Hepatitis in immunocompromised hosts

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Hepatitis in immunocompromised hosts

- Hepatotropic virus infections are common in immunocompromised hosts
- Physiopathological mechanisms are not well known
- Several mechanisms (i.e. humoral and cellular) play a vital role in the elimination of these viruses

Hepatitis in immunocompromised hosts

- Important questions
  - Are clinical and biological aspects of acute viral hepatitis modified by immunosupression?
  - Is the risk of progression to chronicity and severity of hepatic disease influenced by immunosupression?
  - Are both prophylaxis and treatment of viral hepatitis modified in the presence of immunosupression?

Hepatitis in immunocompromised hosts

- Facts
  - Immunosupression itself doesn't increase the prevalence of fulminant hepatitis (i.e. HBV), but the risk of reactivation is high
  - Risk of chronicity is high in the presence of immunosupression, independently of its aetioloy, but it increases based on the degree of the immunological compromise (i.e. HIV +)
  - In dialysis patients the risk of progression is 40-80% (*vs* 2-5%) in HBV and 85-95% (*vs* 70-80%) in HCV

Hepatitis in immunocompromised hosts

1. Hemato-oncologic patients
2. Haemodialysis patients and renal allograft recipients
3. Liver transplant recipients
4. HIV positive patients

1.Hemato-oncologic patients

- Viral reactivation in hepatitis B surface antigen (HBsAg carriers) is now a well-recognized complication in patients who undergo immunosupressive therapy (i.e. chemotherapy or corticosteroids)
- This condition ranges from asymptomatic self-limiting anicteric hepatitis to severe, potencially fatal progressive decompensated hepatitis (i.e.lymphomas)
- Mortality rates due to reactivation -5-37%

1.Hemato-oncologic patients

- HBV reactivation ranges from 14-50%* and has been reported in over 50% of the patients in settings of hematopoietic stem cell transplantation**, associated with 5-12% mortality.
- Reactivation of HVB can occur in

  -haematological malignancies

  -other carcinomas

  -non-malignant conditions (i.e. cryoglobulinemia, vasculitis, malignant histiocytosis or ulcerative colitis)

**Blood 2002; 100 (2): 391-96*

***Hepatology 2006; 43(2): 209- 20*

Mechanisms of HBV reactivation

- Enhancement of viral replication leading to an increase of infected hepatocytes, is due to 2 possible mechanisms*/**:
  - After withdrawal of the immunosupressive agent and restoration of immunocompetence, activated T cells may attack the infected hepatocytes, leading to their rapid destruction
  - The hepatic injury could be a direct cytopathic effect of HBV as a result of accelerated viral replication, leading to hepatocyte lysis

** Blood 1999; 93: 1127-36*

*** Blood 2002; 100 (2): 391-96*

HBV reactivation

- Definition: increase of HBV DNA levels of 10-fold or greater compared with the baseline level or an absolute increased level that exceed > 9 log (cp/mL) during or after chemotherapy in the absence of other infections*

** Hepatology 2006; 43(2): 209- 20*

Groups with prior HBV exposure are at risk for reactivation

- Chronic infection: patients who develop increases in serum HBV DNA and disease activity during chemotherapy
- Inactive carriers: patients who are HBsAg positive and HBV DNA negative and convert to active replication during chemotherapy
- Immune or Viral Clearance: pt with immunity against HBV due to past exposure (HBsAg neg, anti-HBs + and anti-HBsAc+) who reactivate with production of HBsAg and HBV DNA (risk of seroreversion)

Risk factors associated of high risk of HBV reactivation*

- Young age
- Male sex
- Lymphoma

- HBeAg+(?)
- Pre-chemotherapy HBV viral load/ ALT(?)
- cccDNA

- Doses of chemotherapy
- steroids

** Br J Cancer 2004; 90: 1306-11*

Prevention of HBV reactivation

- All candidates for chemotherapy and immunosupressive therapy should be screened for HBsAg and anti-HBc antibodies prior to initiation of treatment
- Vaccination against HBV in seronegative patients is highly recommended*

