

Clinical Management of Chronic Hepatitis B in HIV-Infected Patients

Vincent Soriano

Department of Infectious Diseases

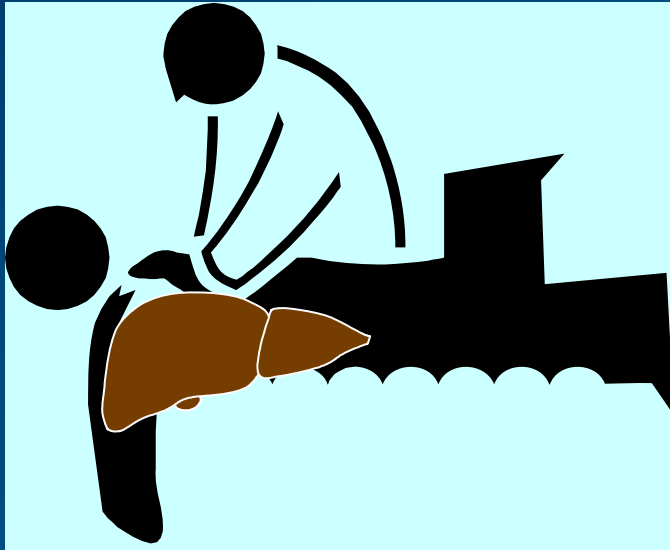
Hospital Carlos III

Madrid, Spain

Hot topics in HBV/HIV care in 2007

- Use of new diagnostic and monitoring methods.
- When to treat and which anti-HBV drugs to use?
- Delta hepatitis.
- HBV and HCV dually infected patients.

HBV care in the old times



Diagnostic procedures:

- Liver enlargement
- Aminotransferases
- Serology (HBsAg, HBeAg)
- Liver biopsy

Treatment approach:

- Stop drinking
- Avoid spicy meals
- relaxing lifestyle

Confronting chronic hepatitis B virus infection in HIV: new diagnostic tools and more weapons

Vincent Soriano, Julie Sheldon, Belén Ramos and Marina Núñez

AIDS 2006, **20**:451–453

- Viral load
- Genotypes
- Resistance
- FibroScan

- LAM/FTC
- adefovir
- entecavir
- telbivudine
- tenofovir

Impact of HBV-DNA Suppression

HBV-DNA (cop/ml)	Clinical outcome
$< 10^5$	Less liver inflammation
$< 10^4$	Durable response of HBeAg loss
$< 10^3$	Reduced emergence of resistance
BLD	HBsAg loss (\rightarrow & \downarrow)

1 IU/ml = 5 cop/ml

Cirrhosis: Iloeje et al. *Gastroenterology* 2006;130:678-86.

Liver cancer: Chen et al. *JAMA* 2006;295:65-73.

Nuñez et al. *Lancet Infect Dis* 2005;5:374-82.

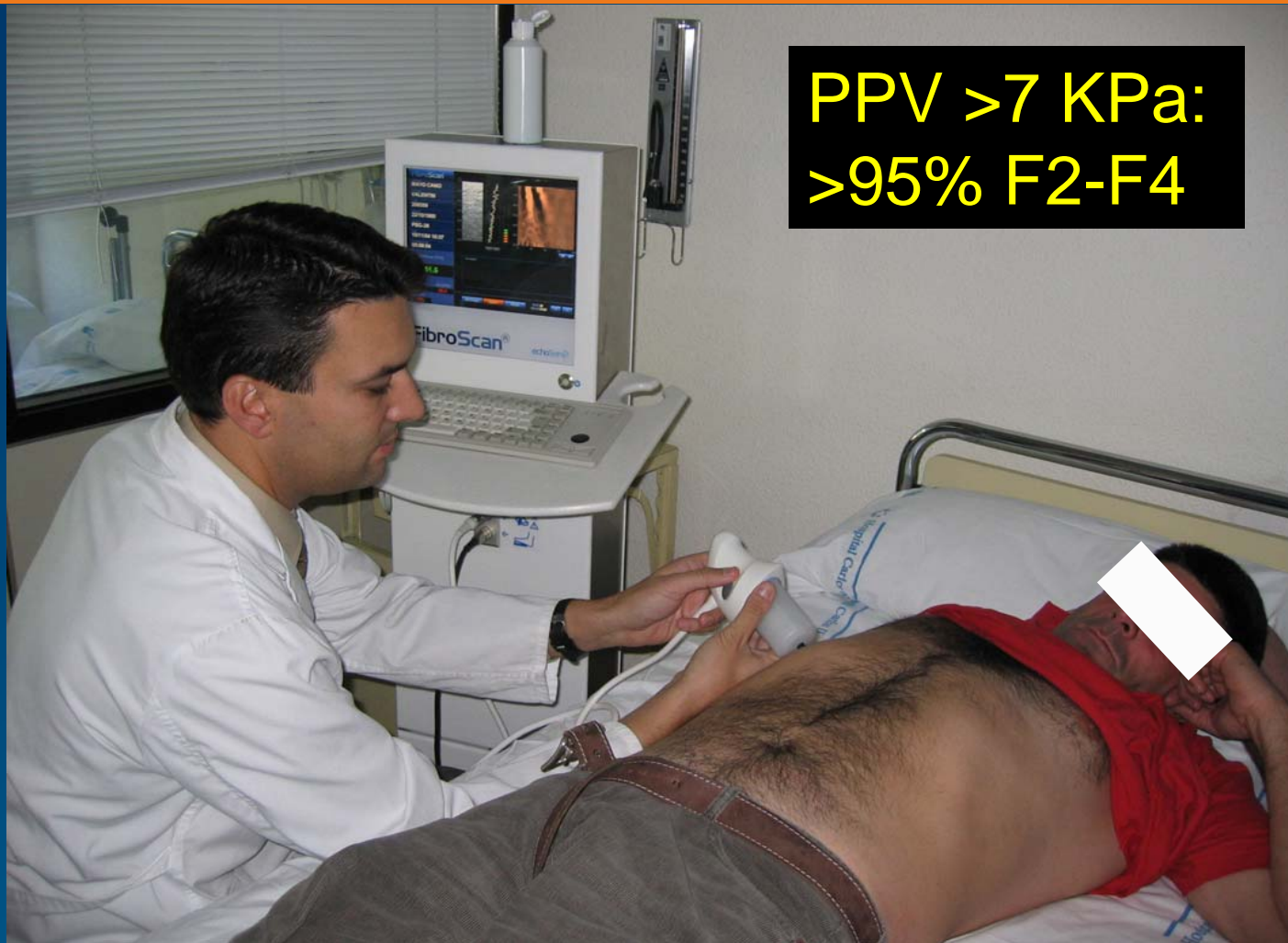
HBV genotypes (8)

<u>Genotype</u>	<u>Region</u>	<u>Comments</u>
A	Northern America Northern Europe India, Africa	More sensitive to IFN ↑ALT more frequently More rapid 3TC resistance
B	Asia	More benign More sensitive to IFN
C	Asia	More HCC
D	Southern Europe Middle East, India	Less response to IFN
E	West & South Africa	
F	Central & South America	
G	USA and Europe	
H	Central America, California	

Kramvis et al. J Viral Hepat 2005; 12: 456-64.

Schaefer et al. Hepatol Res 2007; 37 (suppl): 20-6.

