# Is HBV resistance disappearing ?

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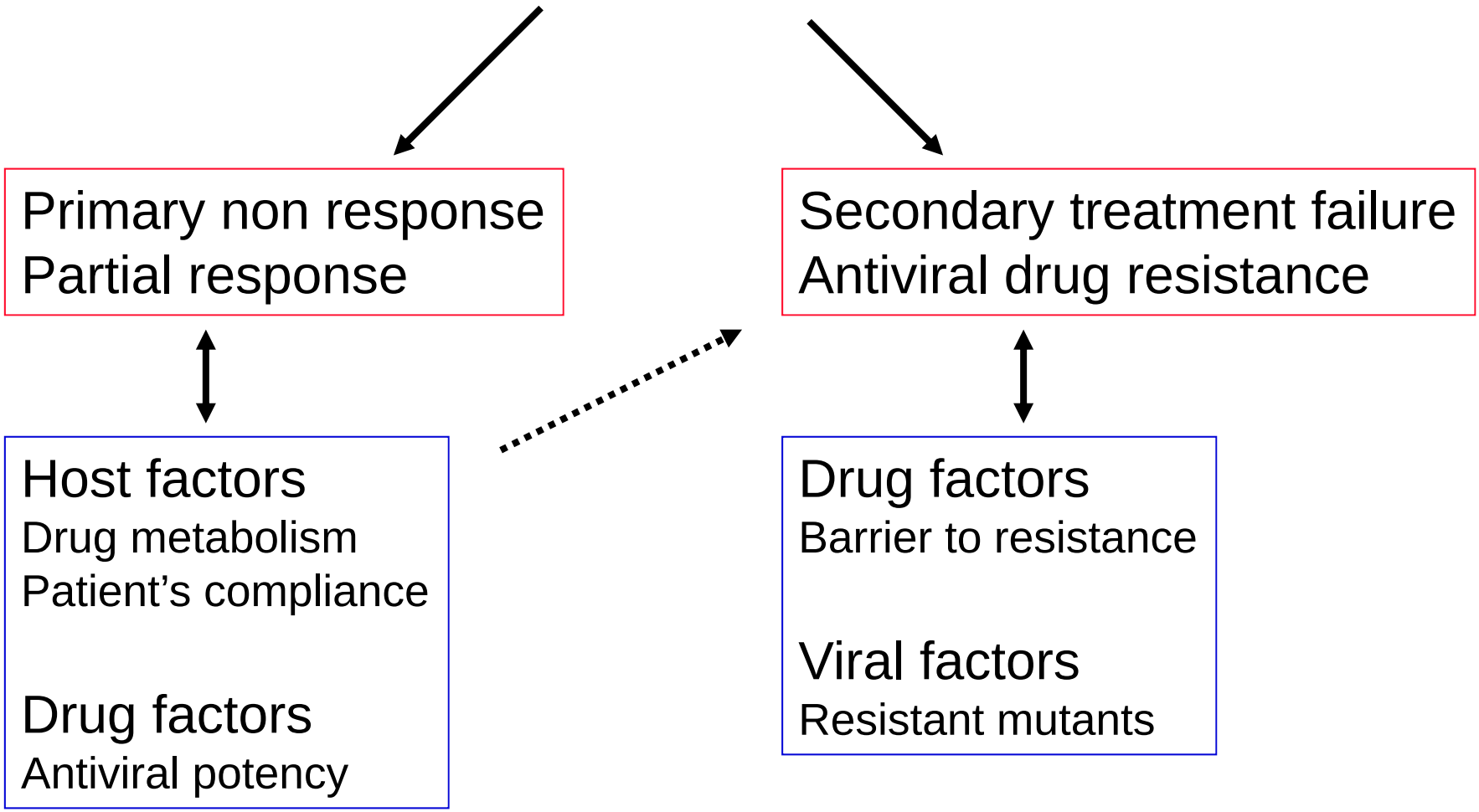
# Antivirals approved for hepatitis B

| Drug Type | Approved | Phase 3 | Phase 2 |
|---|---|---|---|
| Nucleoside analogs | • Lamivudine<br>• Entecavir<br>• Telbivudine | • Emtricitabine*<br>• Clevudine** | ? |
| Nucleotide analogs | • Adefovir dipivoxil<br>• Tenofovir disoproxil fumarate | | ? |
| Cytokines | • Interferon alfa<br>• Pegylated Interferon alfa-2a | | Vaccine therapy<br>IL7<br>IFN lambda |

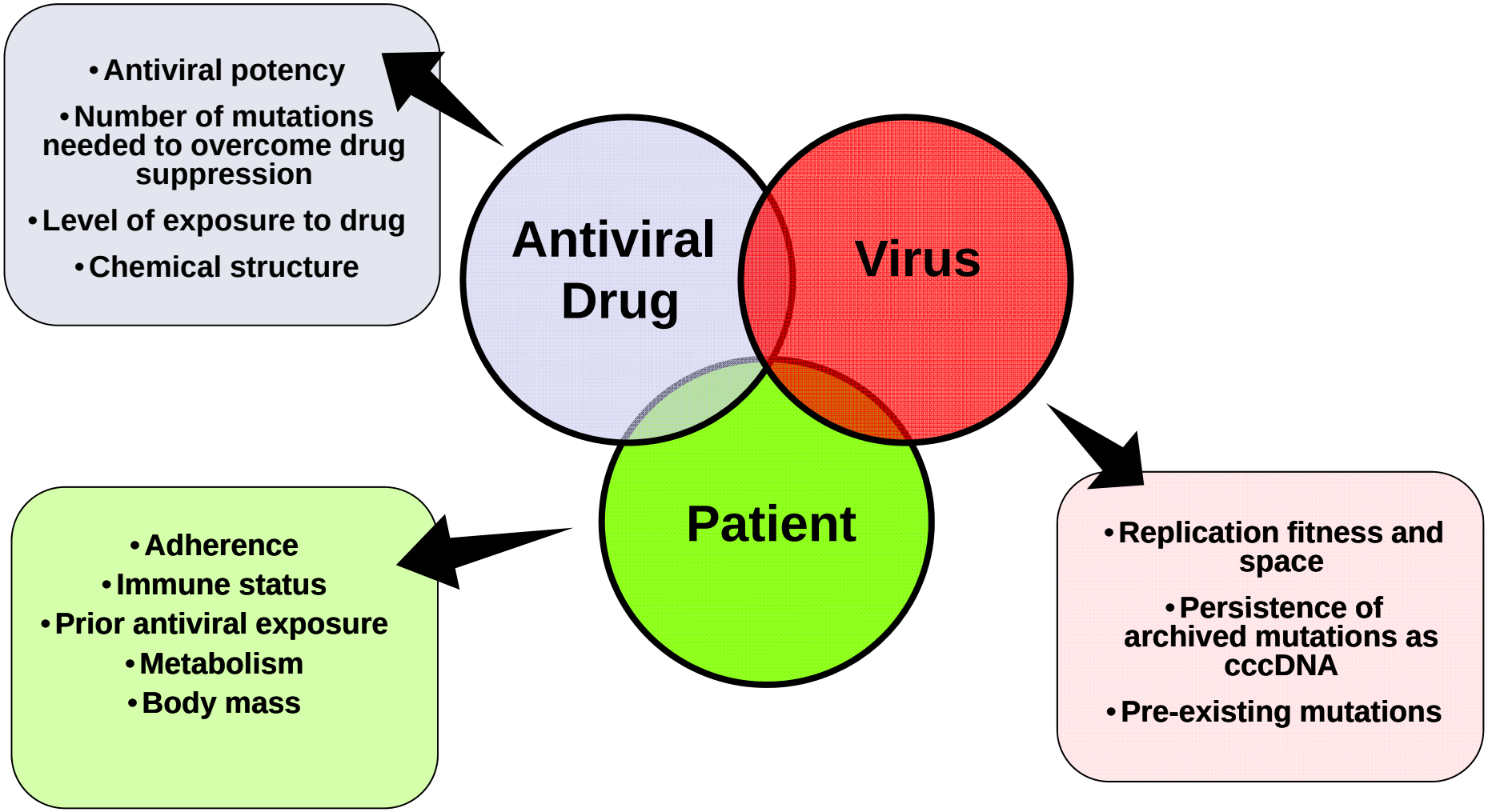
**Currently approved for HIV*
***development on hold*

