV-coinfected patients have deceased rates of Anti-HBs and seroconversion and increased rates of HBV DNA.

In HBV/HIV-coinfected patients hepatocellular carcinoma (HCC) may appear more aggressive and at an earlier age. In addition, it presents with multifocal lesions.

HBV/HIV-coinfected patients have an increased risk for liver-related morbidity and mortality, especially those with low CD4+ counts.

On the contrary, HBV doesn’t affect HIV disease progression.
Before making treatment decision patients should be categorized:

1. Patients not requiring hepatitis B or HIV treatment.
2. Patients requiring only hepatitis B treatment.
3. Patients requiring only HIV treatment.
### Treatment Regimens for HIV/HBV coinfection according Guidelines

<table>
<thead>
<tr>
<th>WHO 2007</th>
<th>EACS 2009</th>
<th>DHHS 2009</th>
<th>WHO 2010 revision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Not requiring any treatment:</strong> CD4 ≥350 cells/mm³; mild or not progressing HBV</td>
<td>CD4&gt;500 mm³, no HAART no HBV treatment: Monitor closely</td>
<td>If treatment is needed for HIV but not for HBV: TDF/FTC or/3TC</td>
<td>Start ART in all patients who require HBV treatment irrespective of CD4</td>
</tr>
<tr>
<td><strong>II. Requiring only HBV treatment:</strong> • PEG-IFN-α 2a, standard IFN-α 2a or 2b, ADF.</td>
<td>CD4&gt;500 mm³, no HAART HBV treatment is requiring: 1. Early HAART including TDF+FTC/3TC 2. Peg INF if Genotype A, High ALT, low HBV DNA</td>
<td>If treatment for HBV is needed: TDF/FTC or/3TC Treating only HBV: PEG-IFN-α, ADF (theoretical risk for development of HIV resistance) Should be avoided: FTC, 3TC, TDF, or entecavir without a full ART</td>
<td>2. Start TDF/FTC or /3TC containing ART in all patients needing treatment</td>
</tr>
<tr>
<td><strong>III-IV. Requiring only HIV treatment or both:</strong> Dual active ART TDF/3TC or TDF/FTC</td>
<td>CD4&lt;500 mm³ or Symptomatic HIV or Cirrhosis: 1.3TC experienced: add or substitute NRTI+TDF 2.3TC Naïve: HAART including TDF+3TC or +FTC</td>
<td>1. Start ART in all patients who require HBV treatment irrespective of CD4</td>
<td></td>
</tr>
</tbody>
</table>
Management of HIV/HCV co-infected patients
• IDUs with Hepatitis C should be considered for treatment with pegilated interferon and ribavirin.

• The sustained viral response rate for this treatment has been reported as 11-29% for genotype 1 and 43-73% for other genotypes.

• For all HIV positive IDUs with HCV co infection treat HIV if indicated.

• OST has been shown to increase treatment adherence.

• HIV-positive active IDUs who are under HCV treatment need to be frequently consulted by psychiatrist
Reciprocal impact of HIV and HCV

• In HCV infected patients HIV accelerates the course of HCV associated liver disease progression. Particularly in patients who are more severely immune deficient.

• In HCV/HIV – co infected patients development of severe fibrosis, cirrhosis, hepatocellular carcinoma, and liver-related mortality is 3 times greater.

• In HCV/HIV – co infected patients the concentration of HCV RNA is much more higher than in monoinfected patients.

• HCV has little or no effect on the response to ARV, or on immunological, virological and HIV-related clinical disease progression.
HCV Treatment algorithm in HCV/HIV co-infected patients

WHO EURO 2007

HCV/HIV co-infection

HCV RNA (+) positive

CD4+ > 350/mm³

HCV Treatment

CD4+ < 350/mm³

HAART

HCV 1,4 G
VL > 800 000 IU/ml

Evaluation of disease severity

F0-F1

Monitor

HCV 1,4 G
VL < 800 000 IU/ml

Moderate/severe
F2-F4

48 weeks

HCV 2,3 G
VL High/low

HCV Treatment
HCV Treatment algorithm in HCV/HIV co-infected patients

- **HCV/HIV co-infection**
- **HCV RNA (+) positive**
  - CD4+ > 350/mm³
    - **HCV Treatment**
      - **Evaluation of disease severity**
        - F0-F1
        - Monitor
      - HCV 1,4 G
        - VL > 500,000-800,000 IU/ml
      - HCV 1,4 G
        - VL < 500,000-800,000 IU/ml
        - Moderate/severe F2-F4
        - Monitor
  - CD4+ < 350/mm³
    - HAART
    - **HCV Treatment**
    - HCV 2,3 G
      - VL High/low
HCV Treatment algorithm in HCV/HIV co-infected patients

HCV/HIV co-infection

HCV RNA (+) positive

CD4+ > 350/mm³

HCV Treatment

CD4+ < 350/mm³

HAART

HCV 1,4 G VL > 400 000 IU/ml

Evaluation of disease severity

HCV 1,4 G VL < 400 000 IU/ml

F0-F1

Moderate/severe F2-F4

HCV 2,3 G VL High/low

Monitor

HCV Treatment

EACS 2009
Proposed optimal duration of HCV therapy in HCV/HIV-coinfected patients

EACS 2009  DHHS 2009

Changes in treatment duration

Proposed optimal duration of HCV therapy in HCV/HIV-coinfected patients

- **W4**
- **W12**
- **W24**
- **W48**
- **W72**

HCV-RNA neg

- **G2/3**
- **G1/4**

HCV-RNA pos

- > 2 log drop in HCV-RNA
- < 2 log drop in HCV-RNA

24 weeks therapy *

48 weeks therapy

72 weeks therapy

Stop
HIV/HCV co infection

Limitations to ARV drugs

- **ddI** is strongly contraindicated during PEG-IFN + Ribavirin therapy in patients with cirrhosis and should be avoided in patients with less severe liver disease (Ribavirin increases the toxicity of ddI).
- **AZT** – should be avoided if possible, due to development risk of anemia and neutropenia.
- **d4T** – should also be avoided.
- **Abacavir** has been associated with decreased response to peginterferon plus ribavirin in some but not all retrospective studies.
- Current evidence is insufficient to recommend avoiding this combination.

*WHO 2007; DHHS 2009; EACS 2009*
• HCV, HBV and TB co infection very common in HIV infected IDU-s;
• All HIV positive IDUs should be screened for HCV, HBV and TB;
• HIV positive IDUs should be vaccinated against HAV and HBV if not immune;
• Opioid substitution therapy (OST) is critical in HIV positive IDUs;
• For HIV infected IDUs with active TB – treat TB first, initiated HAART irrespective of CD4 based on EFV;
• Treat HIV in all HCV co infected IDUs as indicated, consider HCV treatment with PEG/RBV;
• For HIV-positive IDU with HBV co infection dual active NRTI – 3TC/FTC and TDF should be prescribed;
• HIV/Hepatitis and active TB co infection in IDUs – should be take into account drug-drug interaction to avoid the withdrawal symptoms, requirement of ART or TB drugs dose modification and hepatotoxicity.