

HEP DART 2005

frontiers in drug development for viral hepatitis

Co-infection with HIV/HBV/HCV

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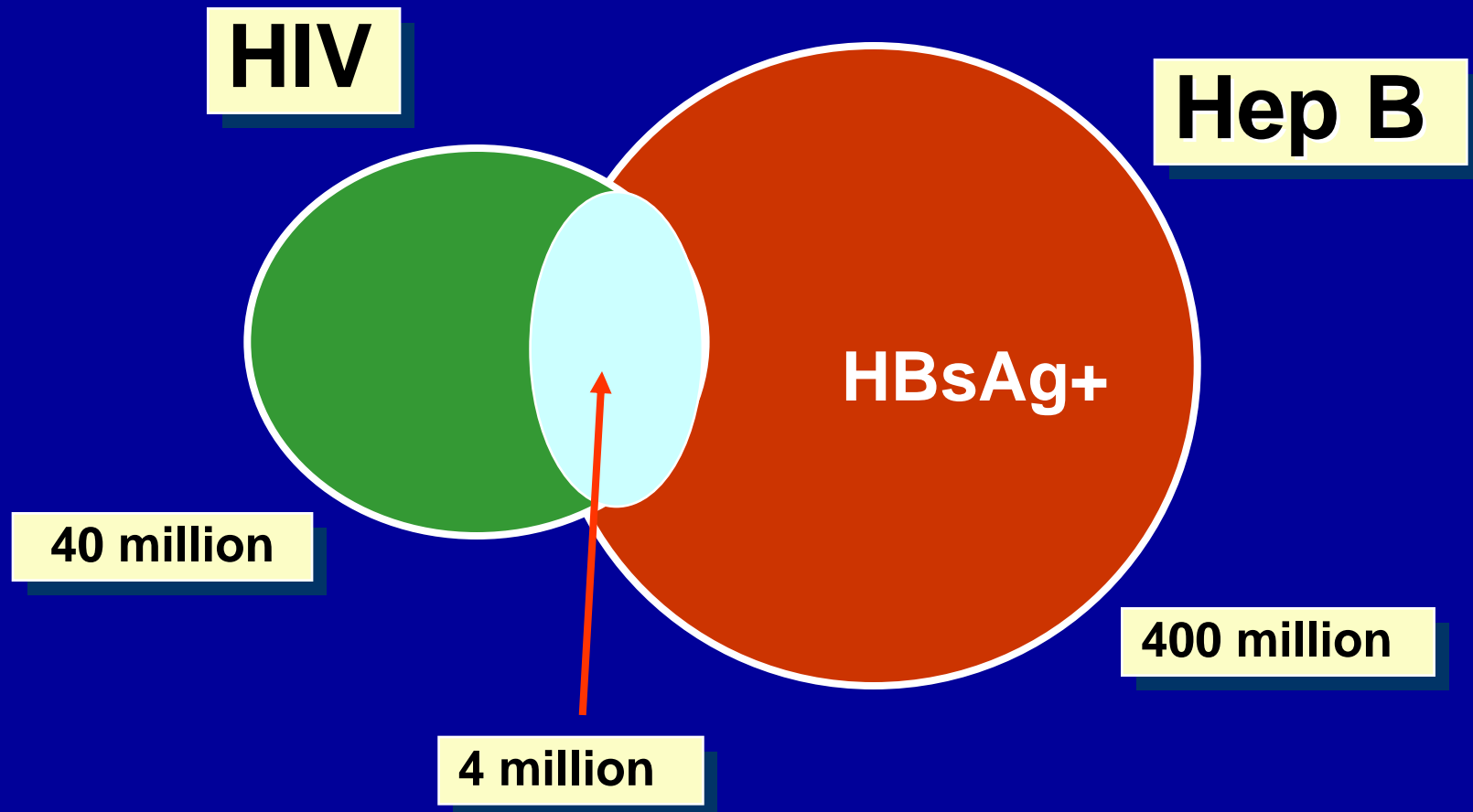
When and how to treat HIV/HBV co-infection