** J Hepatology 2009; 50: 227-42*

Prevention of HBV reactivation

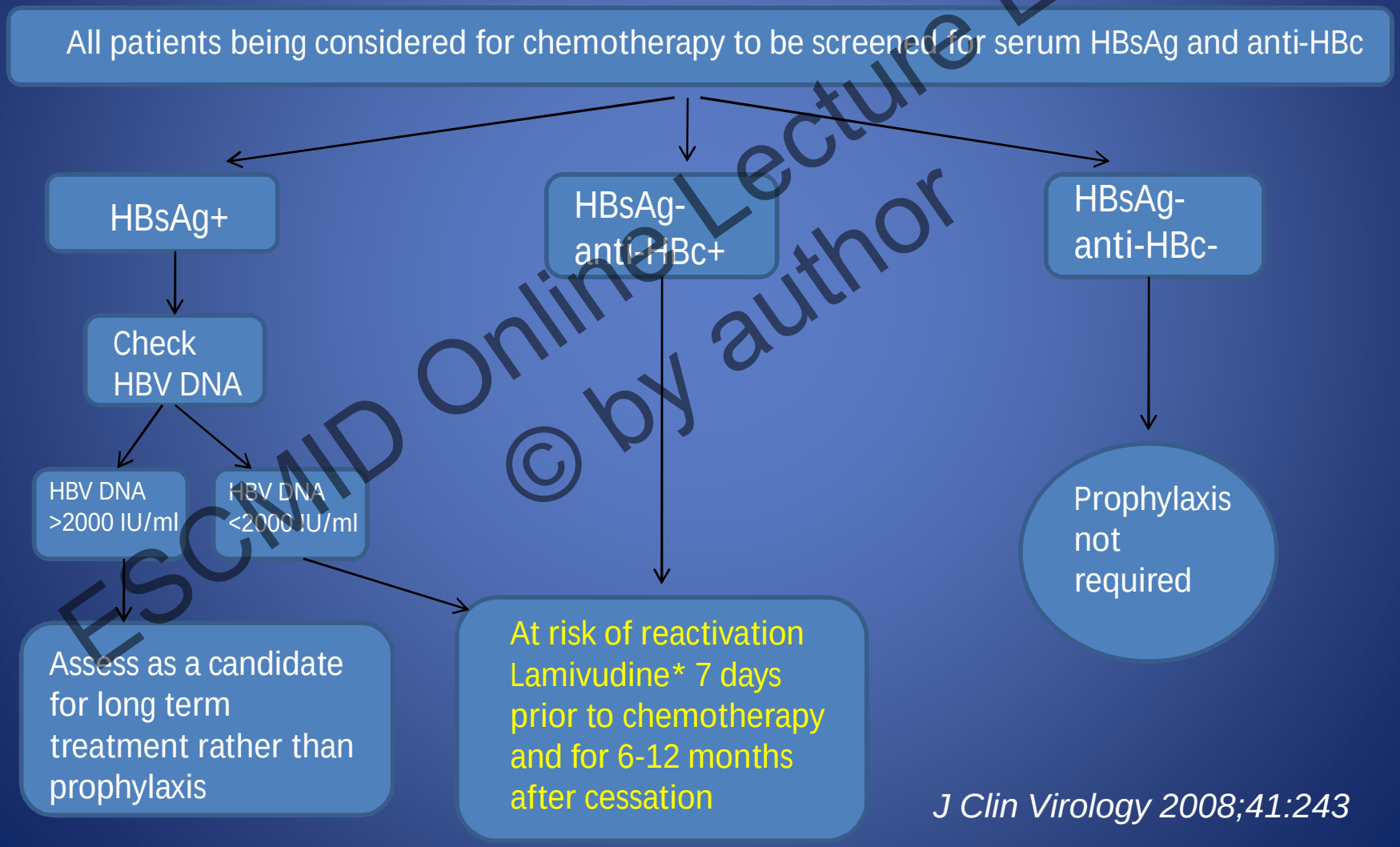
In all HBsAg+

- -check viral load (HBV DNA)
- -start antiviral therapy regardless of HBV DNA status* (preferably within 2-4 w before treatment)
- -follow-up of ALT, HBV DNA
- -consider discontinuation of antiviral agent at 6-12 months after cessation of chemotherapy**

J Hepatology 2009; 50: 227-42

***Br J Haematol 2007; 136: 699*

Algorithm for the prevention of reactivation of hepatitis B infection



J Clin Virology 2008;41:243

2. Haemodialysis patients and allograft recipients

- HVB and HCV are the main responsible for the hepatic decompensation in this population
- After renal transplant (RT) these viruses have a deleterious effect in long survival and in the graft preservation

**Transplantation 2005; 79: 1132-6*

HBV and renal disease

- In this population
  - High percentage of reactivation
  - High viral replication
  - Less spontaneous seroconversion
- Reduction of HBV prevalence mainly (> 90%) due to vaccination and EPO
- Acute HBV infection often subclinical but with evolution to chronicity in 80%
- Portugal: 45% before 1985 / 5% in 2005

HBV and Renal Tranplant

- With the immunosupressive therapy – high risk of increased viraemia even in inactive carriers*
- If a patient is HBsAg+ - less survival after transplant – 5-10 X higher mortality due to hepatic disease

** Revue Francophone des Laboratoires 2008; 403: 31-40*

Haemodialysis patients
HBV

- Therapeutic attitude
  - HBV screening
    - Negative – vaccination
    - Positive – other serological markers / DNA-HBV
    - HBV DNA positive and if it is a RT candidate
      - Treat HBV to avoid viral replication with oral drugs (ETV)*

** Hepatology 2009; 50: 227-42*

Allograft recipients
HBV

- Therapeutic attitude
  - If they are under oral treatment – continue
  - If not (HBV-DNA negative)
    - initiate immediately* or/when reactivation**

-*stop therapy > 2 yrs if HBV DNA undetectable(?)