# Treatment failure




*Zoulim & Perrillo J Hepatol 2008; EASL CPG J Hepatol 2009; Zoulim & Locarnini Gastroenterology 2009*

# Multiple factors are associated with the barrier of resistance




Locarnini S, et al. Antivir Ther. 2004;9:679–93. Locarnini S, et al. Antivir Ther. 2007;12:H15-H23. 3. Ghany M & Liang TJ. Gastroenterology 2007;132:1574-85. Zoulim F, et al. Antiviral Res. 2004;64:1-15. Locarnini S, et al. J Hepatol. 2003;39:S124-S132.; Zoulim & Locarnini Gastroenterology 2009

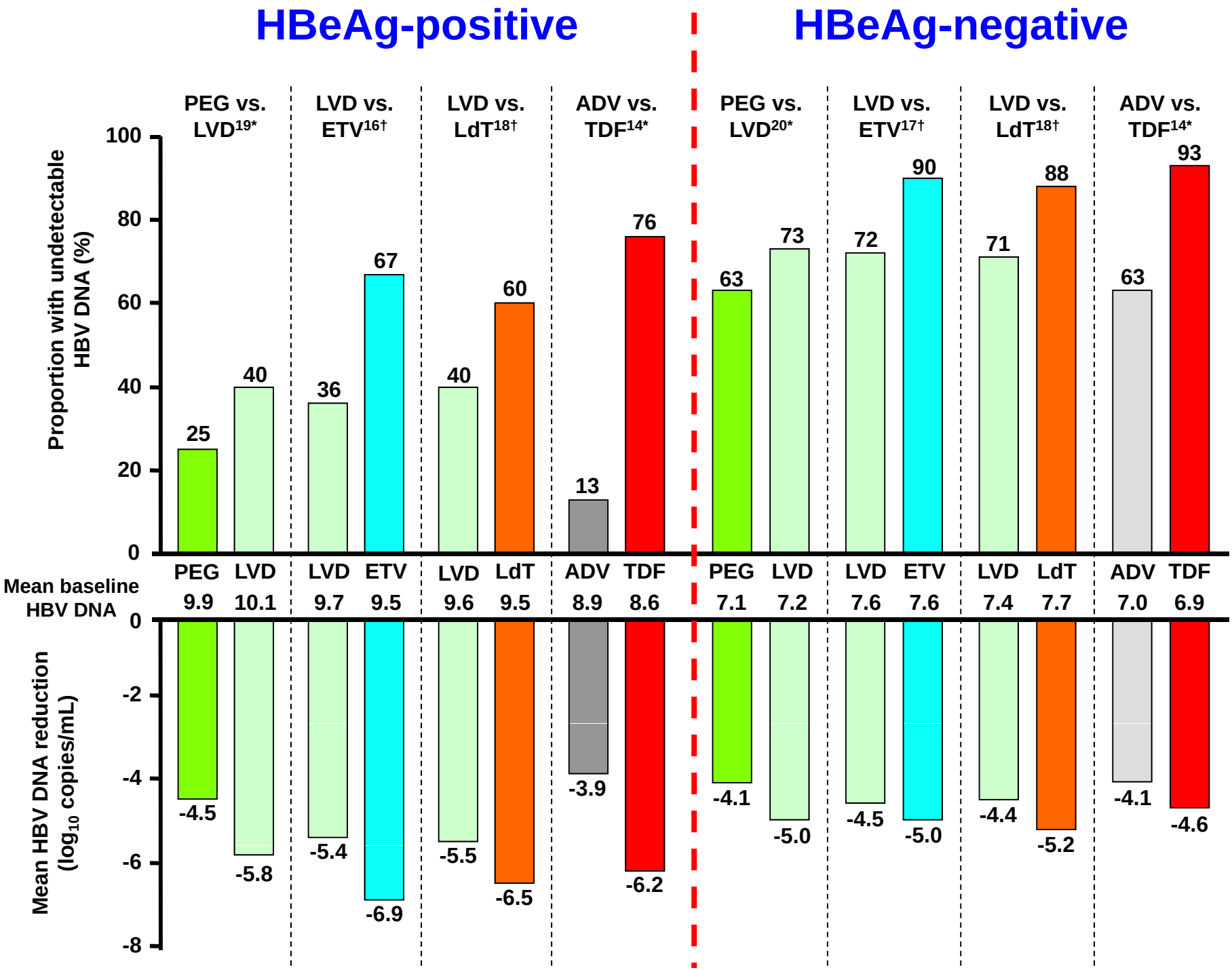
Yes, we can prevent HBV resistance !

