Accelerating the implementation of collaborative
TB/HIV activities in the WHO European Region
16-17 July 2010, Vienna, Austria

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

**Tengiz Tsertsvadze, MD, PhD**
Director General, Infectious Diseases,
AIDS and Clinical Immunology Research Center
Professor, Tbilisi State University Faculty of Medicine


GEORGIA
საქართველო
TBILISI

# 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

***Rockstroh et al. JID, 2005. WHO 2009; 2010; UNAIDS 2009***

# 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 |

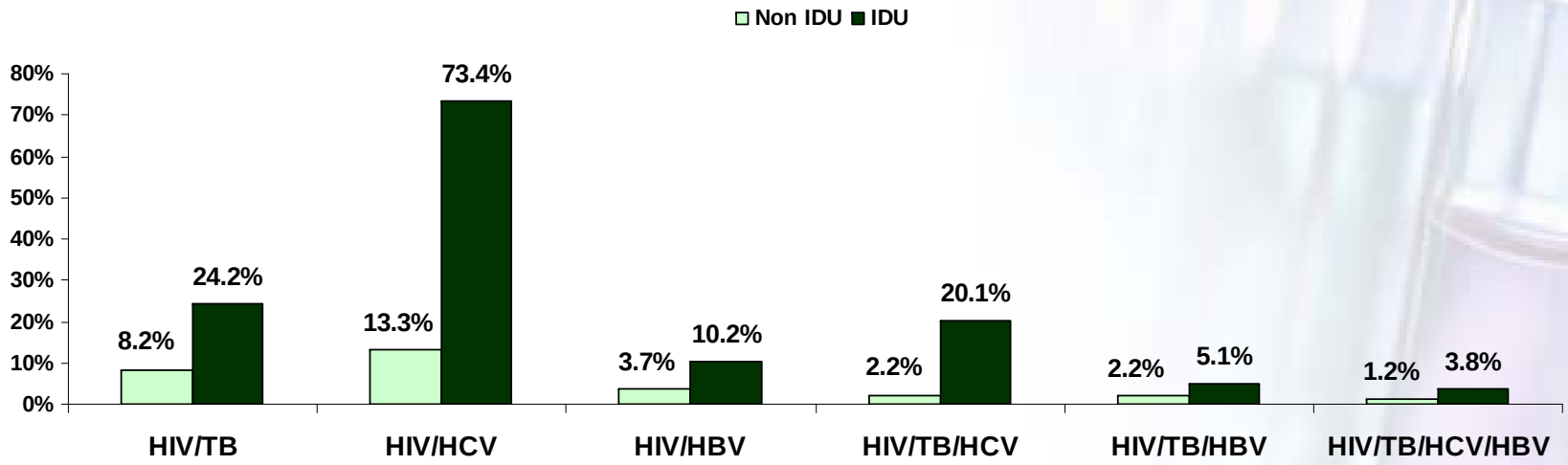
* Number of incident TB cases that are HIV-positive