-**if reactivation – therapy for life

HCV and renal disease

- HCV is the main cause of hepatic disease in haemodialysis patients and allograft recipients
- Well known risk of nosocomial transmition
- Prevalence – 3 – 80% (related with duration of dialysis/different dyalisis units)
- Portugal - 1990’ 60% of incidence
  - 2005 6,7% =

Outcome of HCV in dialysis patients

- The majority of patients have mild disease
- Evolution to cirrhosis and HCC is rare (indolent evolution)
- After RT the outcome is worse*
  - Colestatic hepatitis
  - More progressive hepatic disease (high risk of cirrhosis > 5 yrs)
  - Higher risk of other complications

**Hepatology 2002; 36: 206-10*

Haemodialysis patients
HCV

Therapeutic attitude

- When to treat?
  - If high ALT and RNA-HCV +, consider liver biopsy and treat HCV before transplant
  - If cirrhosis is documented – treatment shoud not be performed
- How to treat?
  - PEGIFN alfa 2a – 135 mic/gr /weekly
  - PEGIFN alfa 2b – 1 mic/gr/weekly
  - Role of Ribavirin (close monitoring)

Allograft recipients
HCV

- Therapeutic attitude
  - Low efficacy
  - Increased risk
  - Interferon is not recommended (risk >50% of alograft rejection)
  - Other oral drugs- improve biochemical markers but not viraemia or histology

3. Liver tranplant recipients

- Virus recurrence after Liver Transplant (LT) is high due to the presence of virus in extrahepatic sites (i.e. mononuclear cells)
  - HCV - major cause of LT in U.S.A.
  - Less frequent:

    -HBV – mainly cirrhosis and hepatocellular carcinoma

    -HBV+HDV

3. Liver tranplant recipients
HBV

- HBV as a cause of LT has decreased due to
  - Vaccination
  - New oral drugs (nuclos(t)ides)
- The risk of reactivation is > 80% (initial hepatic disease /level of replication)
- Therapeutic attitude
  - DNA-HBV undetectable
    - Oral drug +/- HBIg
  - DNA-HVB detectable
    - Oral drug+HBIg (< 10% of recurrence)

3. Liver tranplant recipients
HBV

HBIg schedules

- 10 000 U pre-OLT
- 10 000 U daily during 7 days
- 10 000 U e.v. weekly (1 mo), than monthly*

- 10 000 U e.v. pré-OLT
- 1 000 U e.v. / i.m. daily during stay in LT Unit
- 1 000 U e.v. weekly (1 mo), than monthly**

-main goal: maintain HBsAb titer > 500 IU/ml

**NEJM 1993; 329: 1842-7*

*** Hepatology 1996; 24: 1327-33*

3. Liver tranplant recipients
HCV

- LT is the only therapeutic option in HCV individuals with decompensation cirrhosis and hepatocellular carcinoma
- Recurrence of HCV virus after LT is almost 100% (early)
- Immunosupressive treatment (essential to avoid alograft rejection) accelerate the evolution of fibrosis

3. Liver tranplant recipients
HCV

- The HCV evolution in recipient is variable, ranging from mild disease to severe fibrosis and risk of development of cirrhosis in 2-5 yr > LT
- Level of HCV viraemia (pre-OLT) is the most important negative prognostic factor (more severe recurrence and higher resistance to treatment)
- Other prognostic factors include: age of donour > 55 yr, male, black, genotype 1, “early hepatitis” in the draft and high HCV RNA at 4th month

**Current Opinion Organ Transplantation 2005; 10: 81-9*

*** J Hepatol 2005; 43: 53-9*

3. Liver tranplant recipients
HCV

- HCV treatment should be offer pre-transplant
  - SVR < 50%
    - 30 patients – 30% SVR (Forns*)
    - 102 cirrhotic patients – 20% SVR (Everson**)