Liver fibrosis assessment



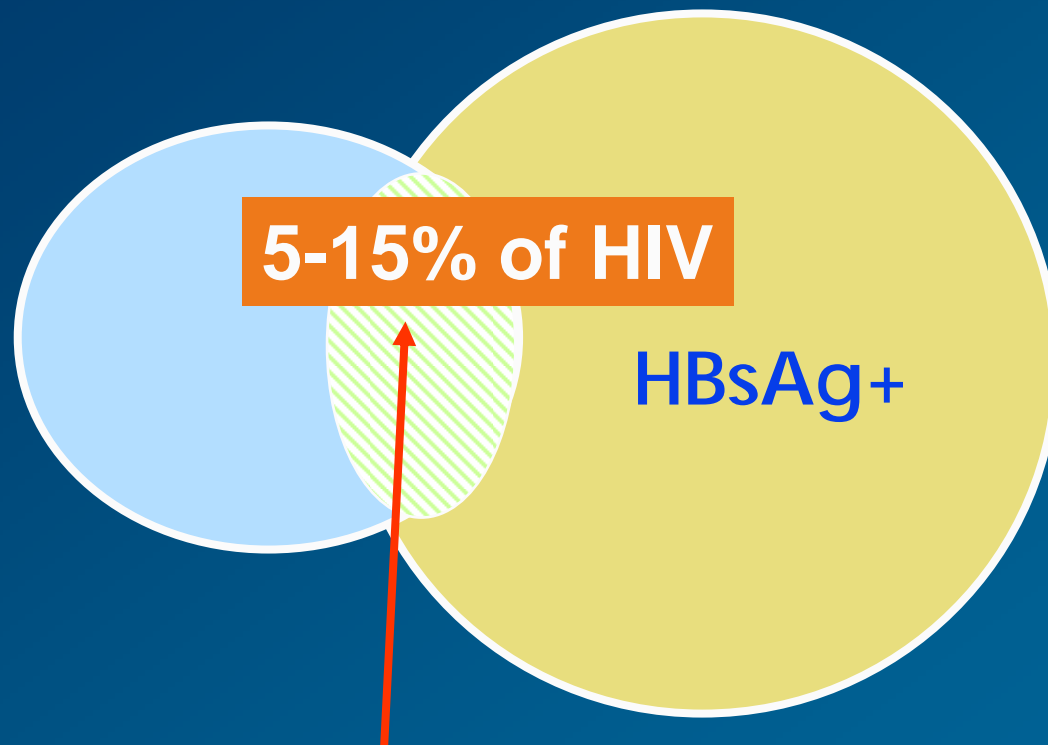
Ziol et al. Hepatology 2004
Castera et al. Gastroenterology 2005
Colletta et al. Hepatology 2005

FibroScan

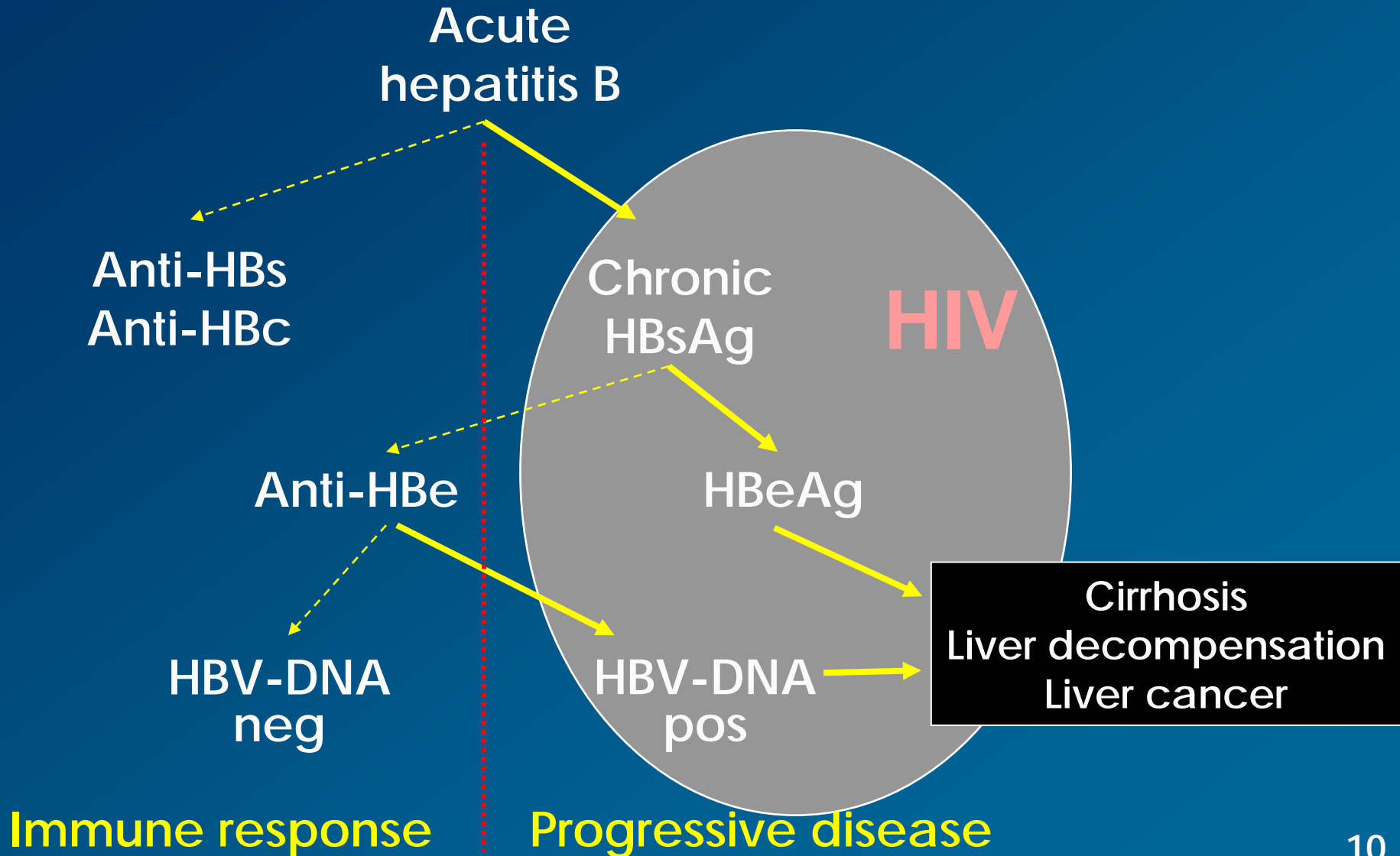
The Treatment of HBV in HIV-infected Persons is a Priority

- Co-infection is common
- Deleterious influence of HIV infection on chronic hepatitis B
 - More rapid progression of liver disease
 - Increased risk of liver-related mortality
 - Higher risk of HAART-related hepatotoxicity
- Guidelines for the treatment of HBV in HIV-coinfected patients
- Therapeutic agents for HBV treatment in co-infected patients