***WHO 2009; 2010. National AIDS Center***

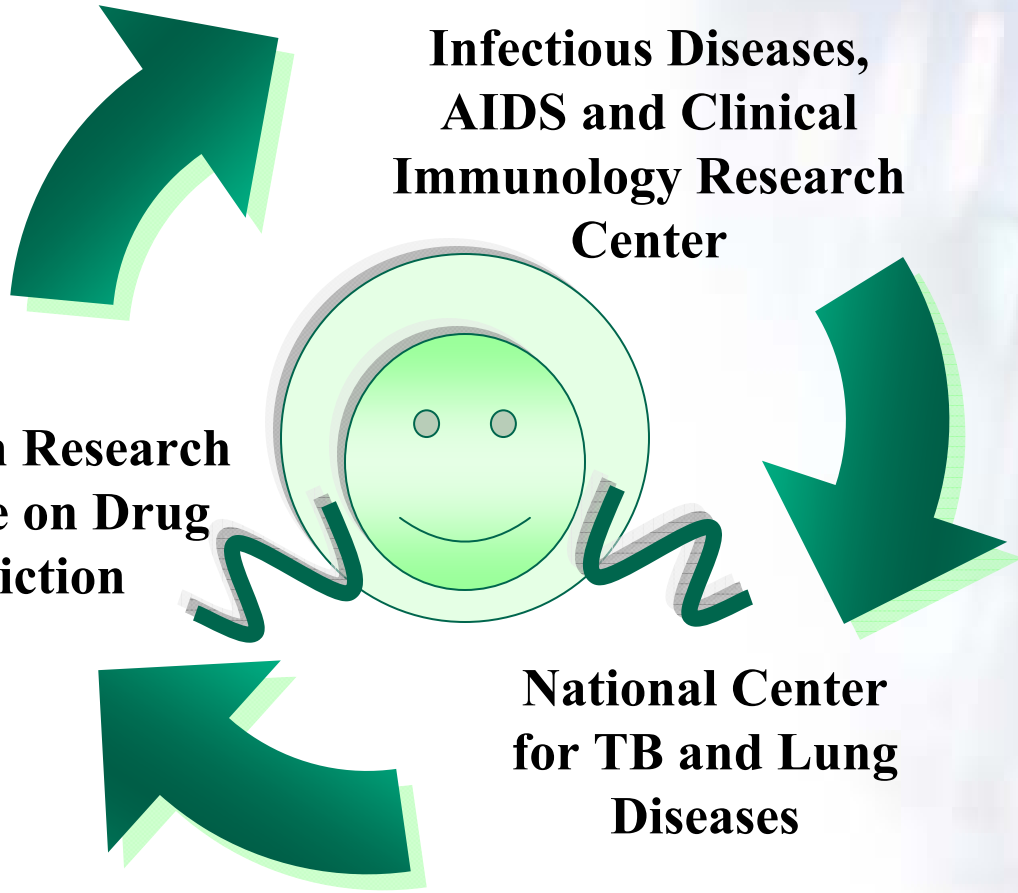
# MDR TB in Georgia

| | |
|---|---|
| MDR among new TB cases | 6.8% |
| MDR among previously treated TB | 27.4% |
| MDR among TB/HIV co-infected patients | 23.8% |

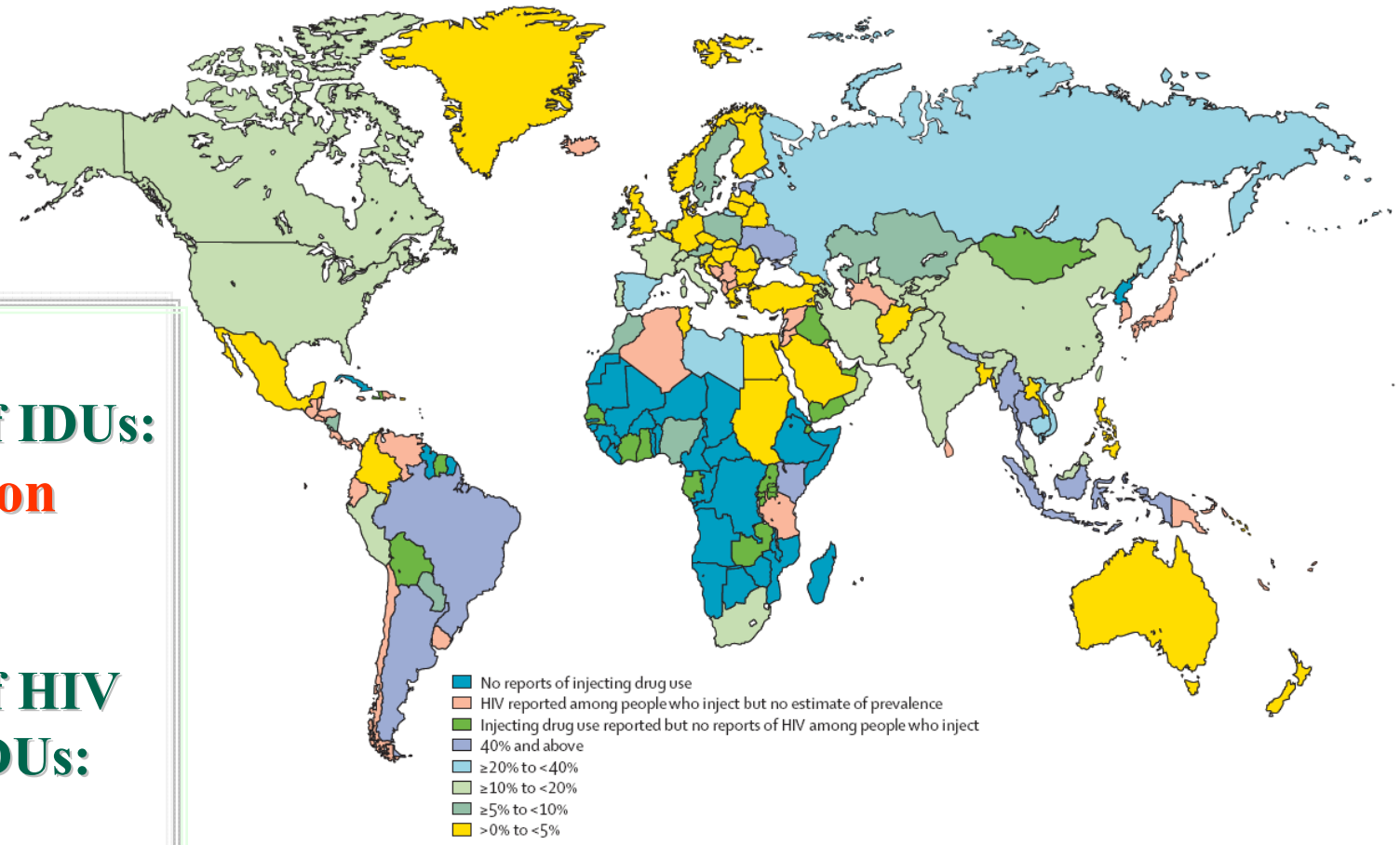
# TB/Hepatitis co-infection among HIV patients in Georgia