# Prevention of resistance
# Impact of first line therapy

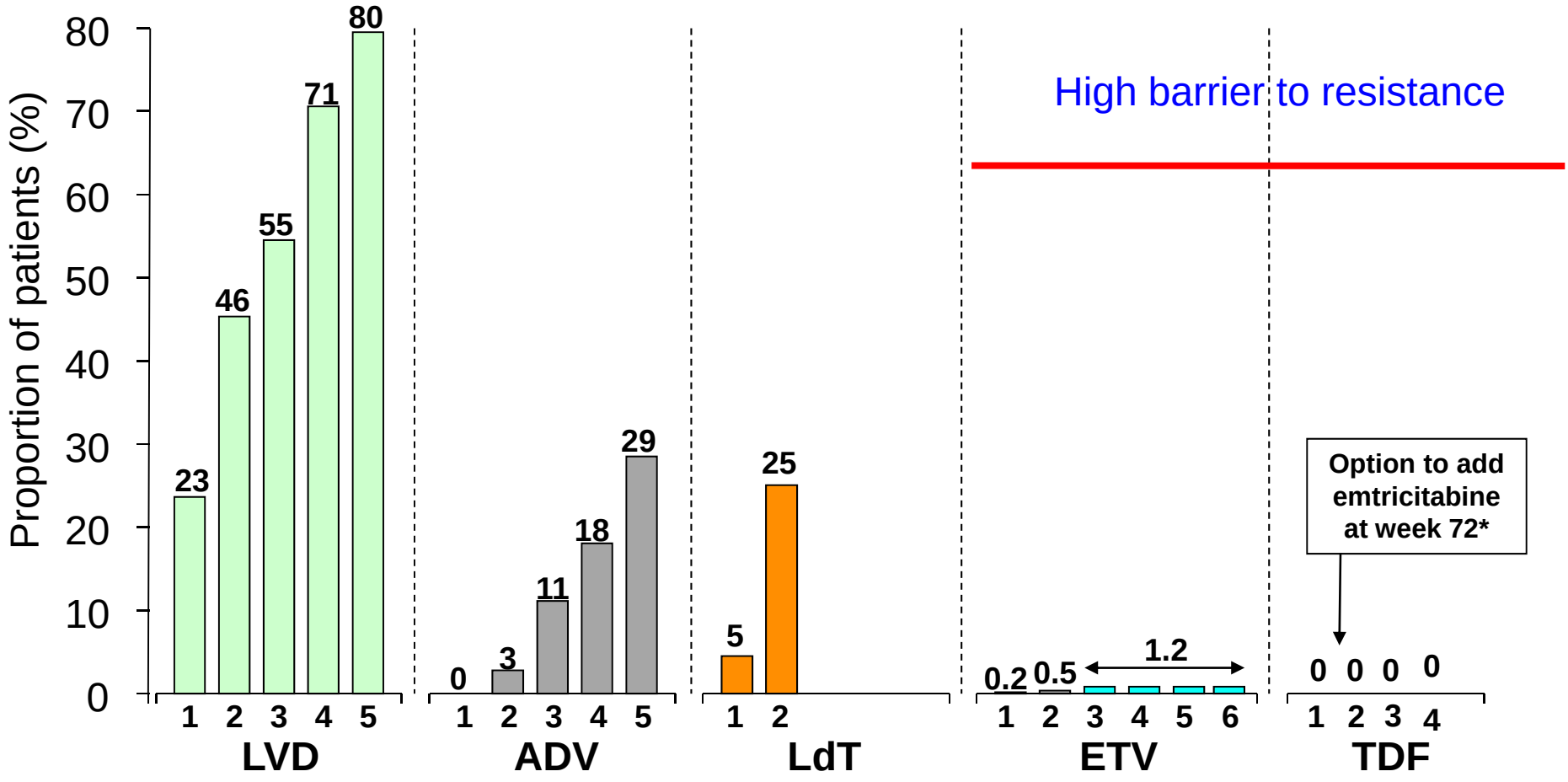
- Choose an antiviral drug with

    1. A potent antiviral activity

    2. A high barrier to resistance


HBeAg-positive
HBeAg-negative
PEG vs. LVD19*
LVD vs. ETV16†
LVD vs. LdT18†
ADV vs. TDF14*
PEG vs. LVD20*
LVD vs. ETV17†
LVD vs. LdT18†
ADV vs. TDF14*
Proportion with undetectable HBV DNA (%)
100
80
60
40
20
0
25
40
36
67
40
60
13
76
63
73
72
90
71
88
63
93
PEG LVD LVD ETV LVD LdT ADV TDF PEG LVD LVD ETV LVD LdT ADV TDF
Mean baseline HBV DNA
9.9 10.1 9.7 9.5 9.6 9.5 8.9 8.6 7.1 7.2 7.6 7.6 7.4 7.7 7.0 6.9
Mean HBV DNA reduction (log10 copies/mL)
0
-2
-4
-6
-8
-4.5
-5.8
-5.4
-6.9
-5.5
-6.5
-3.9
-6.2
-4.1
-5.0
-4.5
-5.0
-4.4
-5.2
-4.1
-4.6

# Rates of resistance with lamivudine (LVD), adefovir (ADV), telbivudine (LdT), entecavir (ETV) and tenofovir (TDF) among NA-naïve patients




*Patients confirmed to be viraemic at Week 72 or beyond could add emtricitabine to TDF at the discretion of the investigator. Clinical data on the safety and efficacy of emtricitabine and TDF in CHB are pending

Yes, we can manage HBV resistance !

# Control of antiviral drug resistance

- Impact of second line therapy
  - Add-on strategy with complementary drugs preferred to sequential monotherapies
  - Early treatment adaptation to prevent accumulation of mutations
  - Choice always based on cross-resistance data

*Zoulim & Locarnini, Gastroenterology 2009; EASL CPG J Hepatol 2009*

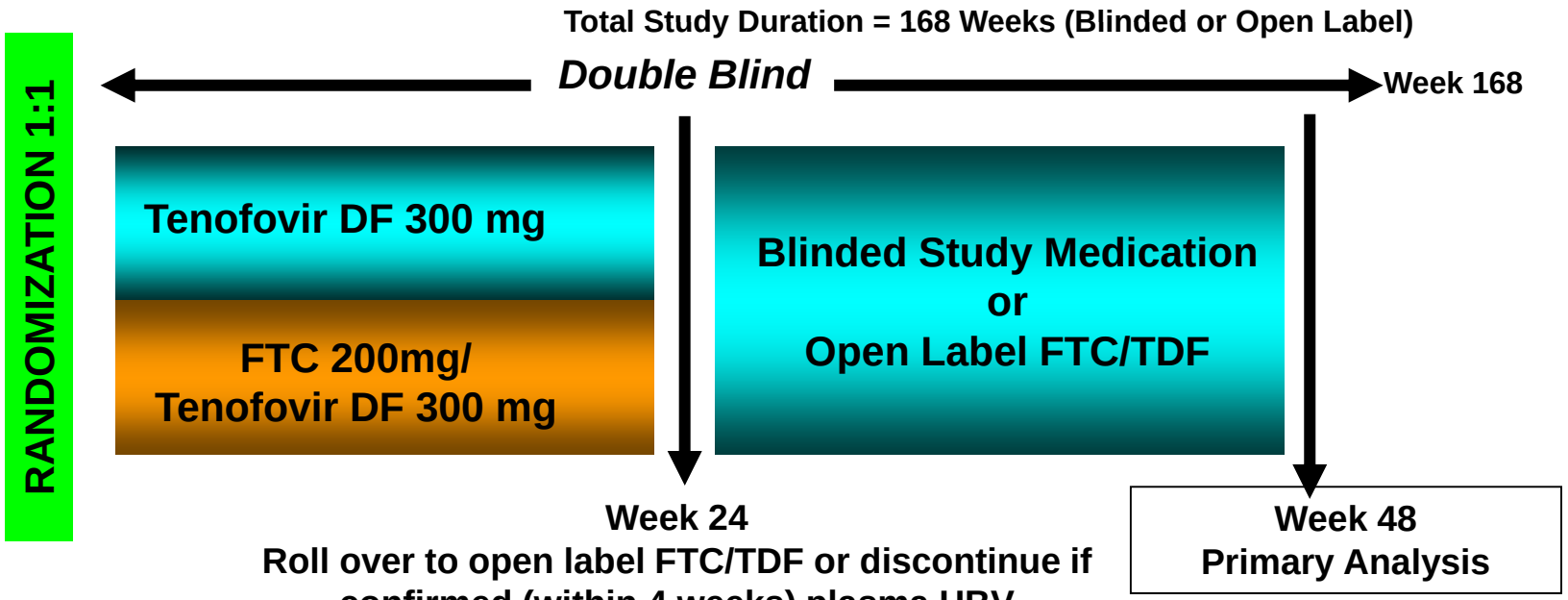
# Cross-resistance data for the main mutants and the commercially available drugs