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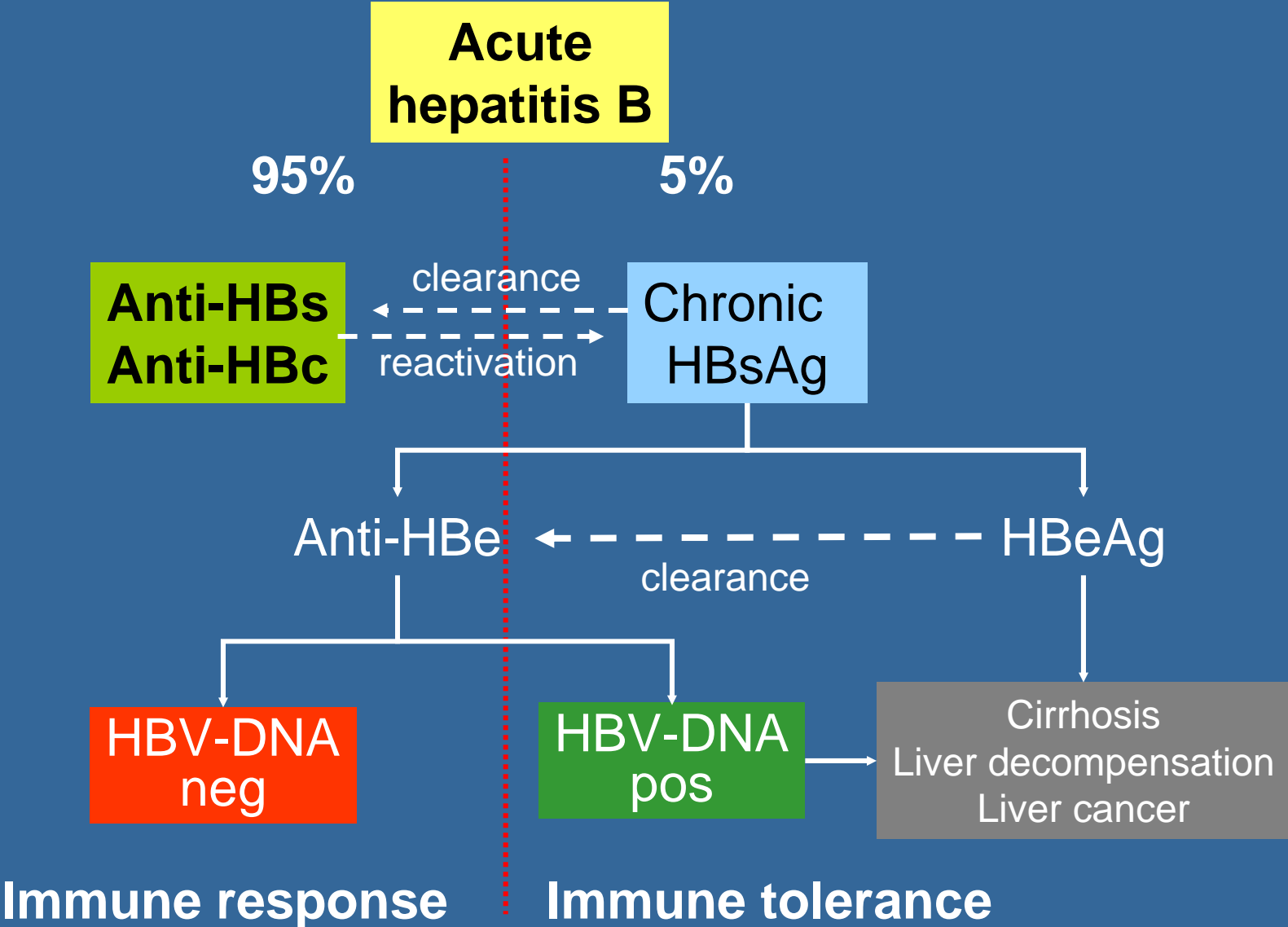
Global Burden of HBV Disease