** J Hepatol 2003; 39: 389-96*

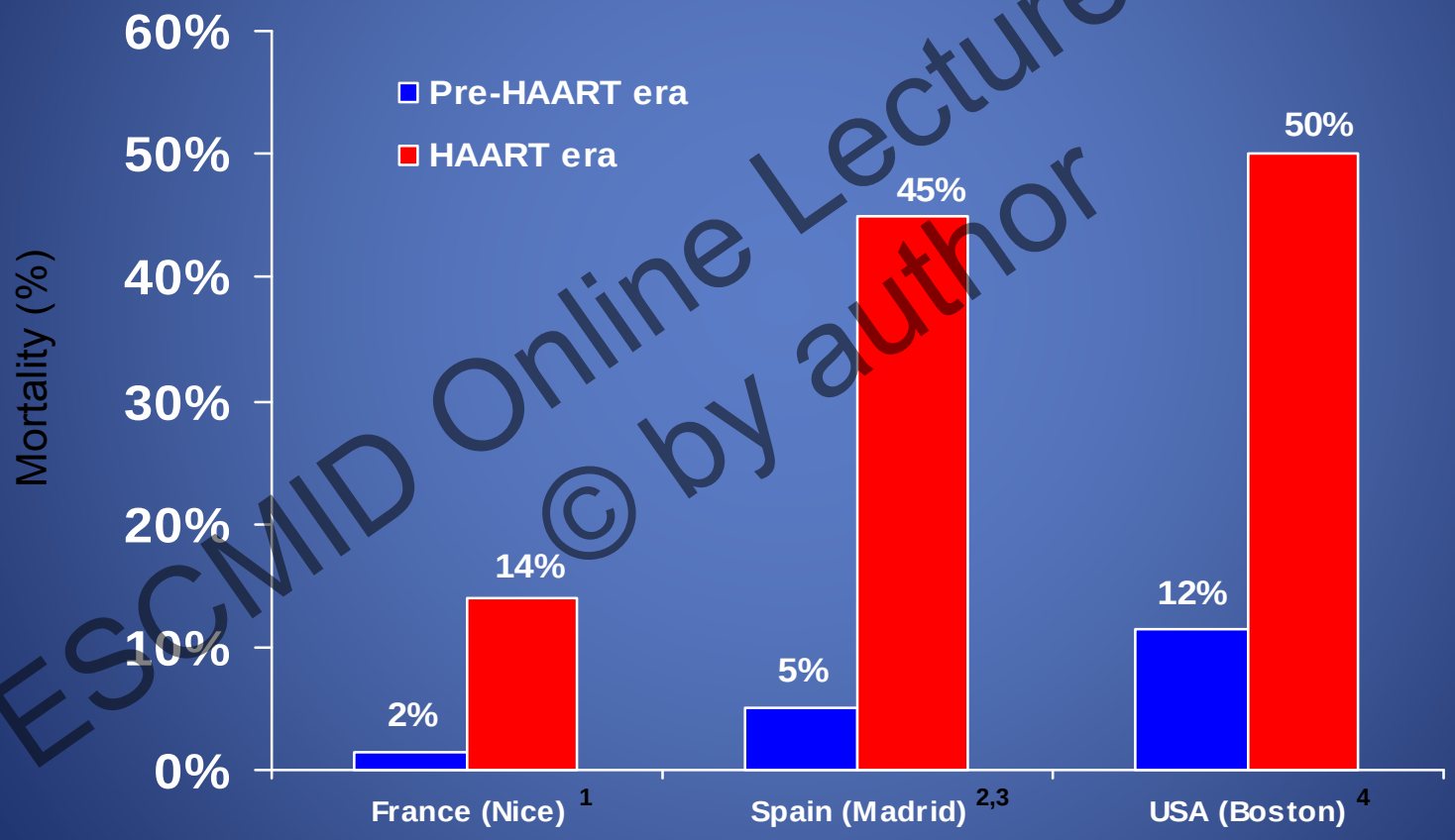
*** Hepatol 2002; 36: A 297*

3. Liver tranplant recipients
HCV

- Therapeutic attitude
  - PEGIFN alfa 2a/2b + Ribavirin – 24 weeks
    - 1 month after LT, if no contraindication
    - At the moment of “stablished”hepatitis in the alograft

4. HIV positive patients

Mortalility and hepatic disease



1. Rosenthal E, et al. AIDS. 2003
2. Martín-Carbonero L, et al. AIDS Res Human Retrovirus. 2001
3. Soriano V, et al. Eur J Epidemiol. 1999
4. Bica I, et al. Clin Infect Dis. 2001

Prevalence of HIV/HBV Co-infection

- Among 9,803 subjects in the EuroSIDA Cohort:
  - 5,883 (60%) had an HBsAg test at the time of enrolment
  - 530 (9%) were positive

Regions:
South
Central
North
East

Konopnicki D et al. *AIDS* 2005;19:593–601.

HIV/HBV – how they interact?

- High levels of DNA-HBV
- Less spontaneous recovery after acute hepatitis
- Higher evolution to chronicity
- Less “e” and “s” seroconversion
- Normal or mild elevated transaminases

HIV/HBV co-infection : (MACS)

Liver related mortality in a cohort of 5293 patients, 1984 /1987 - 2000

Nº	viral status		death related	Death	p
	HIV	HBsAg	with liver (n)	(1000 /year)	
3093	-	-	0	0.0	
139	-	+	1	0.8	0.04
2346	+	-	35	1.7	<0.0001
213	+	+	26	14.2	<0.0001
5293			62	1.1	

Mortalility
18 X HIV/HBV vs HBV

Thio CL et al. Lancet 2002; 360: 1921-1926.

HAART and impact on HBV

- Double action against HIV and HVB
- Less cases of acute HBV infection
- “e” and “s” seroconversion increased
- Improvement in histology and slow progression to cirrhosis and ESLD