| Pathway | Amino acid substitutions in the rt domain | Lamivudine | Telbivudine | Entecavir | Adefovir | Tenofovir |
|---|---|---|---|---|---|---|
| | Wild type | **S** | **S** | **S** | **S** | **S** |
| L-nucleoside | M204I | **R** | **R** | **I** | **S** | **S** |
| L-nucleoside | L180M+M204V | **R** | **R** | **I** | **S** | **S** |
| Alkyl phosphonate | N236T | **S** | **S** | **S** | **R** | **I** |
| Shared | A181T/V | **I** | **I** | **S** | **R** | **I** |
| D-Cyclopentane (ETV) | L180M+M204V/I ±I169T±V173L± M250V | **R** | **R** | **R** | **S** | **S** |
| D-Cyclopentane (ETV) | L180M+M204V/I ±T184G±S202I/ G | **R** | **R** | **R** | **S** | **S** |

*Fournier & Zoulim Clin Liver Dis 2007; Zoulim & Locarnini Gastroenterology 2009*

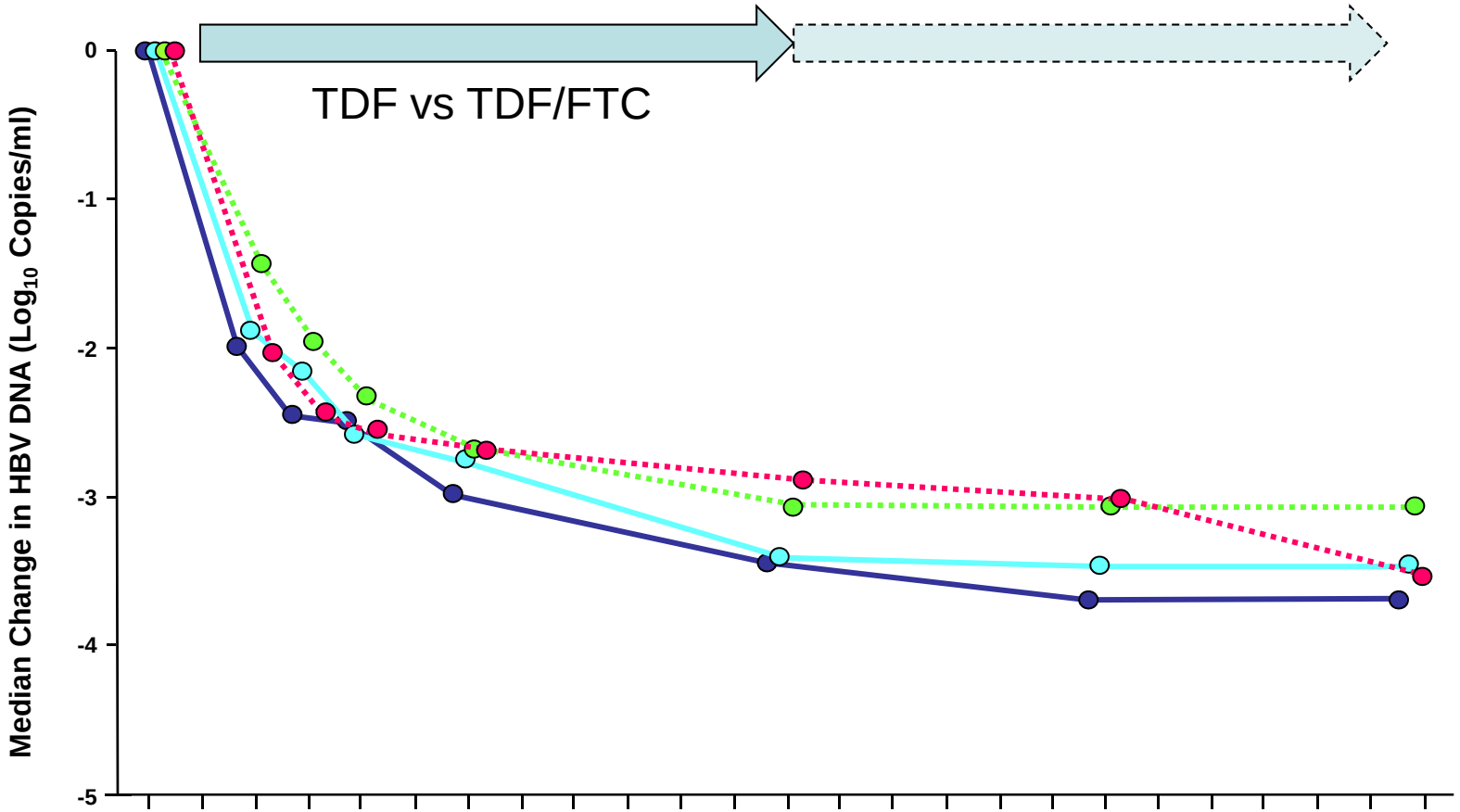
# STUDY DESIGN

- 105 Patients with chronic hepatitis B **refractory to ADV** randomized in a controlled trial of **TDF versus TDF + FTC**.
- 63 Patients had been exposed to lamivudine before the trial.