- 2 billion people have evidence of current or past HBV infection
 - 300 million to 400 million people have chronic HBV disease
 - Geographic variation in disease prevalence
- Transmission of HBV infection by two routes
 - Vertical: mother to newborn child
 - Horizontal: infected blood products, sexual intercourse, intravenous drug use, other contaminated needles
- Age at infection is a major determinant of future chronic HBV progression

Overlapping HBV & HIV Epidemics



Natural history of HBV infection



Interaction between HIV & HBV

- both share common routes of infection with 60 - 70% of HIV patients showing evidence of previous HBV exposure
- depending on the population surveyed, between 5 – 10% of HIV patients are surface antigen positive
- As survival of HIV infected patients improves with the introduction of HAART, incidence of long-term complications of HBV is increasing

Impact on natural history of each

HBV influence on HIV

- Increases HIV replication
- Increases HAART-related hepatotoxicity
- Decreases CD4 cell counts in cirrhosis with hypersplenism
- Decreases CD4 cell counts due to HBV infection itself?

Impact on natural history of each

HIV influence on HBV

- Increases HBV chronicity
- Increases HBV replication
- Decreases anti-HBe and anti-HBs seroconversion
- Increases hepatitis flares
- Increases progression to cirrhosis
- Increases hepatocellular carcinoma?
- Diminishes efficacy of anti-HBV treatment
- Decreases response to interferon- α
- Increases lamivudine resistance mutations

HIV/HBV Co-infection: natural course of hepatitis B

- HIV patients are 3-6 times more likely to become chronic carriers of hepatitis B than those who are HIV negative
- Hepatitis B in HIV is characterized by an increased frequency of markers of HBV-replication
- mostly normal or only slightly elevated liver enzymes

HBV vaccine response rate

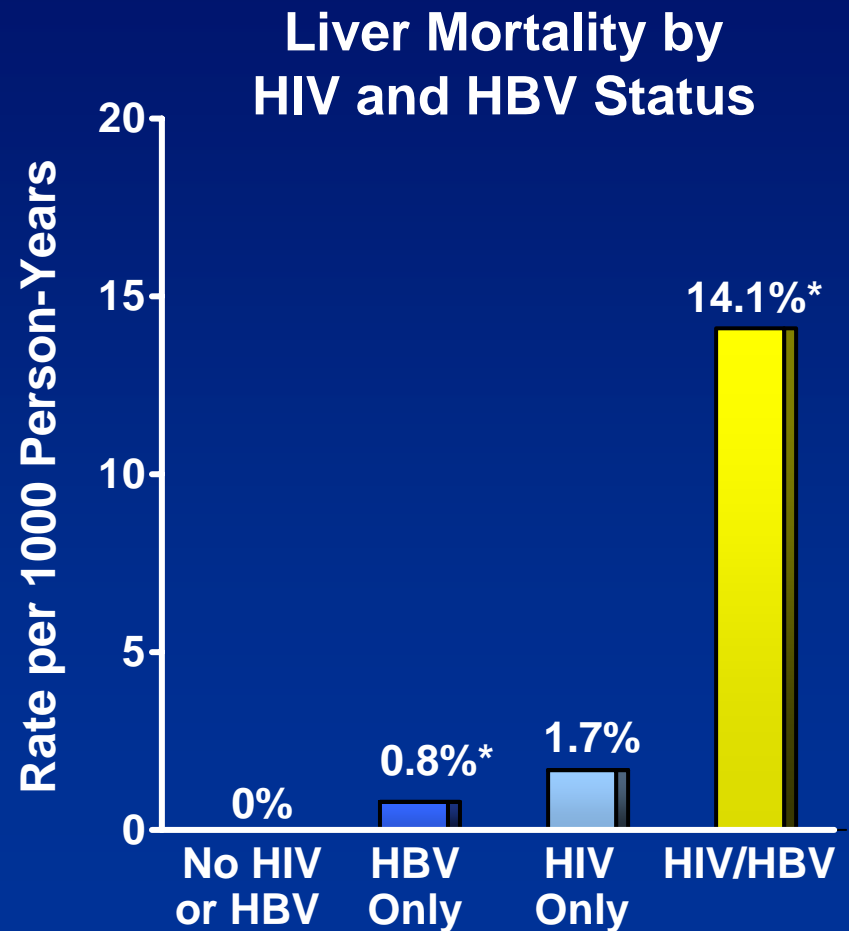
- HIV positive patients respond less well to the HBV vaccine especially if the CD4-count is below 500/ μ l and loose protective antibodies faster
- after 3 vaccinations response rate is > 87% in HIV-patients with CD4-cells >500/ μ l but only 33% in patients with a CD4-count between 200 and 500/ μ l