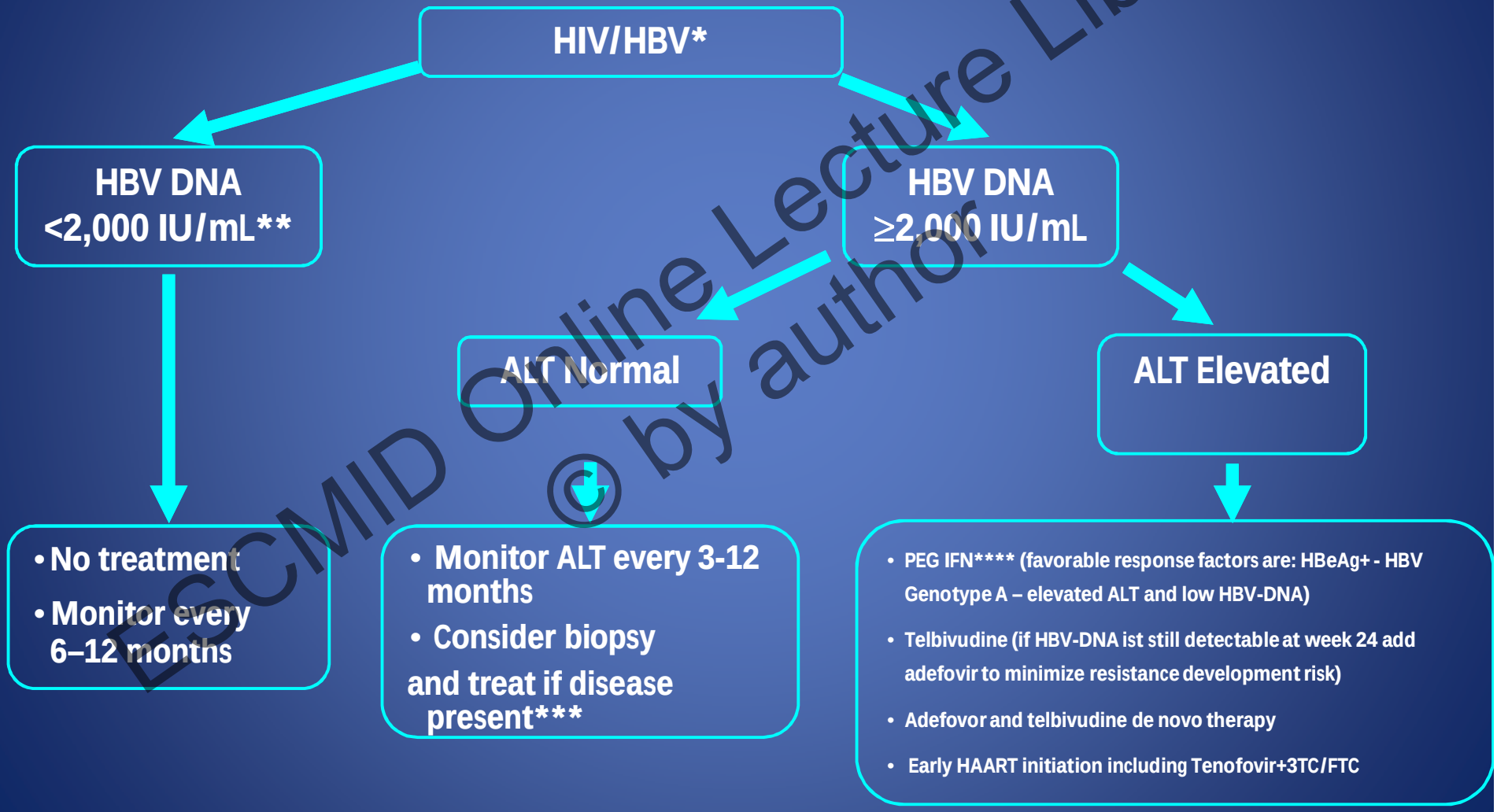
** Lam-Kellerman SE. JID. 2003; 188. 571-7*

Anti HBV Treatment

Interferon alfa-2b	HBV	e+/e-
Lamivudine	HBV/HIV	e+/e-
Adefovir dipivoxil	HBV	e+/e-/lam-R
Entecavir	HBV (HIV?)	e+/e-/lam-R
Peg IFN alfa-2a	HBV	e+/e-/lam-R
Telbivudine	HBV (HIV??)	e+/e-
Tenofovir	HIV/HBV	e+/e-/lam-R
Emtricitabine	HIV/HBV	e+/e-

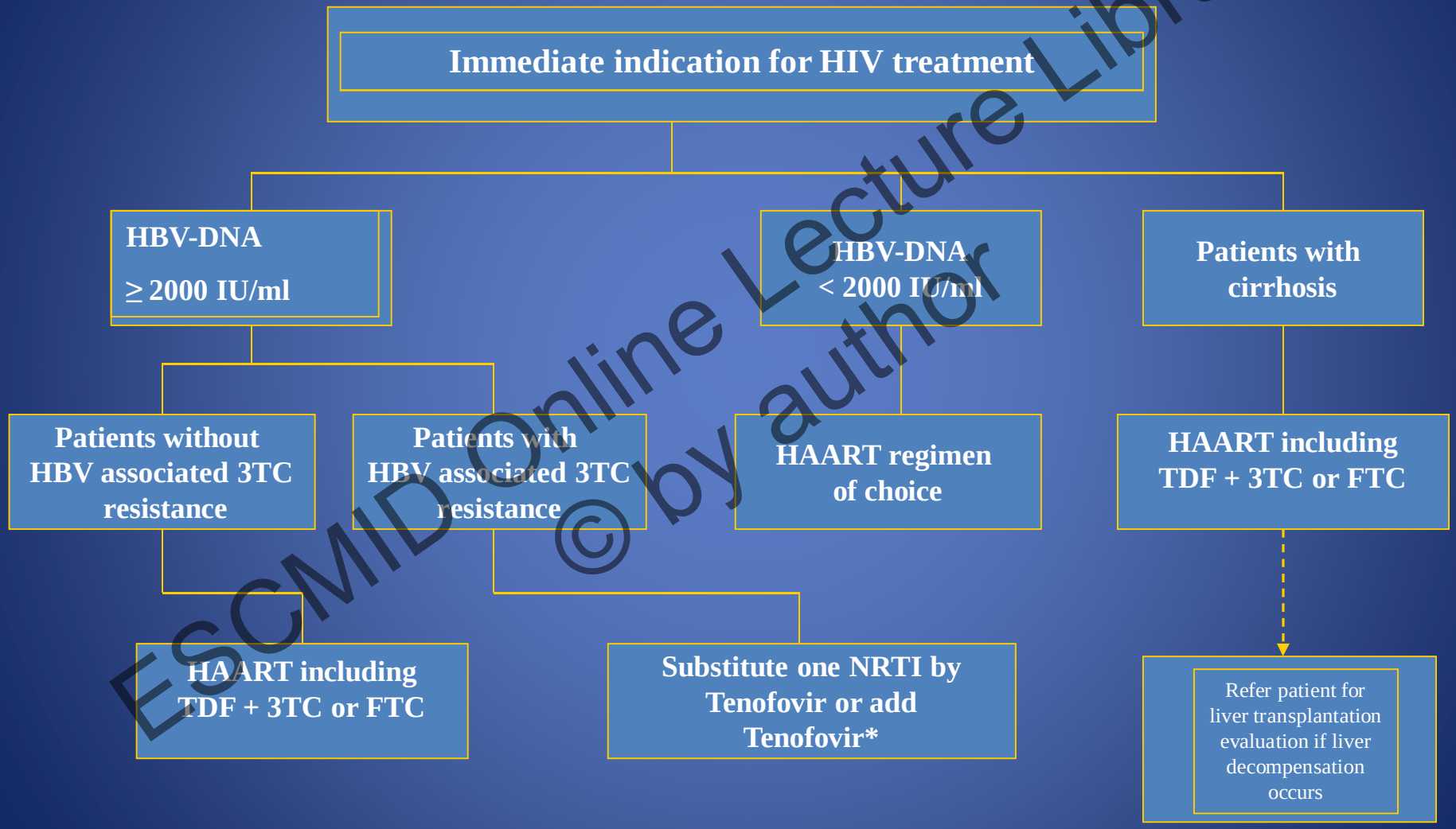
Treatment Algorithm:

Patients with Compensated Liver Disease and No indication for HIV therapy (CD4 count > 350/µl)



Soriano V, *et al. 4th IAS, Sydney* 2007, #MoBS104;
Benhamou Y, 3rd International Workshop on HIV and hepatitis coinfection, Paris 2007

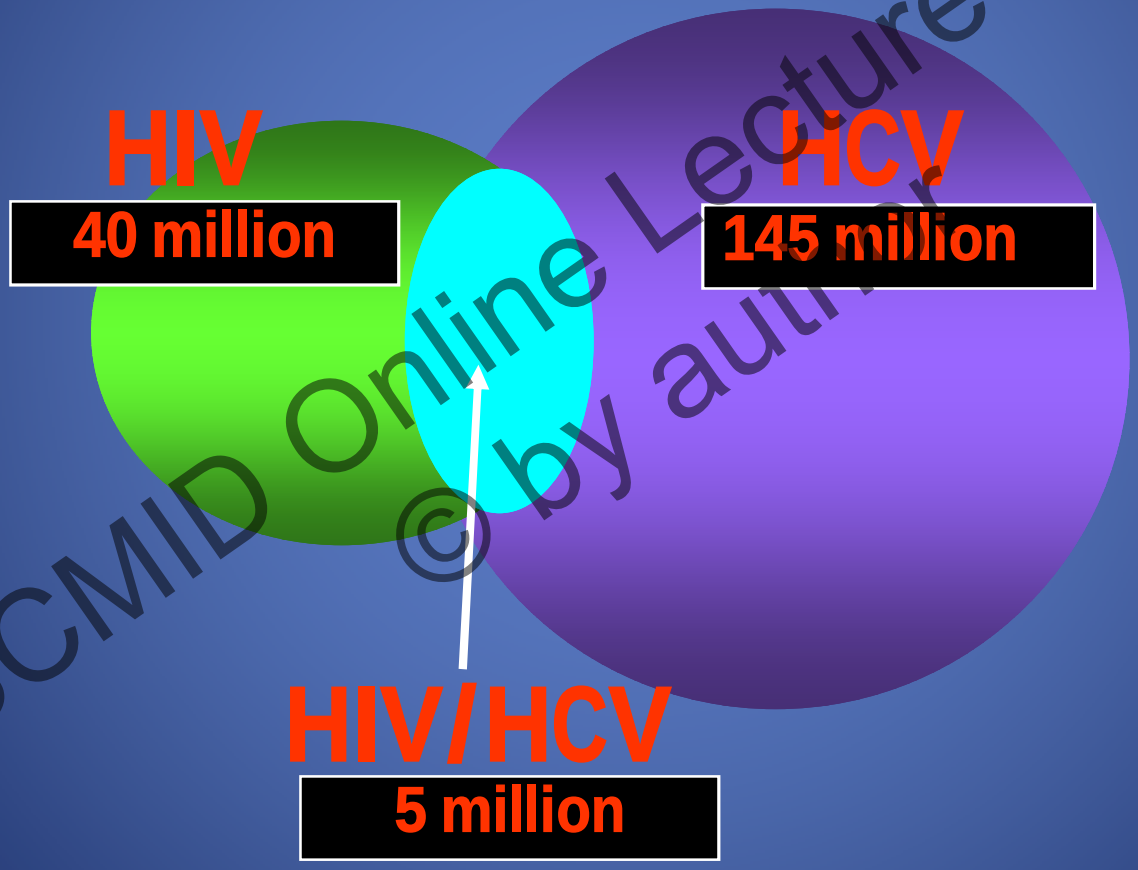
Management and therapeutic options in HIV-HBV co-infected patients with an indication of anti-HIV therapy