*Berg et al, Gastroenterology 2010*

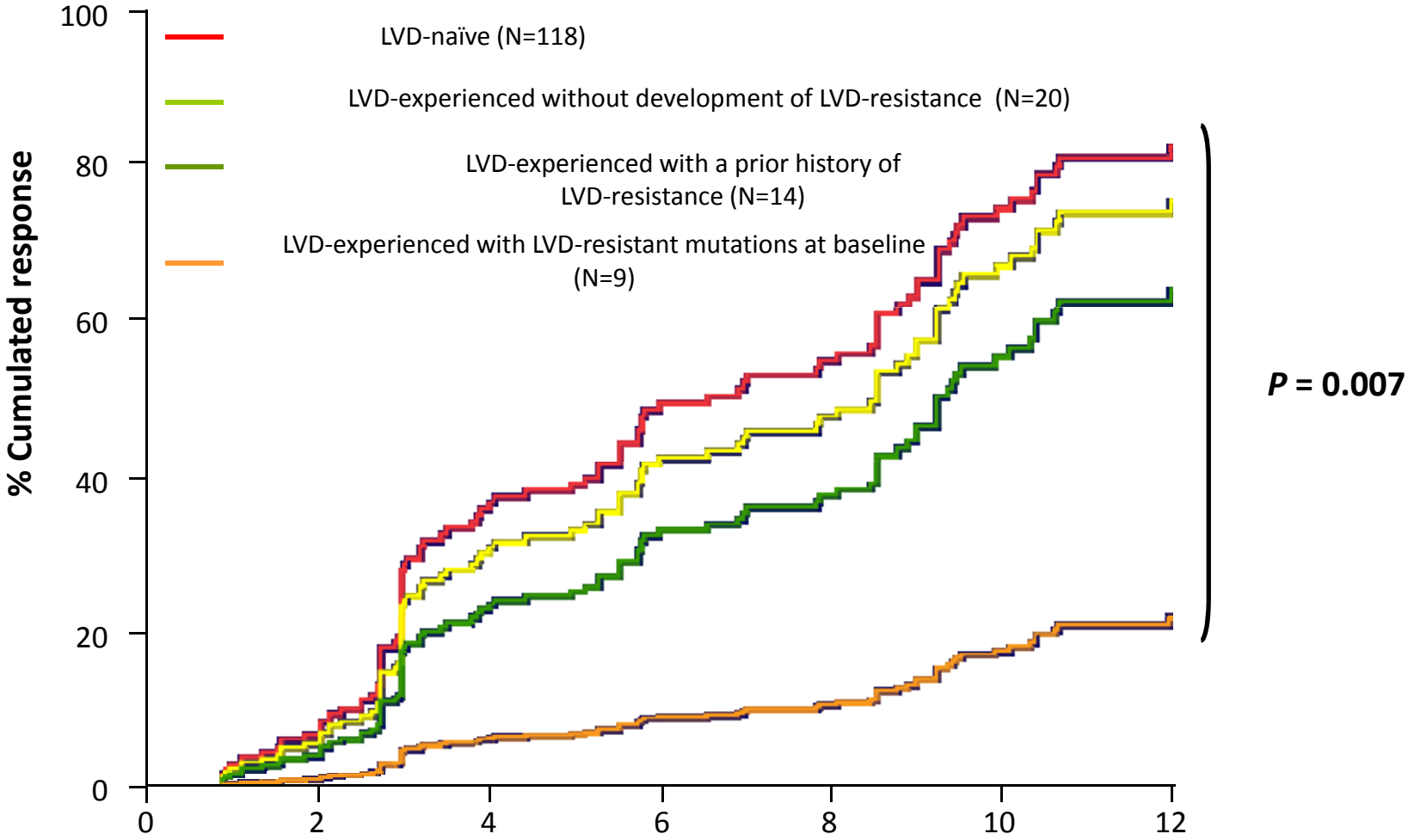
# Tenofovir versus tenofovir + emtricitabine in patients with adefovir failure




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| TDF L/A Res | N=24 | 24 | 23 | 23 | 23 | 23 | 23 | 23 |
| TDF W-T | N=29 | 29 | 25 | 28 | 29 | 29 | 29 | 29 |
| FTC/TDF L/A Res | N=19 | 19 | 19 | 18 | 19 | 19 | 18 | 19 |
| FTC/TDF W-T | N=33 | 33 | 31 | 32 | 33 | 33 | 32 | 31 |

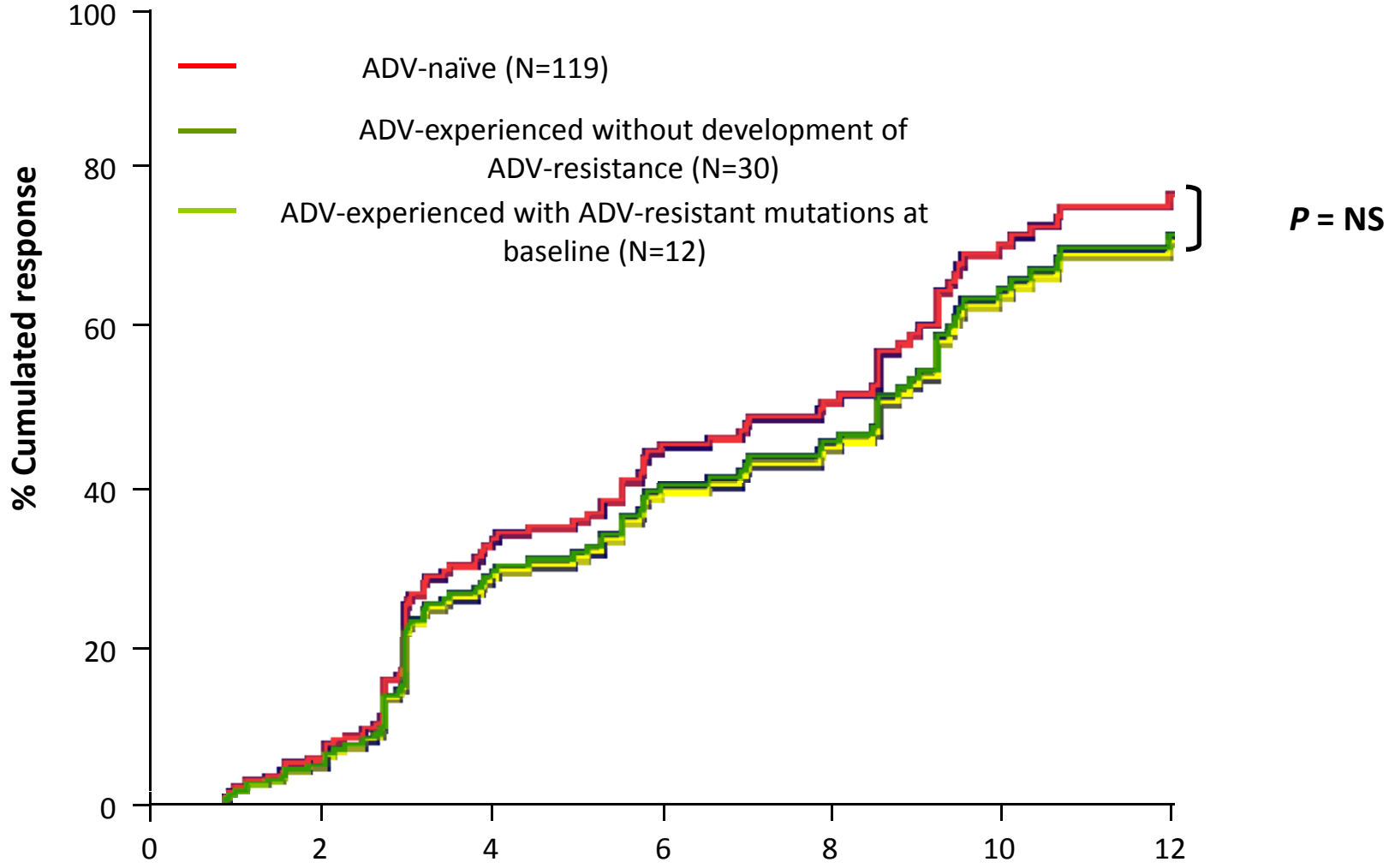
*Lavocat et al, EASL 2009; Berg et al Gastroenterology 2010*