Rey D et al. Vaccine2000;18:1161

BHIVA guidelines 2003

HIV Coinfection Increases the Risk of ESLD Due to HBV

- **Multicenter Cohort Study**
 - 4967 HBsAG negative MSM
 - HIV: 47% (n=2346)
 - 326 HBsAG positive
 - HIV: 65% (n=213)
- **HIV/HBV coinfection**
 - 19-fold higher risk of liver death compared with HBV monoinfection
 - Risk of liver-related mortality increased with:
 - Alcohol consumption
 - Low nadir CD4 cell counts
 - Antiretroviral therapy



* $P < 0.0001$.

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

Treatment of chronic hepatitis B

- **Goal:** achieve sustained suppression of HBV replication and remission of liver disease, in order to prevent decompensated cirrhosis and HCC.
- **Surrogate markers (5):** ALT, HBV-DNA, HBeAg, HBsAg, liver histology

Treatment of chronic hep B

Goals: from more modest to more ambitious

- Normalization of transaminases
- Undetectable HBV-DNA
- HBeAg seroconversion
- HBsAg seroconversion

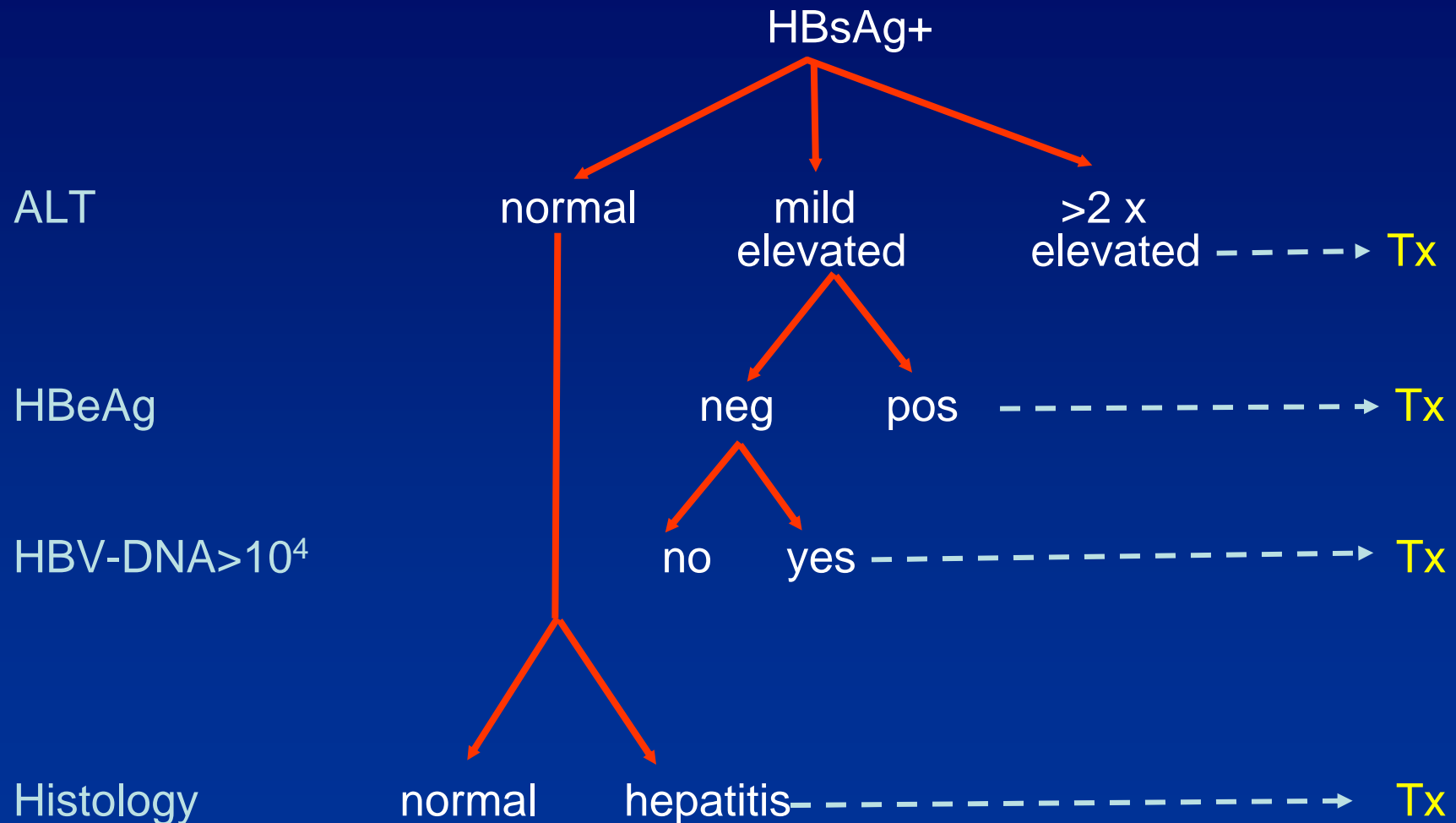
Nuñez et al. CID 2003; 37: 1678-85.

When to treat Chronic Hepatitis B?

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

EASL Consensus Conference.
J Hepatol 2003; 38: 533-40.