ECC Statement J Hepatol 2005

*if feasible and appropriate from the perspective of maintaining HIV suppression

HIV/HCV co-infection



Alter MJ. J of Hepatology. 2006
UNAIDS, WHO. 2006

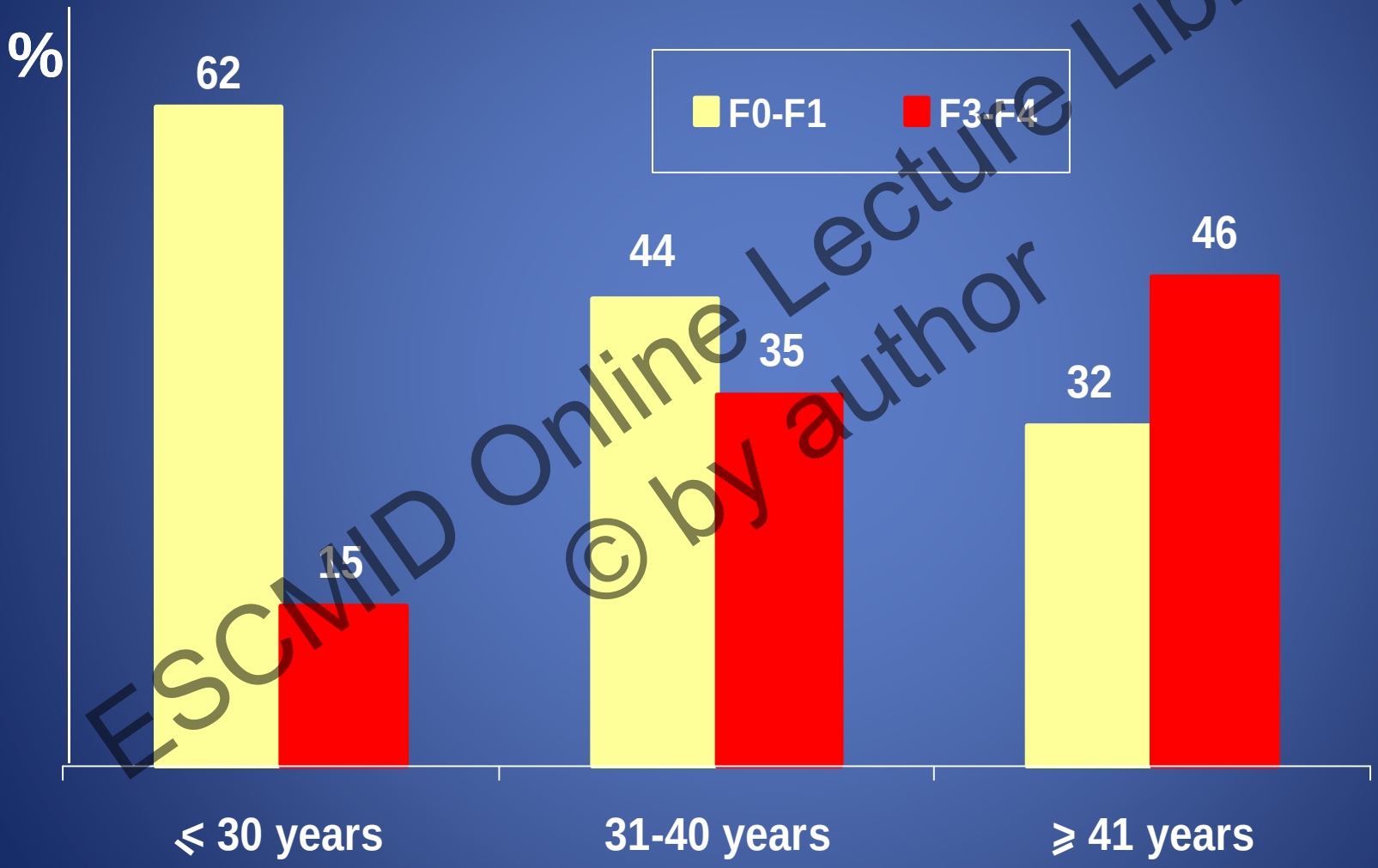
Treating HCV is Increasingly Important for Improved Survival in HIV/HCV-Coinfected Patients

- **HCV coinfection adversely impacts HAART efficacy**
  - **Increased risk of antiretroviral drug-associated hepatotoxicity and drug discontinuation**
  - **Decreased likelihood of CD4+ cell increases during HAART[1]**
- **HIV accelerates time to HCV-related liver disease**
  - **Faster time to cirrhosis[2-3]**
  - **Faster time to HCC[4]**

1. Braitstein P, et al. 2nd IAS Conference on HIV Pathogenesis and Treatment. 2003
2. Soto B, et al. J Hepatol. 1997
3. Mohsen A. Gut. 2003
4. Giordano T, et al. 2nd IAS Conference on HIV Pathogenesis and Treatment. 2003

HIV influence

914 HIV/HCV patients with CCH and elevated ALT



Martin-Carbonero et al. CID 2004; 38: 128-33.