# Virologic response to ETV according to lamivudine exposure




*Reijnders, JGP et al. J Hepatol 2010*

# Virologic response to ETV according to adefovir exposure



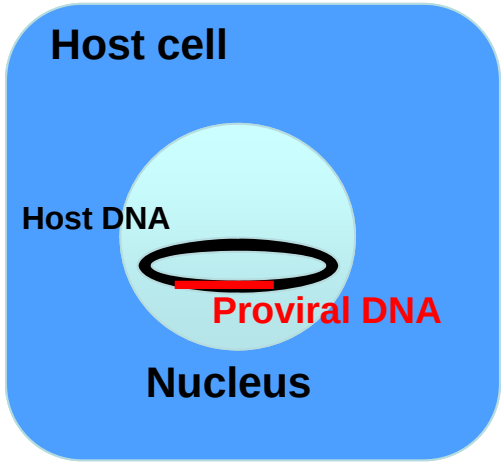

*Reijnders, JGP et al.. J Hepatol. 2010*

Yes, we can suppress viral replication,
but HBV cannot be eradicated…

Will HBV resistance re-emerge
as a novel clinical problem ?

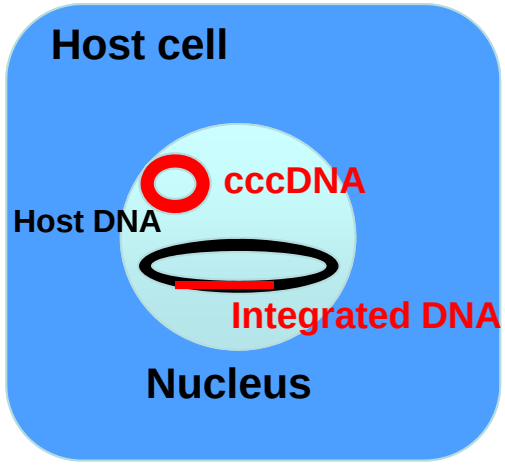
# The main differences between HIV, HBV and HCV

## HIV



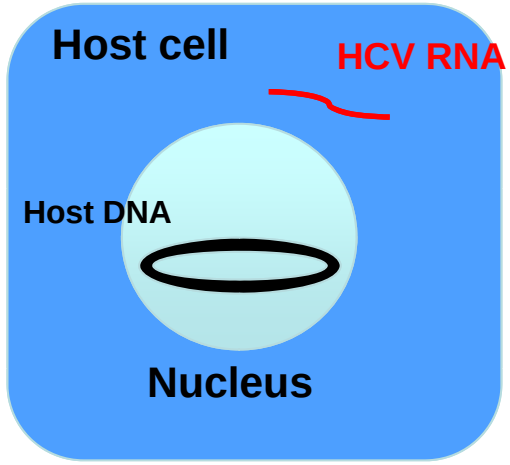

Lifelong suppression of viral replication

## HBV




Longterm suppression of viral replication

## HCV



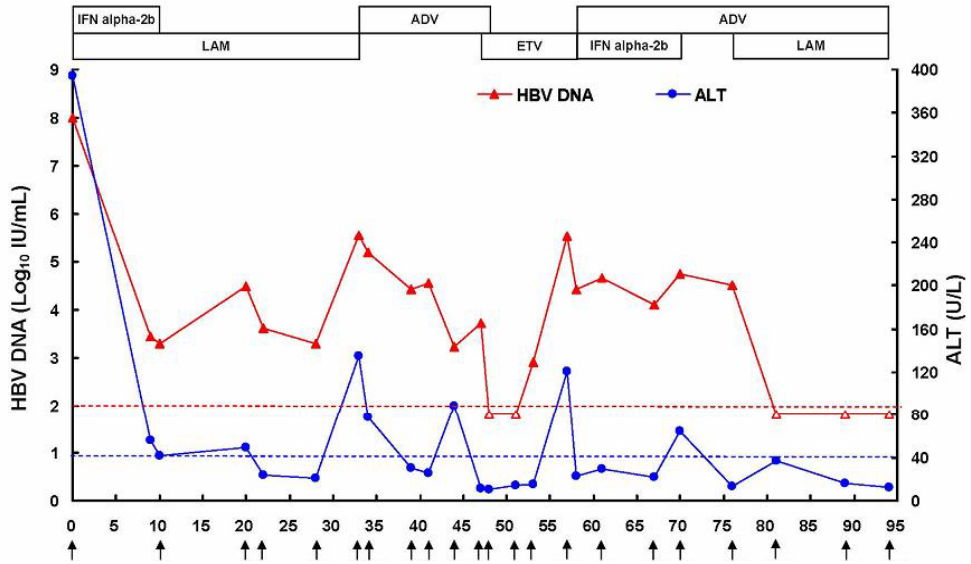

Definitive viral clearance and SVR

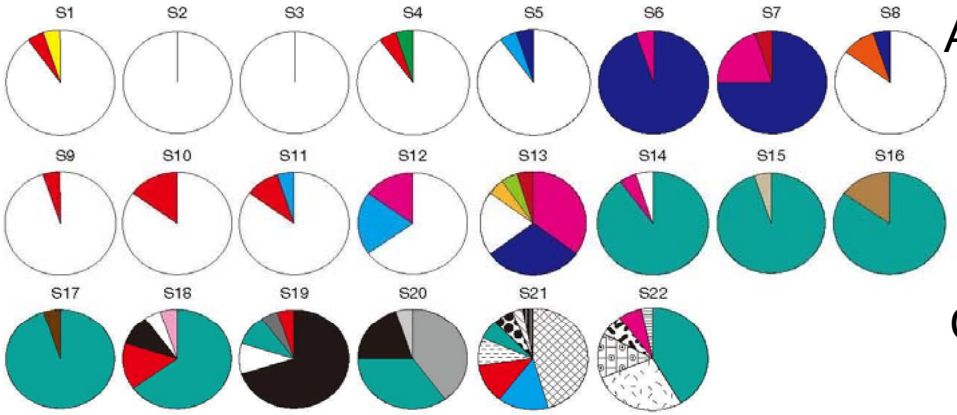
Kieffer et al. J Antimicrob Chemother 2010; Sorriano et al. J Antimicrob Chemother 2009; Clavel et al. New Engl J Med 2004; Zoulim &Locarnini Gastroenterology 2009; Sarrazin & Zeuzem Gastroenterology 2010