HBV treatment decision algorithm



HIV-HBV International Panel.
Soriano, et al. AIDS 2005

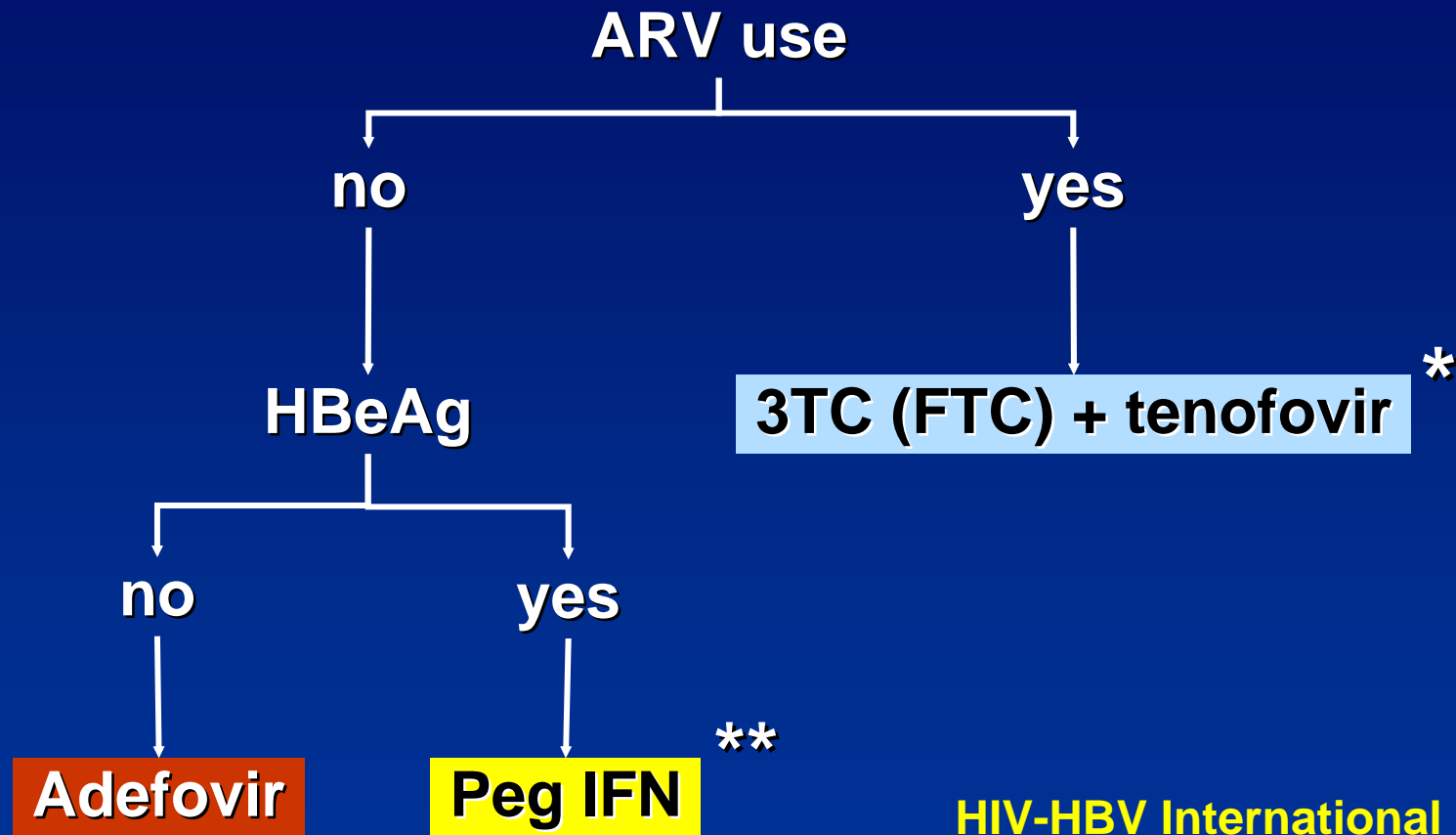
Antivirals for HBV infection

Agent	Advantages	Disadvantages
Interferon	HBsAg loss Short duration Rx	Parenteral Poor tolerance Works best in HBeAg+, high ALT patients
Lamivudine	Oral Excellent tolerance Use in ESLD Use in ADV failures	Drug resistance common (~20%/year)
Adefovir	Oral Excellent tolerance Use in ESLD Use in LAM failures	Drug resistance rare (~2% at year 2)

New Drugs for HBV

- **Pre-clinic** (more than 15 identified ...)
- **Clinic**
 - **TDF** (already available for HIV)
 - **Emtricitabine (FTC)** (already available for HIV)
 - **Entecavir (ETV)**
 - **Telbivudine (LdT)**
 - **Clevudine (L-FMAU)**