# HIV/HCV/HBV/TB/IDU Collaborating Network in Georgia



# Prevalence of HIV Among People Who Inject Drugs

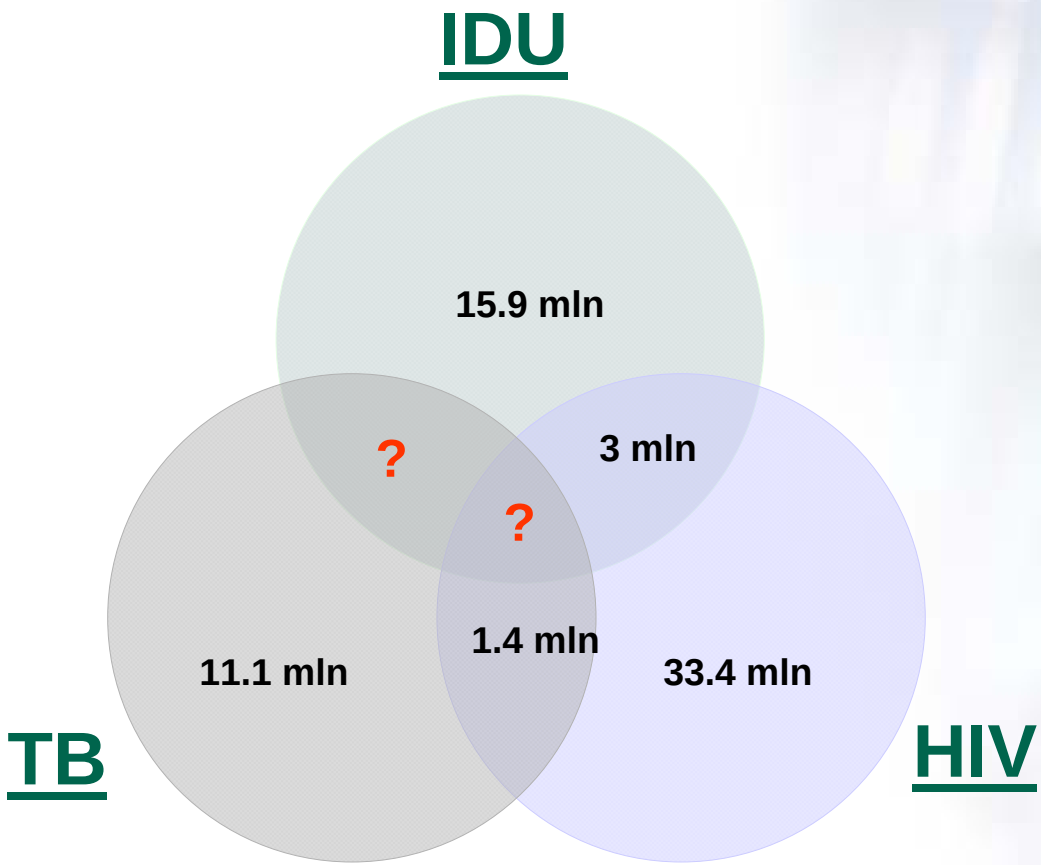



**Estimated number of IDUs:**
**15.9 million**

**Estimated number of HIV positive IDUs:**
**3 million**

***Mathers et al. Lancet, 2008***

# The overlap between TB, HIV and injecting drug use




*Mathers et al. Lancet, 2008. WHO 2009*

# 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

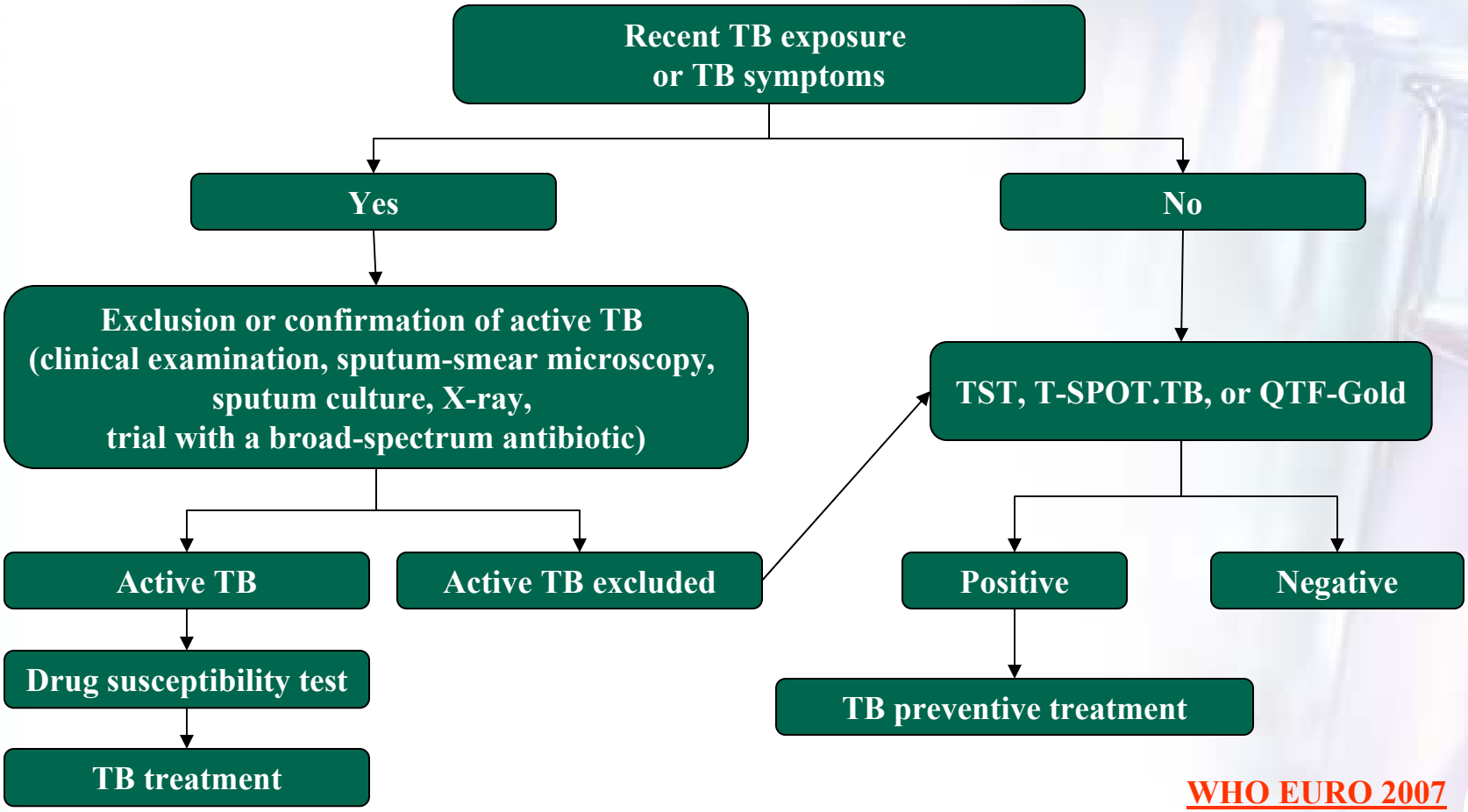
# WHO 2008: The Three 'I's

**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)
- TB **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




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

| | Initial phase | Continuation phase |
|---|---|---|
| Preffered | SHRE 2 months | HR 6 months |
| 1st altrenative | SHE 2 months | HE 10 months |
| 2nd altrenative | RE 9 months | – |

*Management of tuberculosis and HIV co infection WHO 2007*

# HAART in TB/HIV co-infection
# When to start

| CD4 count, cells/mm$^3$ | WHO – EURO 2007 | DHHS, 2009 | EACS, 2009 | WHO - 2010 |
|---|---|---|---|---|
| <100 | Start ART as soon as TB treatment is tolerated (2-8 weeks) | Start ART after 2 weeks of TB treatment | As soon as practical | - Irrespective of CD4 cell counts, TB should be started on ART as soon as possible after starting TB treatment. |
| 100-200 | | Start ART after 8 weeks of TB treatment | 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 | |
| 200-350 | Start ART after completion of initial TB treatment phase (earlier if severely compromised) | Start ART after 8 weeks of TB treatment (on case-by-case basis in clinician's judgment) | | |
| >350 | Monitor! Consider ART if CD4 drops below 350 cells/mm3 | Start ART after 8-24 weeks or after end of TB treatment | As physician discretion | |