Overlapping HBV & HIV Epidemics



Natural history of HBV infection & effect of HIV



EuroSIDA: Clinical Progression and Mortality HBsAg+ vs. HBsAg-

Univariate and **multivariate** analysis

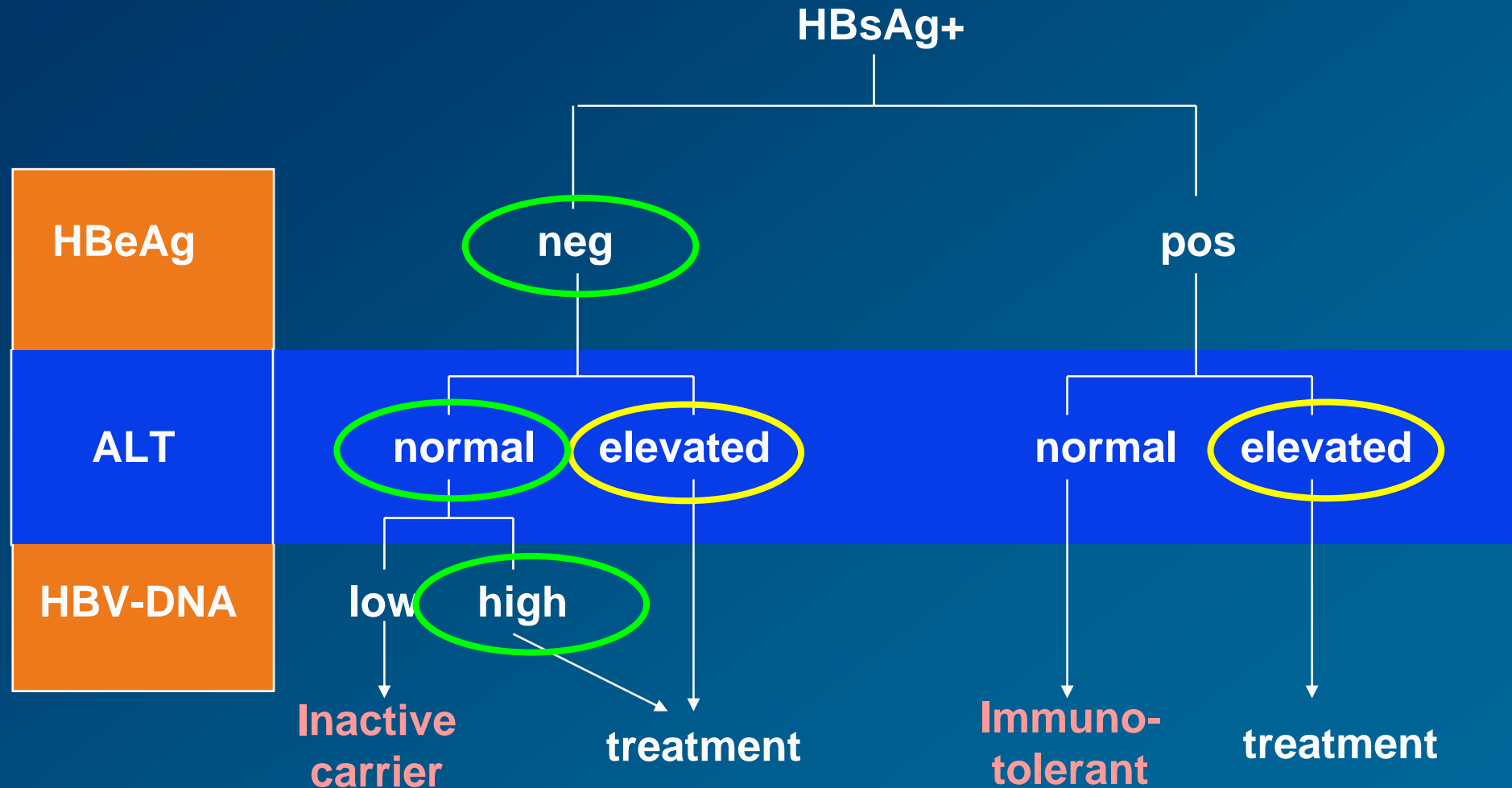
	Incidence rate ratio	95% CI	p
New AIDS	1.02	0.82-1.27	0.88
	0.96	0.73-1.27	0.79
Global mortality	1.48	1.19-1.83	0.0004
	2.02	1.48-2.77	<0.0001
Liver-related mortality	3.52	1.95-6.35	<0.0001
	4.15	1.97-8.77	0.0002

EASL HBV Guidelines

- ALT ↑ > 2-fold
- HBeAg+
- HBV-DNA > 10^5 copies/mL

In all these situations, advanced hepatic damage and/or accelerated liver disease progression occurs

AASLD HBV treatment algorithm



Therapeutic Agents Available for HBV

Registered

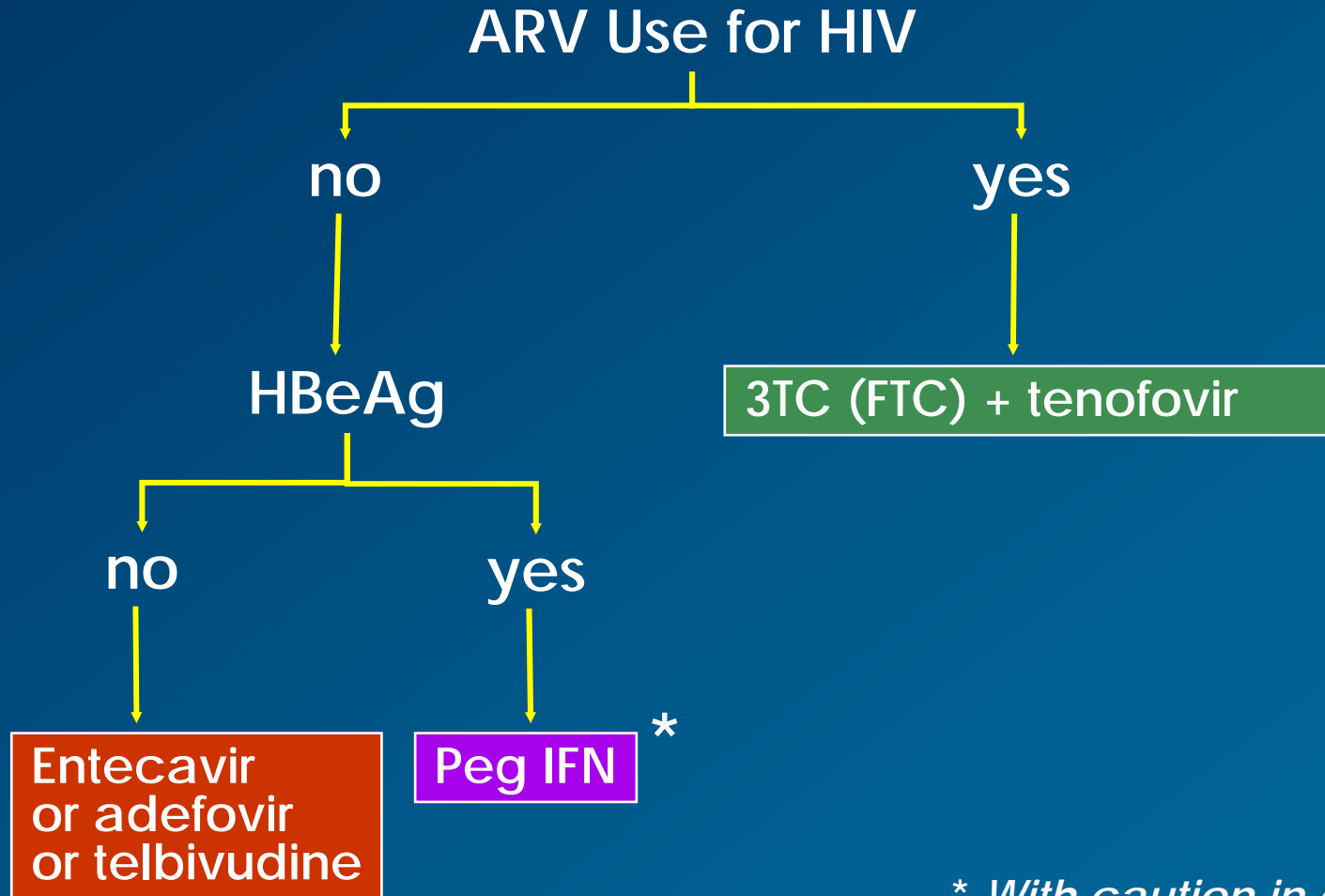
- Interferon-alpha
- PEG-Interferon
- Lamivudine
- Adefovir
- Entecavir
- Telbivudine (L-dT)
- (Emtricitabine) †
- (Tenofovir) †