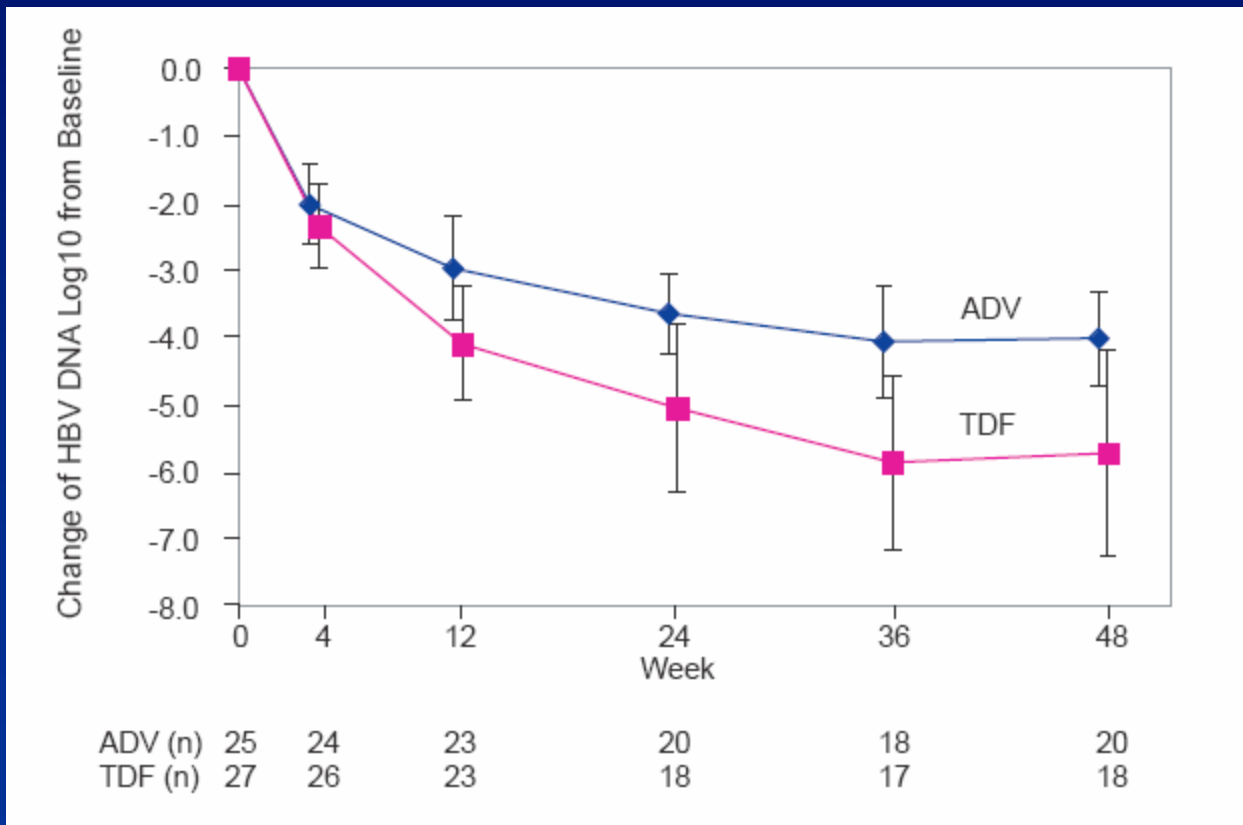
Preferred anti-HBV agents in drug-naive HBV/HIV-coinfected patients candidates for HBV therapy



HIV-HBV International Panel.
Soriano, et al. AIDS 2005

- * In patients already on HAART without TDF/3TC (FTC),
 - adefovir might be added
 - 6-12 month course of interferon might be recommended
- ** With caution in cirrhotics