# HAART in TB/HIV co-infection
# What to start

| | WHO - EURO 2007 | WHO – 2010 | |
|---|---|---|---|
| What antiretroviral therapy to start | Preferred - 2 NRTIs + 1 NNRTI<br>AZT (TDF) +3TC (FTC)+EFV (NVP)<br><br>Alternative - 3 NRTI s<br>AZT+3TC + ABC (TDF) | No change | |
| Recommended second-line antiretroviral therapy | 2 NRTIs + 2 PIs<br>(one of them boosted)<br><br>Preferred –<br>ABC (TDF) + ddI + LPV/r + RTV<br><br>Alternative –<br>ABC (TDF) + ddI + SQV/r +RTV | If rifabutin available (150 mg 3 times/Week) | Same regimens as recommended for adults (without TB) |
| | | If rifabutin not available | Same NRTI backbones recommended for adults (without TB) Plus LPV/r or SQV/r with adjusted dose of RTV |

# Clinical management of TB/HIV co-infection

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

**Izoniazid, 300mg/d + piridoxin 50mg/d 6 moths**

**TB disease (Active TB)**

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

**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**

| | Duration | Characteristics |
|---|---|---|
| **Initial phase** | **At least 6 mo and until sputum smears and cultures are negative** | **Close monitoring for side-effects<br>At least five drugs Includes injectable** |
| **Continuation phase** | **12-18 months** | **Fewer side effects<br>Usually only oral drugs** |

**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**

# Reciprocal impact of HIV and HBV

- **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.**

# Treatment of HIV/HBV co-infected patients

**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.**
4. **Patients requiring both hepatitis B and HIV treatment.**

# Treatment Regimens for HIV/HBV co infection according Guidelines

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

# Management of HIV/HCV co-infected patients

# HCV treatment
# Approaches in HIV-positive active IDUs

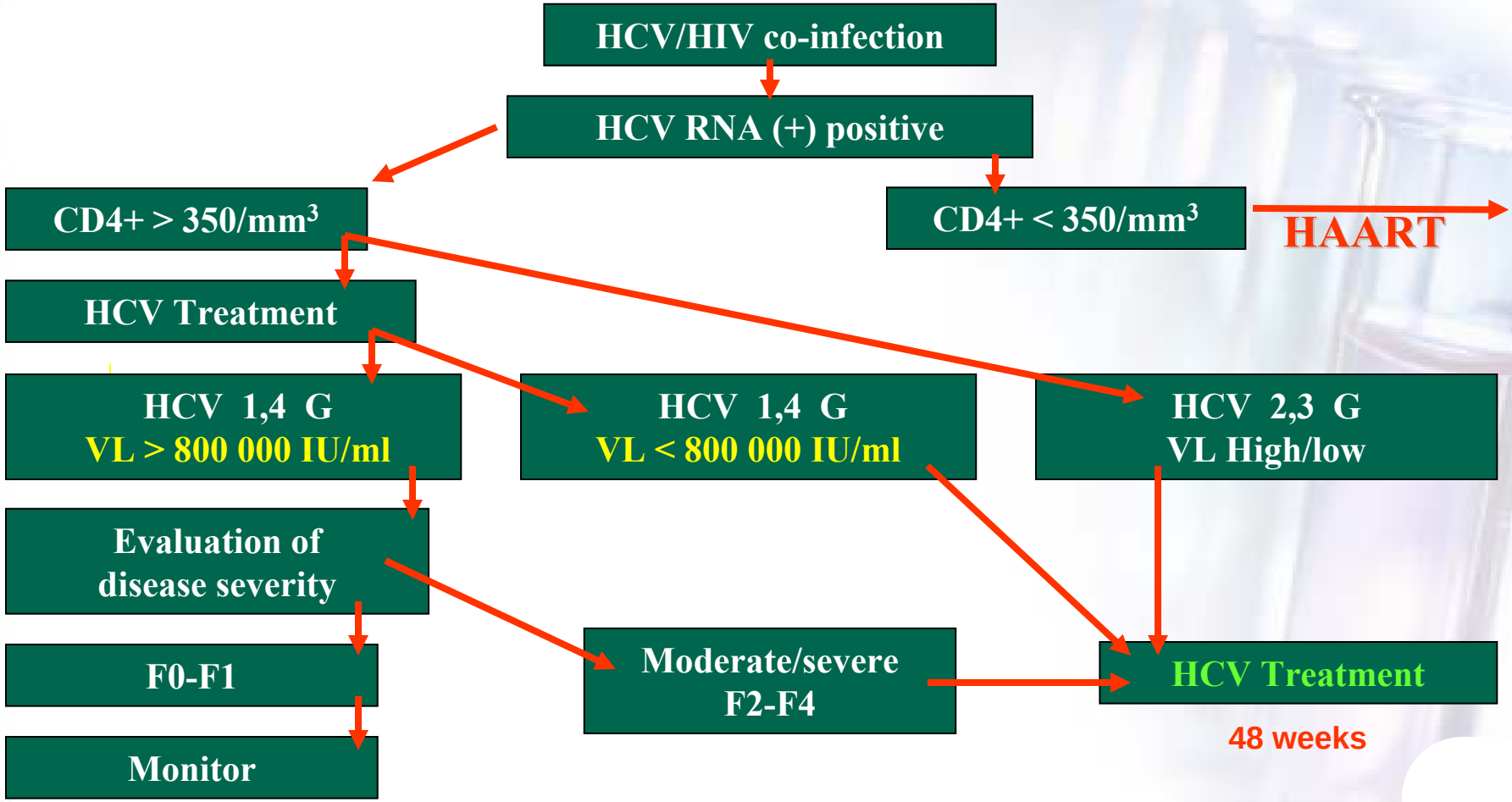
- **IDUs with Hepatitis C should be considered for treatment with pegilated interferon and ribavirin.**
- **The sustained viral responce rate for this treatment has been reported as 11-29% for genotype 1 and 43-73% for other genotypes.**
- **For all HIV positive IDUs with HCV co infection treat HIV if indicated.**
- **OST has been shown to incerase treatment adherence.**
- **HIV-positive active IDUs who are under HCV treatment need to be frequently consulted by phsyciatrist**