Under Development

- Clevudine (L-FMAU)

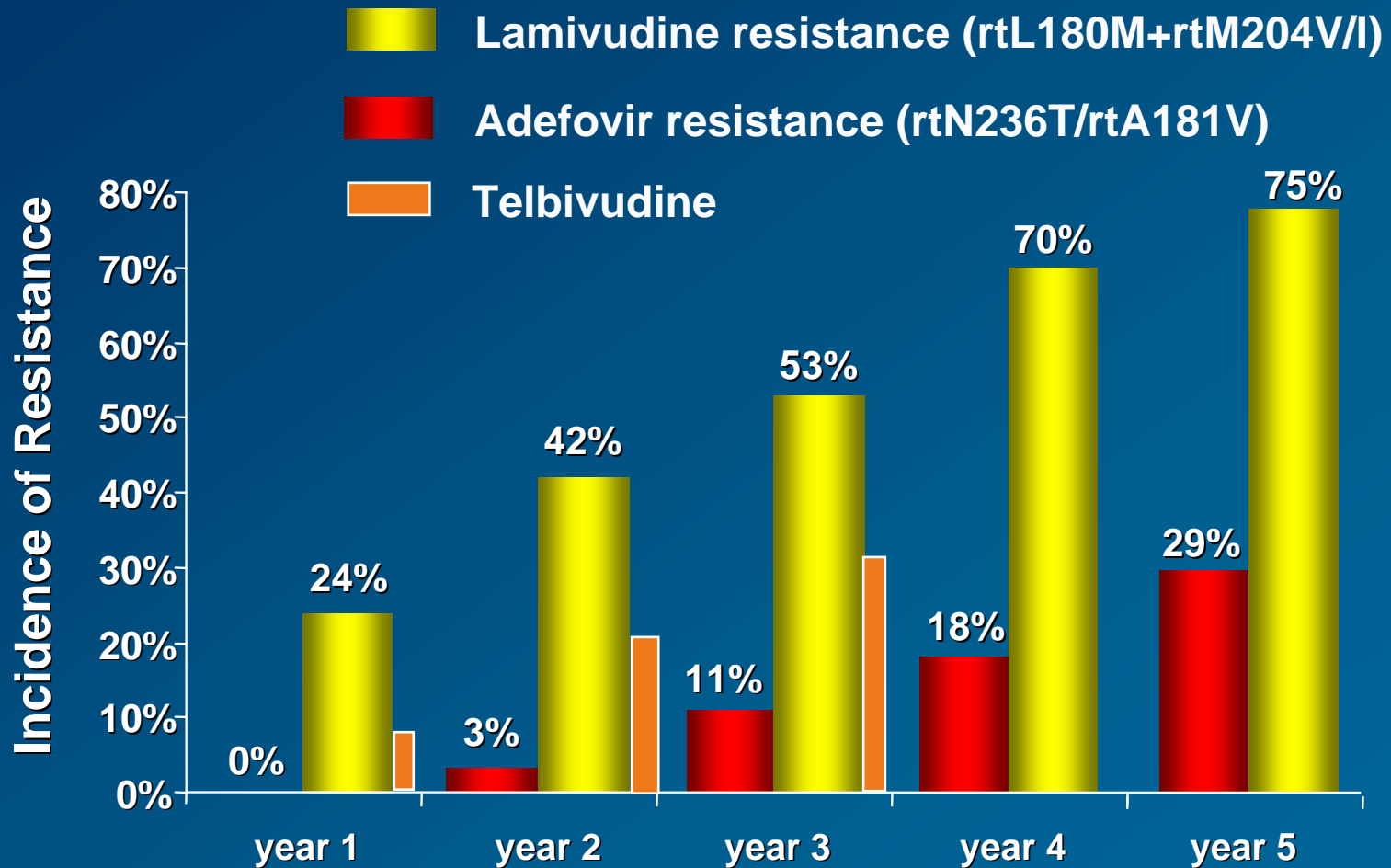
† Licensed for the treatment of HIV, but also have anti-HBV activity.

Preferred Anti-HBV Agents in HBV/HIV-Coinfected Patients



* *With caution in cirrhotics*

Incidence of HBV Resistance



Transmission of 3TC-Resistant HBV

- ♦ 28-year old homosexual men
- ♦ not previously vaccinated against HBV
- ♦ typical acute hepatitis
- ♦ incubation period of 2-3 months
- ♦ Virus with rtL180M plus rtM204V
- ♦ lower viral replication level during acute phase

Adefovir

- Effective in the long term
 - HBsAg seroconversion in 2% per year ¹
 - HBeAg seroconversion is durable in >90% ²
- Selection of resistance: slowly and at low rate
 - N236T and/or A181V appear in 29% at 5 years.
- No/poor activity in 5% of patients ³
- No selection of HIV resistance ⁴

1. Shiffman et al. *J Hepatol* 2004; 40 (suppl 1): 17.

2. Chang et al. *J Hepatol* 2004; 12 (suppl 1): 126.

3. Schildgen et al. *NEJM* 2006; 354: 1807-12.

4. Sheldon et al. *AIDS* 2005; 19: 2036-8.

Reasons to fail Adefovir

- **Low antiviral activity +/- Poor drug exposure**
- **Polymorphisms causing natural resistance (I233V)**
- **LAM cross-resistance (A181T/V)**
- **HBV genotype A2 (L217R)**

Schildgen et al. NEJM 2006; 354: 1807-12.

Chang et al. NEJM 2006; 355: 322-3.

Schildgen et al. AIDS 2004; 18: 2325-7

Entecavir

- 50 HBV/HIV-coinfected patients with prolonged exposure to lamivudine
- 3TC resistance mutations in HBV documented in 48
- 9% achieved undetectable serum HBV-DNA
- 2 patients selected entecavir resistance mutations