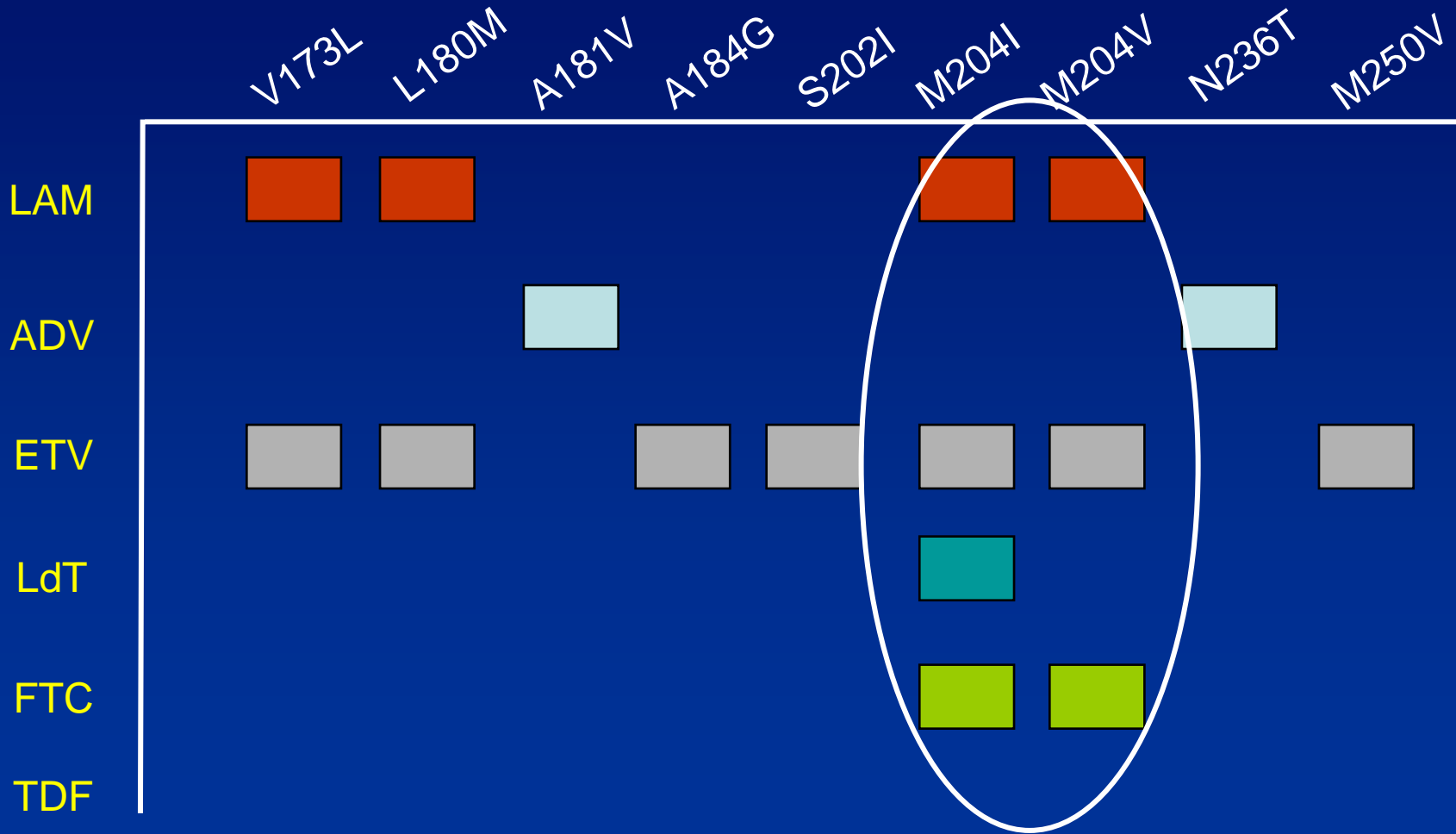
A5127: TDF non-inferior to ADV in HIV/HBV Coinfection



Treatment Approach

Virus needing treatment	Considerations	Avoid
HBV only	PEG-IFN or adefovir (entecavir)	LMV/FTC/TDF without anti-HIV regimen
HIV only	Reserve LMV, FTC and TDF	LMV/FTC monotherapy
HIV and HBV Naive	LMV/FTC+TDF	LMV/FTC monotherapy
Prior LMV	TDF +/- LMV/FTC Adefovir +/- LMV/FTC	

HBV polymerase resistance mutations



Locarnini et al. Antiviral Ther 2004