# 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.**

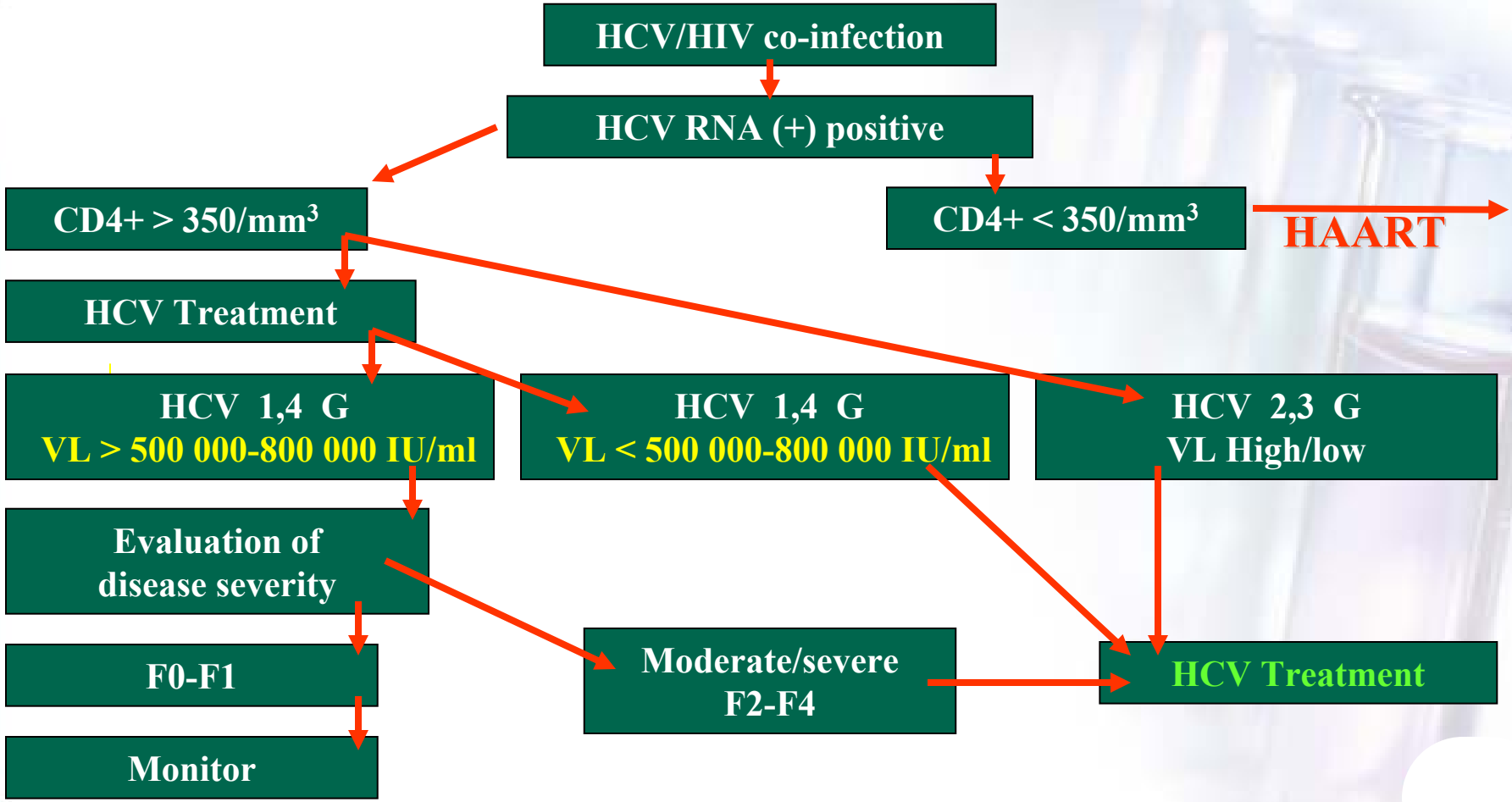
# HCV Treatment algorithm in HCV/HIV co-infected patients