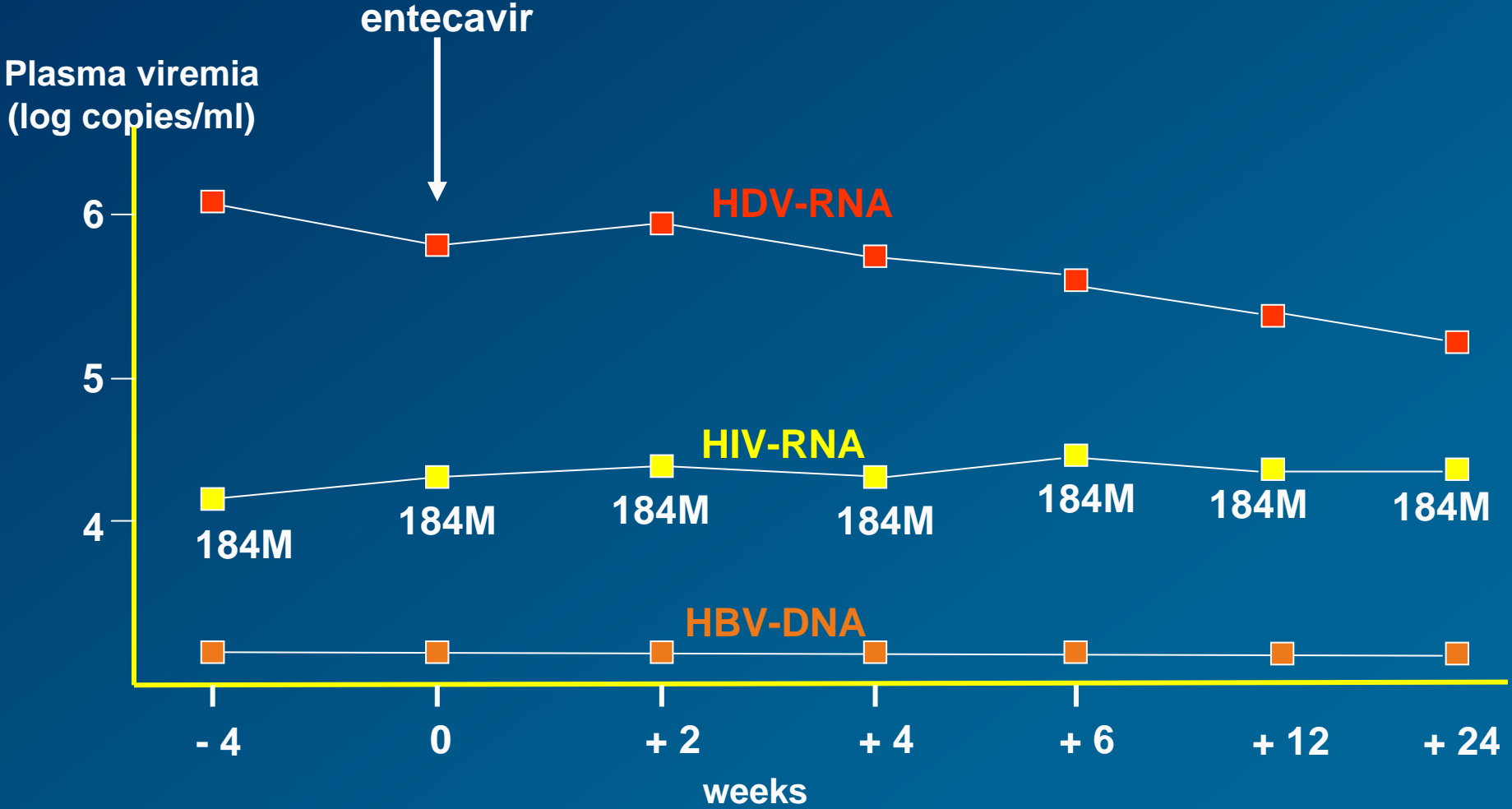
Serum HBV-DNA
(log copies/mL)



Entecavir in HIV/HBV patients

- 3 patients initiated ETV in the absence of HAART and showed ~1 log reduction in plasma HIV-RNA in parallel with a decline of ~ 5 logs in HBV-DNA.
- 1 patient showed an slow, steadily increase in M184V in the HIV population during the first 24 weeks of ETV therapy. He had been treated with lamivudine in the past. Another patient did not select M184V during 7 months of ETV monotherapy.
- Exposure of HIV-1 to ETV in viral culture showed that the drug was active against HIV-1.
- FDA warning: avoid ETV use without HAART in HIV/HBV patients.

Entecavir in an HIV patient with HIV/HBV/HDV coinfection



Nucleos(t)ide analogs used as antiviral agents

	Pyrimidine analogs		Purine analogs	
	Cytidine	Thymidine	Adenosine	Guanosine
HIV	3TC FTC ddC	AZT d4T	ddl TDF	Abacavir
HBV	3TC FTC Clevudine	Telbivudine	Adefovir	Entecavir
HCV				Ribavirin
CMV	Cidofovir			Gancyclovir
Herpes		Trifluridine	Vidarabine	Famcyclovir Acyclovir Valacyclovir

Tenofovir

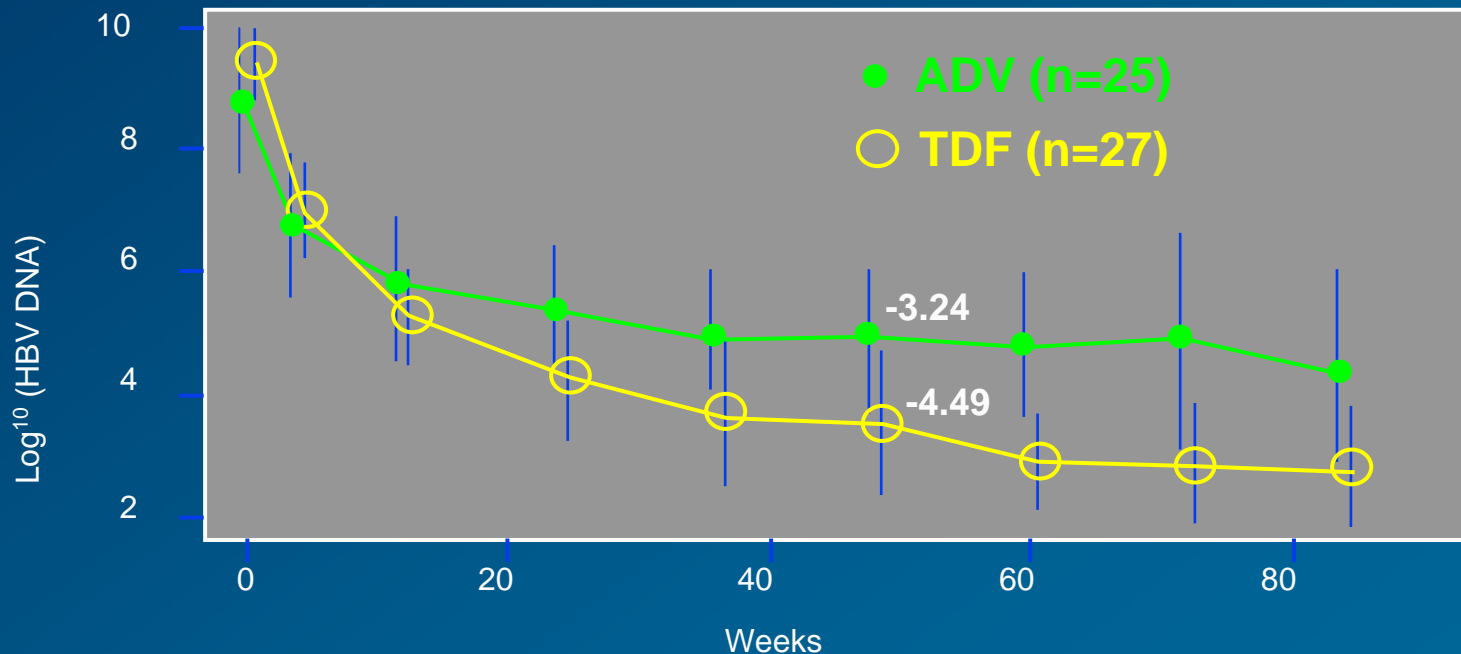
Study	No. of patients	Week 12*	Week 24*
Núñez et al.	12	-	- 3.78
Nelson et al.	15	- 2.47	- 3.15
Bochet et al.	11	- 3.11	- 3.67
Cooper et al.	12	-	-4.40
Ristig et al.	6	- 3.10	- 4.30
Portsmouth et al.	20	-	- 4.00

* Serum HBV-DNA \log_{10} decrease

Tenofovir vs Adefovir

- Not licensed for the treatment of HBV
- Non-inferior to ADV in a randomized trial in HBV/HIV co-infected patients.