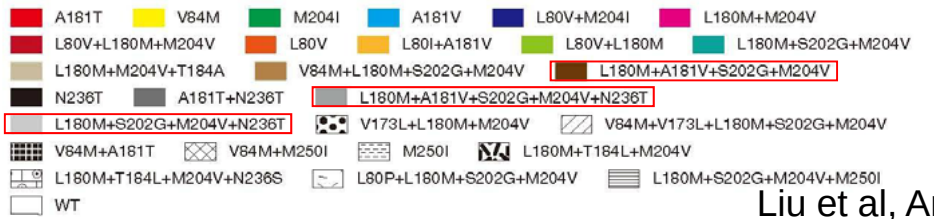
# Patients heavily exposed to NUCs: a real treatment challenge

- Risk of multidrug resistance by sequential accumulation of resistance mutations
  - See the Asian situation…
- Risk of partial response, even with the newest NUCs -> long-term impact ?
  - See the Australian experience

# Sequential therapy with NUCs: the Asian experience and the risk of MDR




Accumulation of multiple mutations on the same viral genome

Complete change of the viral quasi-species

Liu et al, Antivir Ther. 2010;15(8):1185-90.

# Impact of rtA181 and rtN236 mutations on antiviral drug efficacy and cross-resistance

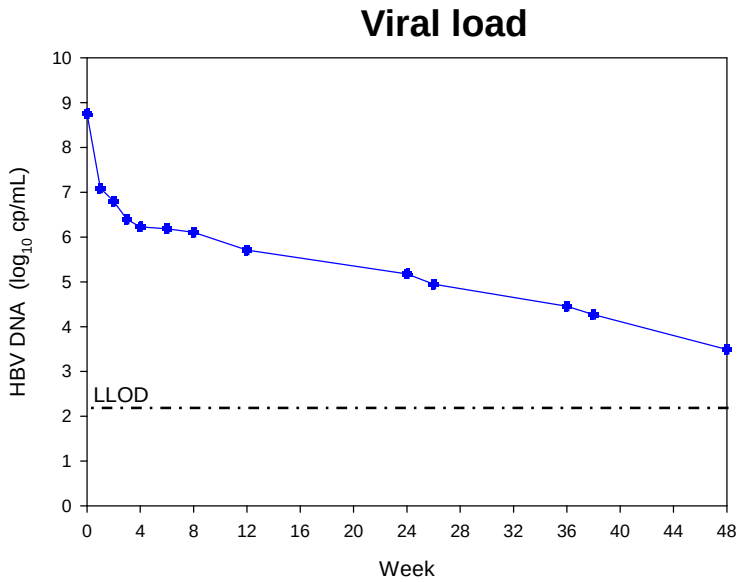
***In vitro*** **susceptibility to nucleos(t)ide analogs of the rtA181T, rtA181V, rtA181T+N236T, rtA181V+N236T, and rtN236T+N238T mutants isolated from patients with virological failure**

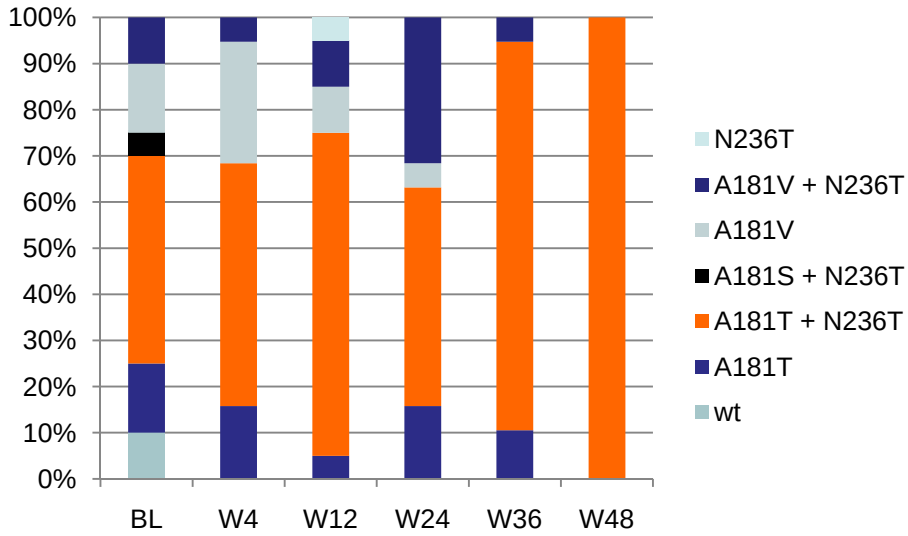
| Mutant | Patient | LAM FR | ADV FR | TDF FR | ETV FR |
|---|---|---|---|---|---|
| rtA181T | #2 | 5.7 ± 2.6 | 4.5 ± 0.8 | 2 ± 0.6 | nd |
| | #9 | 8.7 ± 4.2 | 3.2 ± 1.6 | 2.8 ± 1.6 | 1 ± 0.08 |
| | #7 | 10.8 ± 2.9 | 2.1 ± 1 | 2.9 ± 1.5 | 1 ± 0.5 |
| rtA181V | #9 | 7.7 ± 3.6 | 7.8 ± 3.5 | 2.4 ± 1.4 | 1 ± 0.05 |
| | #4 | 7.1 ± 3.8 | 3 ± 0.6 | 1.2 ± 0.4 | 1.5 ± 0.5 |
| | #5 | 1.5 ± 0.3 | 2.4 ± 0.2 | 3.2 ± 0.4 | 1.2 ± 0.4 |
| rtA181T+N236T | #9 | 35 ± 5 | >10 | 6.8 ± 2.9 | 1 ± 0.1 |
| rtA181V+N236T | #3 | 43 ± 10 | 4.5 ± 2.7 | 1.2 ± 0.2 | 1 ± 0.05 |
| rtN236T+N238T | #4 | 1.5 ± 0.7 | 2.6 ± 0.6 | 1.4 ± 0.6 | 1.1 ± 0.6 |