HIV influence

- Higher HCV RNA
- More rapid progression of the disease (i.e. fibrosis)
- Higher incidence of hepatocellular carcinoma in young age
- 25% of co-infected individuals develop cirrhosis in 15 years (*vs* 5% in VIH-)*

**Sanchez QA, EJCMID, 1995; 14:949-53*

HCV treatment – ideal candidate?

- All co-infected patients with detectable HCV RNA
- CD4 > 350 cells/mm3
- Individualize treatment
- Take into account other factors

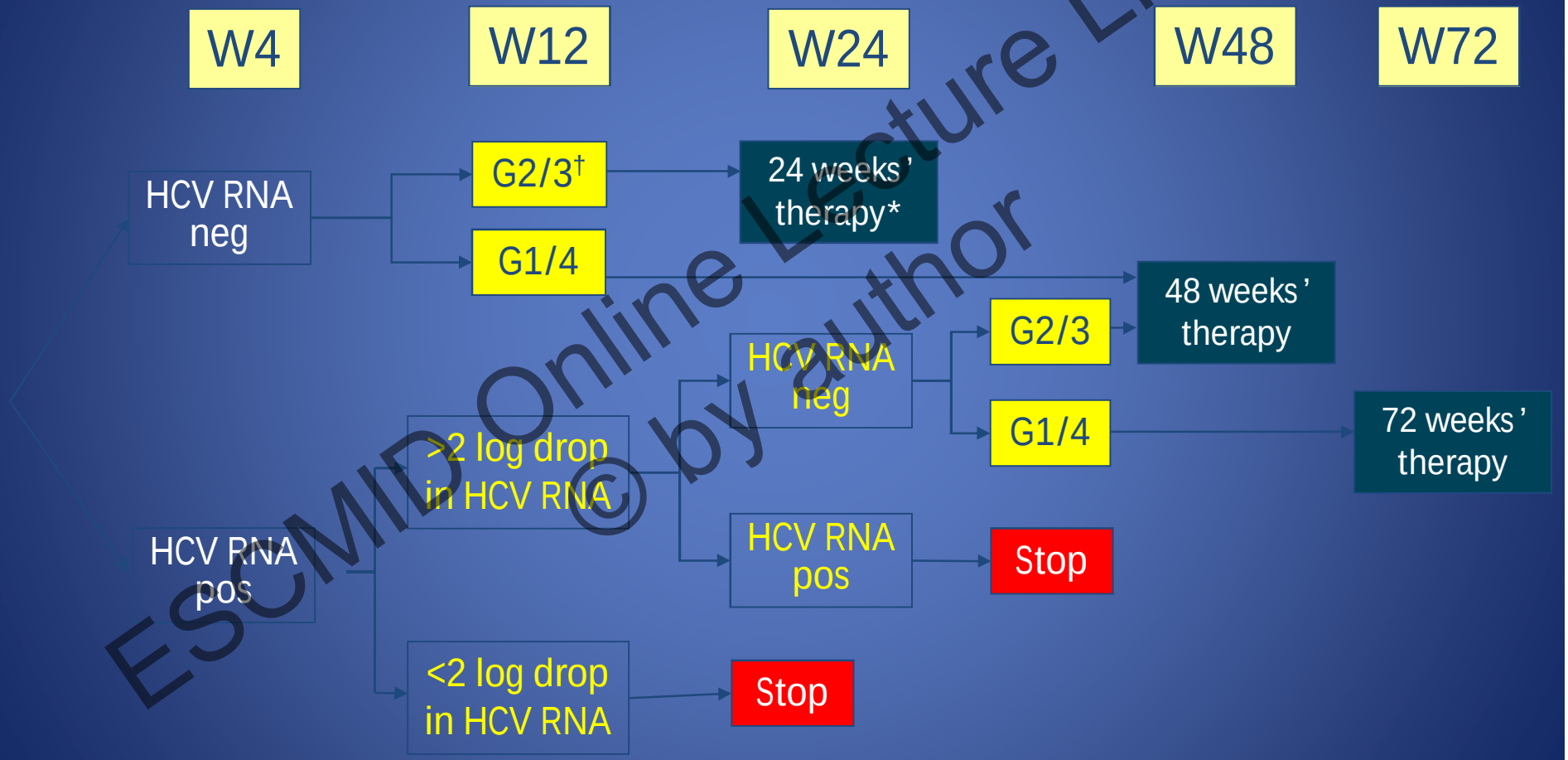
HCV treatment

PEGIFN alpha 2a/2b /weekly

+

Ribavirin 1000 or 1200 mg/daily (< 75 >Kg)

Current Algorithm for HCV Therapy in HIV Co-infected Patients



International Panel. *AIDS* 2007;21:1073–89.

**In patients with baseline low viral load and minimal liver fibrosis.*
†G1–G4 refer to genotypes 1–4

Drug interactions

- Didanosine - Contraindicated
- Zidovudine – avoid
- Stavudine - avoid

Conclusions

- Important messages:

  -immunosupression facilitates hepatitis reactivation, chronicity and histological impairment

  -early recognition of these conditions is crucial

  -prophylactic and therapeutic measures should be taken to ameliorate the prognosis of these patients