Mean change in serum HBV-DNA



Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir

Julie Sheldon¹, Nuria Camino¹, Berta Rodés¹, Angeline Bartholomeusz², Michael Kuiper³, Frank Tacke⁴, Marina Núñez¹, Stefan Mauss⁵, Thomas Lutz⁶, Gerd Klausen⁷, Stephen Locarnini² and Vincent Soriano^{1}*

¹Hospital Carlos III, Madrid, Spain

²Victorian Infectious Diseases Reference Laboratory, Victoria, Australia

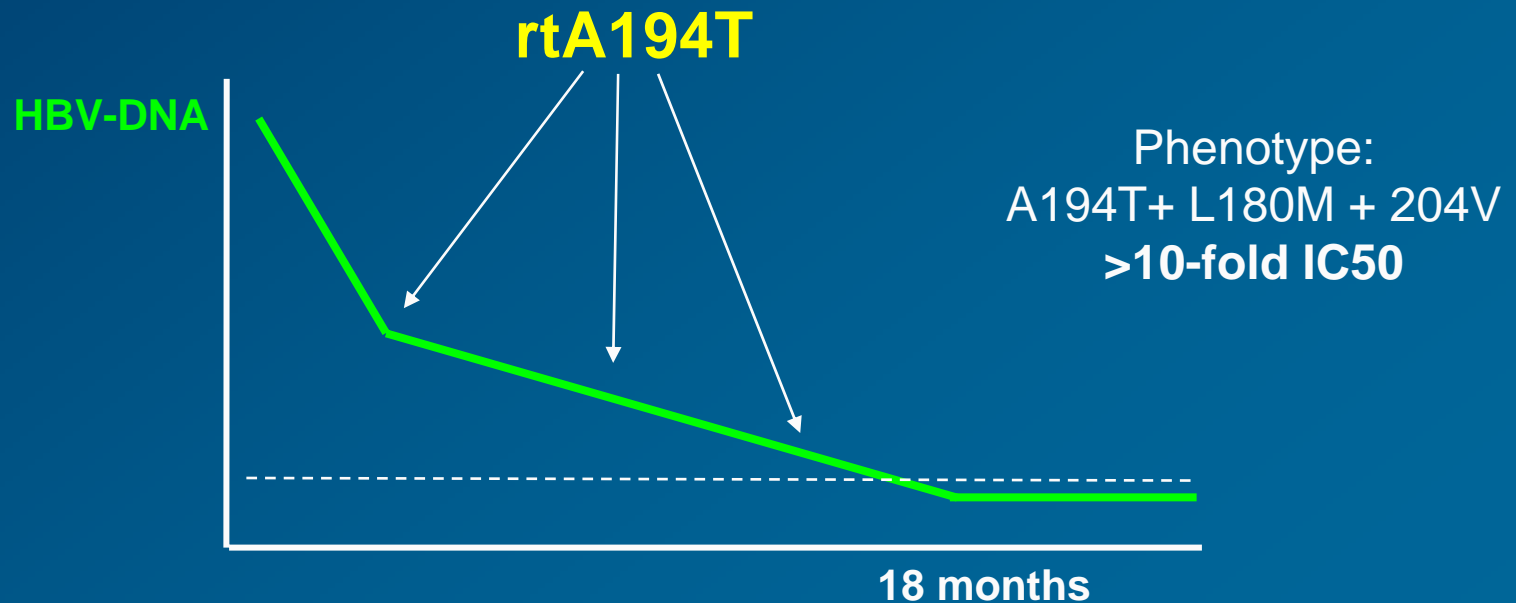
³Victorian Partnership for Advanced Computing, Victoria, Australia

⁴Department of Gastroenterology, Hepatology and Endocrinology, Hanover Medical School, Germany