WHO EURO 2007



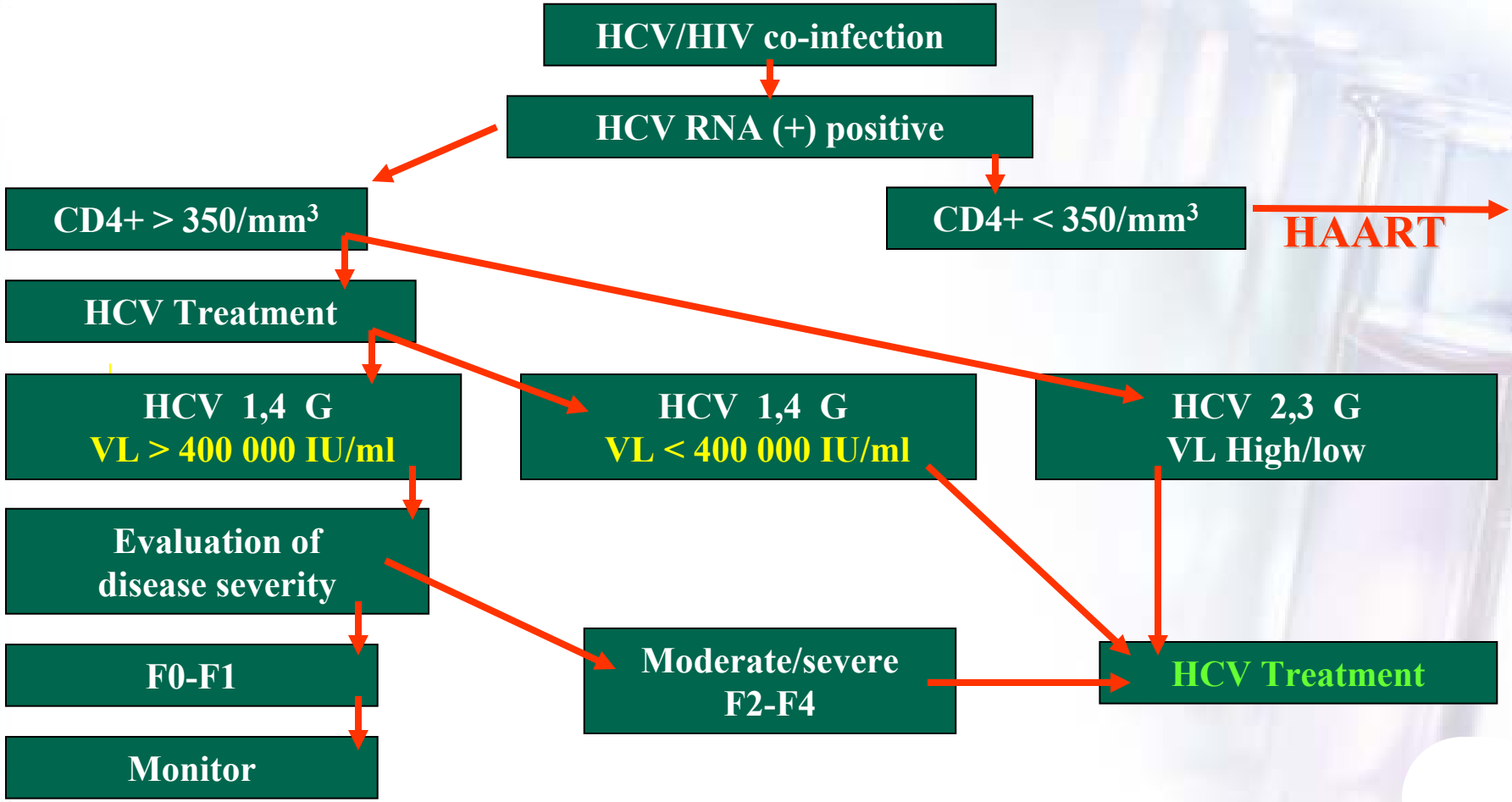
# HCV Treatment algorithm in HCV/HIV co-infected patients