*Villet et al, J Hepatol 2008*

# Evolution of viral genome during Tenofovir therapy in patients who prevously failed ADV

## Patient #1051




**Patient 1051 data:**

**BL viral load = 8.75log**

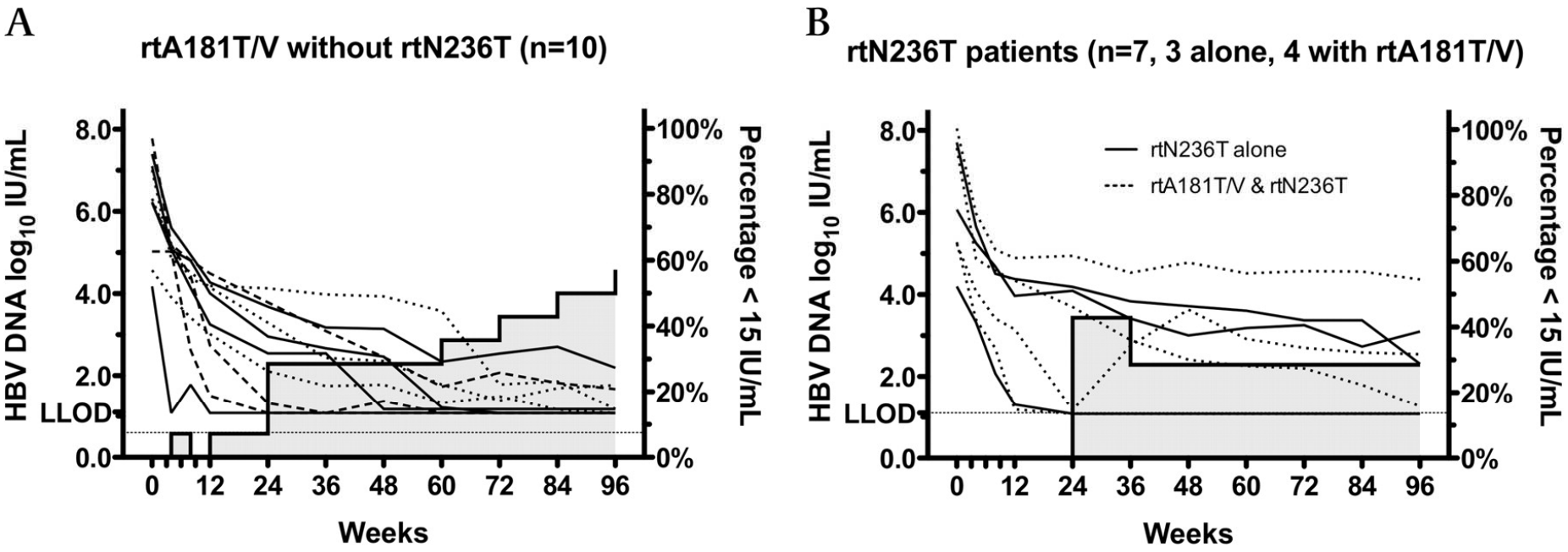
**Treatment: TDF**

**Adherence : 95.2%**

**Impact of persisting low viremia levels on treatment outcome ?**
**Impact of persisting resistant mutants ?**

*Lavocat & Zoulim, AASLD 2010.*

# Virologic response to TDF according to ADV resistance mutations at baseline - The Australian Experience



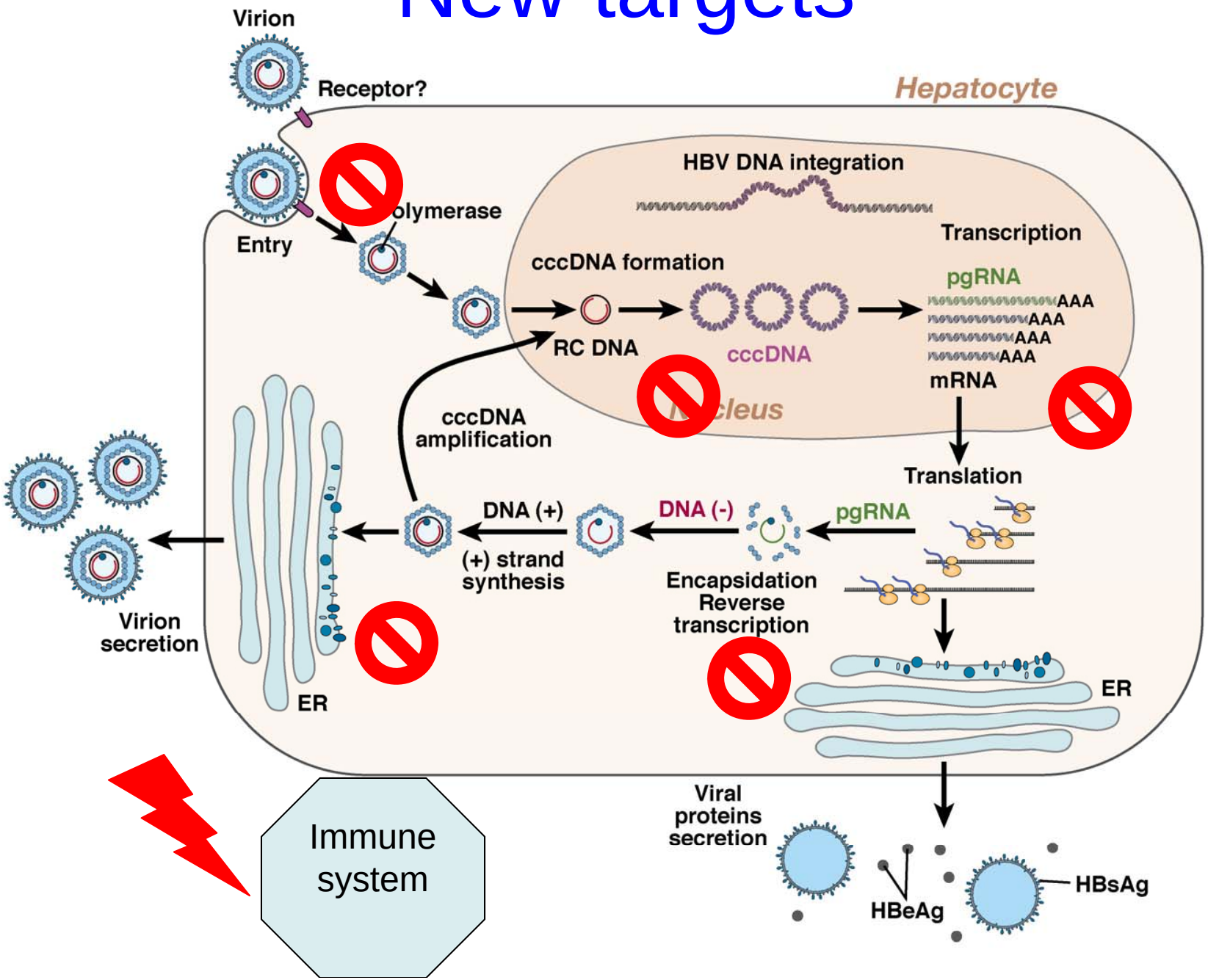

Patterson S J et al. Gut 2011;60:247-254

GUT

# HBV resistance: new challenges

- Poorer response in second or third line therapy
  - Persisting low viremia levels
- Risk of selection of MDR mutants
- Potential risk of transmission of mutants
- Early detection of mutants (UDP sequencing)
- Identification of new targets for true combination therapy, prevention of resistance, and finite duration therapy

# New targets


Virion
Receptor?
Hepatocyte
HBV DNA integration
Transcription
olymerase
Entry
cccDNA formation
pgRNA
AAA
AAA
AAA
AAA
RC DNA
cccDNA
mRNA
cccDNA
amplification
Translation
DNA (+)
DNA (-)
pgRNA
(+) strand
synthesis
Encapsidation
Reverse
transcription
Virion
secretion
ER
ER
Immune
system
Viral
proteins
secretion
HBeAg
HBsAg

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