⁵Center for HIV and Hepatogastroenterology, Dusseldorf, Germany

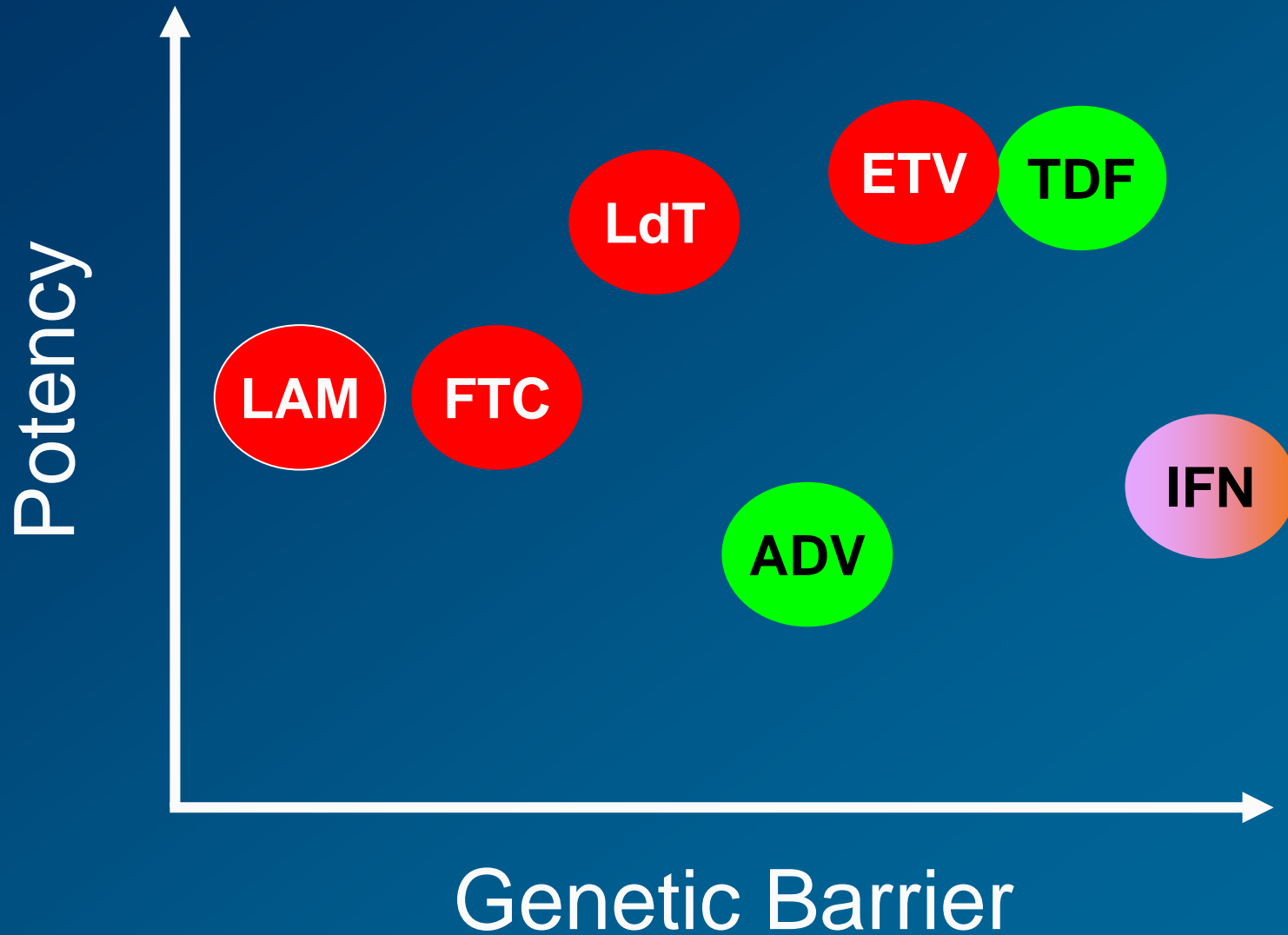
⁶HIV-Kohorte Frankfurt, Germany

⁷Praxiszentrum Kaiserdamm, Berlin, Germany



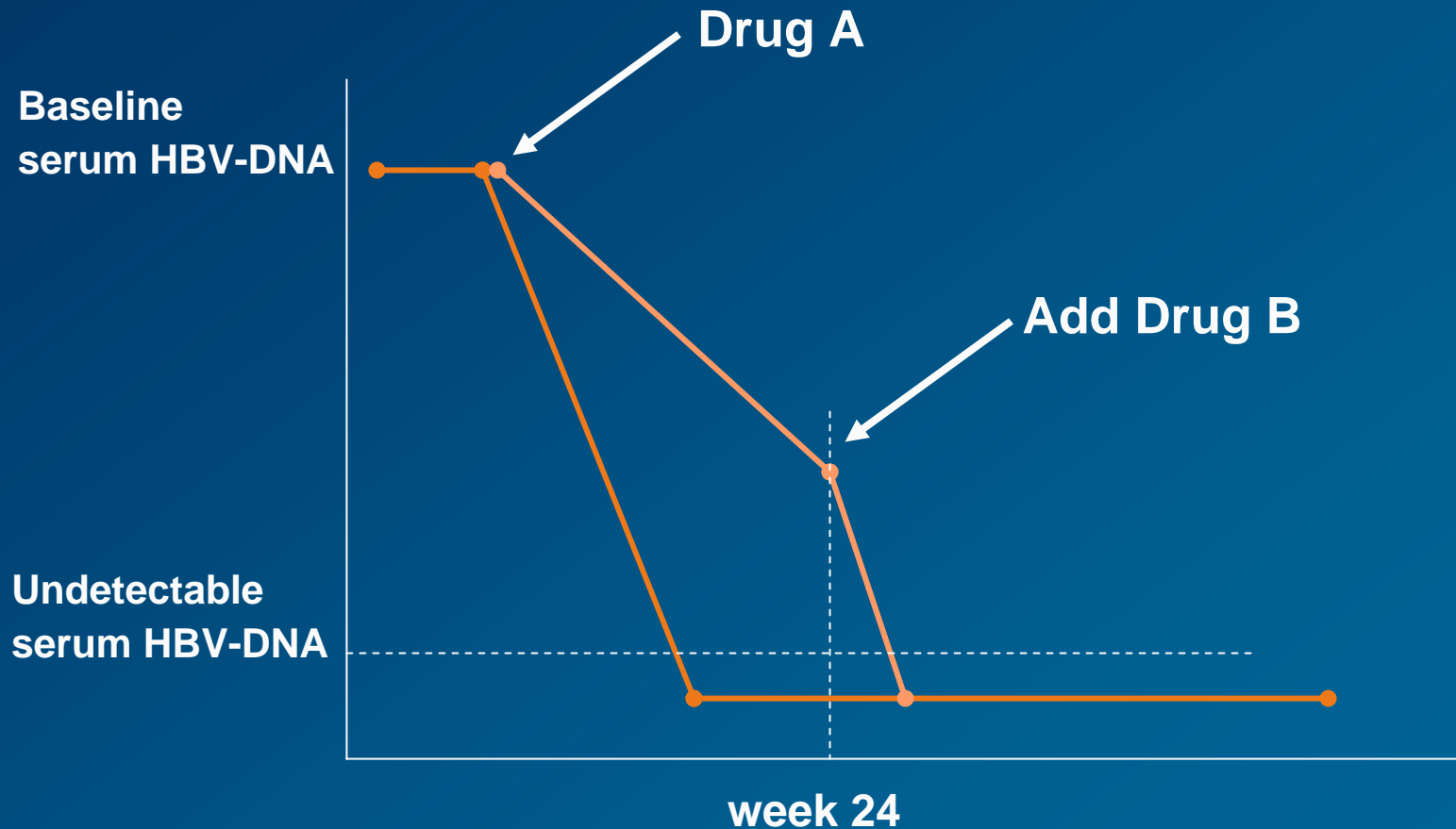
Anti-HBV Drugs

-  Nucleoside analogue
-  Nucleotide analogue



Initial treatment approach for HBV

The principle of “very early add-on therapy” to keep viral load as low as possible



Virological Outcome of Chronic Hepatitis B Virus Infection in HIV-Coinfected Patients Receiving Anti-HBV Active Antiretroviral Therapy

MARINA NÚÑEZ, BELÉN RAMOS, BEATRIZ DÍAZ-POLLÁN, NURIA CAMINO,
LUZ MARTÍN-CARBONERO, PABLO BARREIRO, JUAN GONZÁLEZ-LAHOZ,
and VINCENT SORIANO

ABSTRACT

The immune suppression caused by HIV infection accelerates the course of liver disease caused by chronic hepatitis B virus (HBV) infection. We assessed the outcome of HIV/HBV-coinfected patients exposed to highly active antiretroviral therapy (HAART) including anti-HBV active drugs. Baseline and follow-up plasma HBV-DNA and HIV-RNA levels, HBV serological markers, and CD4 counts were longitudinally evaluated in all HBsAg⁺ individuals with HIV infection on regular follow-up at an urban HIV reference clinic. Out of 79 HBsAg⁺ chronic carriers identified, 39 (50%) were HBeAg⁺. Lamivudine (3TC) alone had been received by 37% of patients, while 3TC plus tenofovir (concomitantly or consecutively) had been taken by 58% of them. The median follow-up was of 52 months. Loss of HBeAg or HBsAg occurred in 28% (10/36) and 13% (10/75) of patients, respectively. In multivariate analysis, only undetectable plasma HIV-RNA levels [OR 4.58 (95% CI 1.25–16.78); $p = 0.02$] and greater CD4 gains on HAART [OR 1.003 (95% CI 1.000–1.006); $p = 0.03$] were associated with undetectable serum HBV-DNA at the end of follow-up. Anti-HBV active HAART makes it possible to achieve HBsAg clearance, anti-HBe seroconversion, and suppression of HBV replication in a substantial proportion of HBV/HIV-coinfected patients, particularly in those with complete HIV suppression and greater immune recovery. Thus, HBV/HIV-coinfected patients might benefit from an earlier introduction of HAART.

AIDS RESEARCH AND HUMAN RETROVIRUSES 2006; 22: 842-848.