DHHS 2009



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

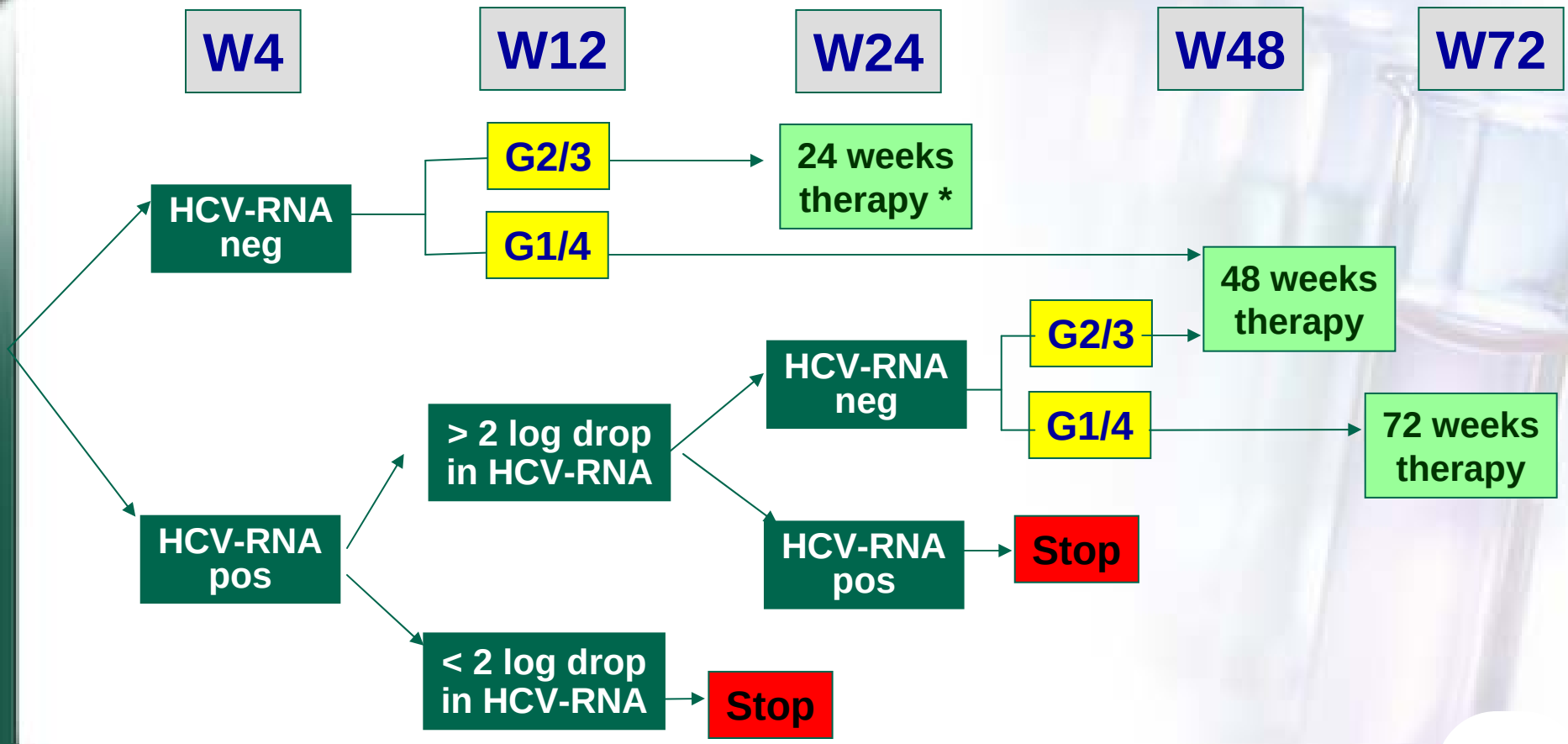
EACS 2009



Changes in treatment duration

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

*EACS 2009 DHHS 2009*



# 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***

# Conclusion

- 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.