Co-infected patients treated with anti-HBV HAART: >50% no or minimal liver fibrosis

Liver Fibrosis in HIV-Infected Patients with Chronic Hepatitis B Extensively Exposed to Antiretroviral Therapy with Anti-HBV Activity

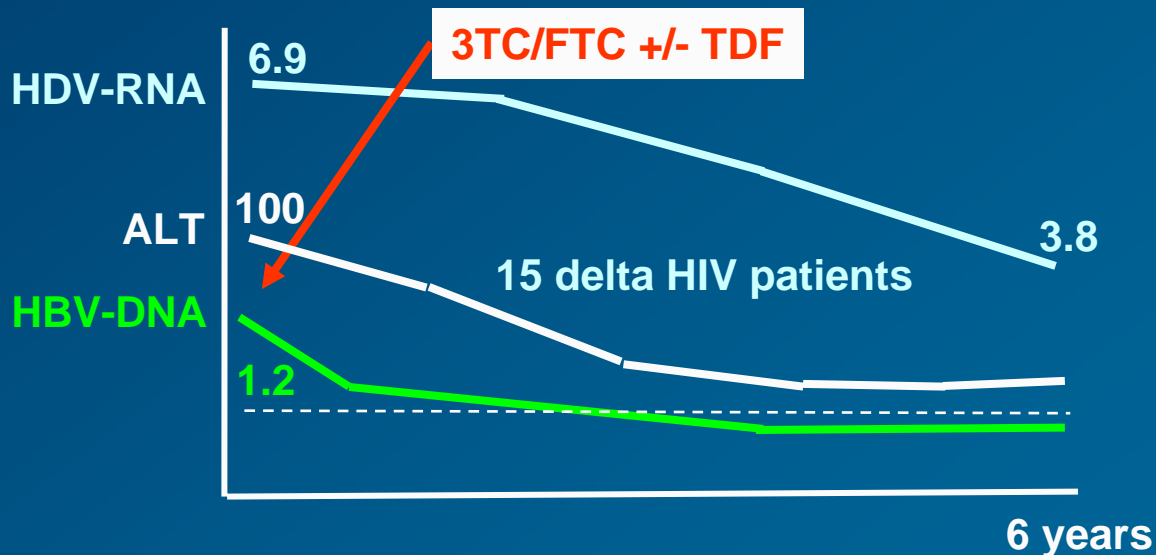
Ivana Maida, MD,^{1,2} Vincent Soriano, MD, PhD,¹ Carol Castellares, MD,¹ Belén Ramos, MD,¹ Giovanni Sotgiu, MD,² Luz Martin-Carbonero, MD, PhD,¹ Pablo Barreiro, MD, PhD,¹ Pablo Rivas, MD,¹ Juan González-Lahoz, MD, PhD,¹ and Marina Núñez, MD, PhD¹

¹Service of Infectious Diseases, Hospital Carlos III, Madrid, Spain; ²Istituto Malattie Infettive, University of Sassari, Sassari, Italy

Purpose: The extent and predictors of liver fibrosis were examined in a HIV/HBV-coinfected cohort with extensive exposure to anti-HBV active HAART. **Method:** Liver fibrosis was measured using transient elastography. **Results:** Thirty-seven patients of a median age of 43 were included in the study. All but 2 patients had received anti-HBV drugs for a median time of 40 months in the context of HAART. F0-F1 METAVIR fibrosis scores (minimal or no fibrosis) as measured by elastography were found in 21 (57%) patients. AST levels were significantly lower among F0-F1 patients (33 IU/L) compared to F2-F4 patients (48 IU/L) ($p = .01$). ALT levels were also lower in F0-F1 patients (38 IU/L) than in F2-F4 patients (54 IU/L) ($p = .05$). **Conclusion:** In this HIV/HBV-coinfected cohort, with extensive HAART exposure including anti-HBV agents, more than half of the patients had no or minimal liver fibrosis. Higher transaminase levels were recognized in patients with higher degree of fibrosis.

Delta virus

- Subviral satellite of HBV which uses HBsAg for genome encapsidation.
- Circular, single-stranded RNA molecule nearly 1,700 bp long.
- 5% of HBsAg carriers (15 million worldwide).
- Half of patients progress to liver cirrhosis within 20 years.
- HDV replication uses host polymerases.
- Intensive interferon therapy as the only treatment option - limited success.



Le Gal et al. Emerg Infect Dis 2006; 12: 1447-50

Sheldon et al. 3rd Coinfection Workshop, Paris, June 2007. Abstract 36

HBV – HCV dual infections in HIV

21 HIV / HBsAg+ / HCV Ab+ patients exposed to treatment for either HBV or HCV.

Serum virologic marker(s)	Subjects, no.	Treatment	Outcome
HCV RNA+ only	5	Pegylated IFN- α 2a plus ribavirin	Three subjects experienced HCV sustained virological response; no single rebound in HBV DNA
HBV DNA+ only	9	Lamivudine and/or tenofovir	No single rebound in HCV RNA
HCV RNA+ and HBV DNA+	2	Pegylated IFN- α 2a plus ribavirin	Negative for HBV DNA on anti-HBV therapy
		Lamivudine and/or tenofovir	Rebound in HCV RNA on completion of anti-HCV therapy in all
HCV RNA- and HBV DNA-	1	Lamivudine	No changes
HDV Ab+ only	3	Lamivudine and/or tenofovir	No changes in HDV serostatus; no rebound in HCV RNA
HDV Ab+ and HCV RNA+	1	Pegylated IFN- α 2a plus ribavirin	No changes in HDV serostatus
		Lamivudine and tenofovir	Rebound in HCV RNA on completion of anti-HCV therapy

Summary

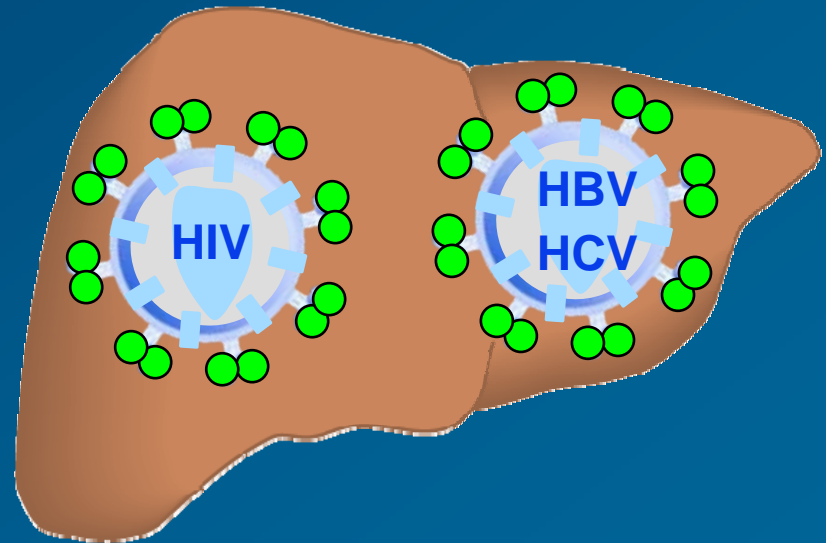
- **Chronic hepatitis B progresses faster in HIV.**
- **It increases the risk of hepatotoxicity of ARV agents.**
- **Treatment of HBV should be considered as a priority in HIV-infected persons.**
- **All HBV/HIV patients should be tested for viral load, genotype and liver fibrosis assessed by either non-invasive tools or biopsy.**
- **Don't use 3TC (FTC) as only anti-HBV agent up front.**
- **HBV treatment plan should be individualized, based on the need for HIV treatment and prior 3TC therapy.**
- **Stop and regression of advanced liver fibrosis can be seen with prolonged sustained suppression of HBV replication.**
- **Exclude delta hepatitis in all HBsAg+ patients.**
- **Treat active replicating virus in HBV-HCV dually infected patients.**

Closing remarks: HBV in HIV; a disease of neglect

- Review of 362 HBV/HIV-coinfected patients at the University of Texas Southwestern Medical Center.
- Only 16% had HBeAg and/or serum HBV-DNA testing at baseline, and only one third had these measurements before HAART.
- Among 162 patients who began HAART, the median number of HIV-RNA tests obtained at 1 year was 3. In contrast, for serum HBV-DNA was 0.
- The frequency of hepatic ultrasound was only 31%.
- Only 43% of cirrhotics had alpha-fetoprotein measurements.
- *Conclusion: “Their providers did much better in HIV care than in HBV care in coinfecting patients.”*

4th International Coinfection Workshop

Madrid, 19-21 June 2008



www.virology-education.com

Acknowledgments

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