Optimal management of CHB patients with treatment failure

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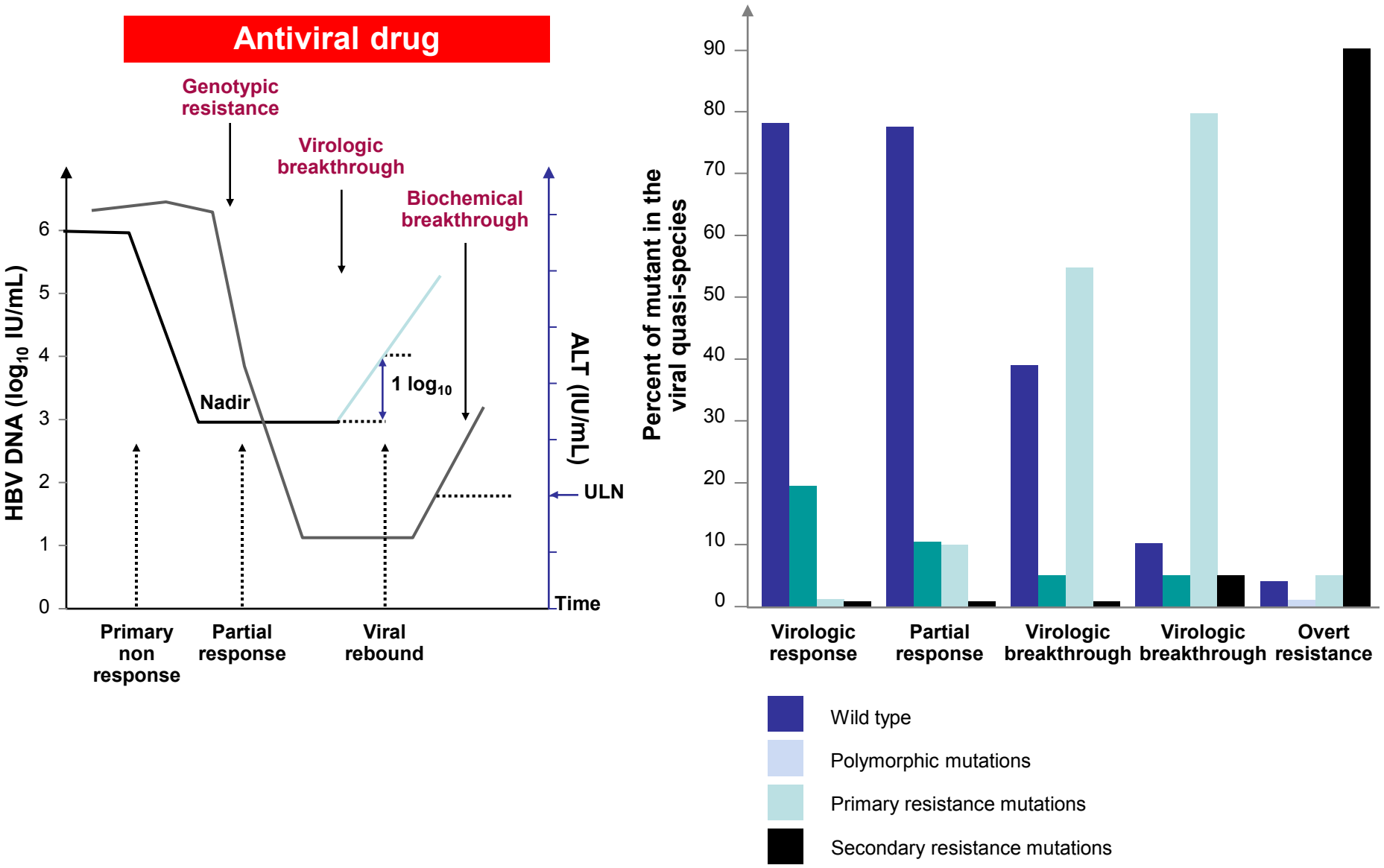
Hôpitaux de Lyon

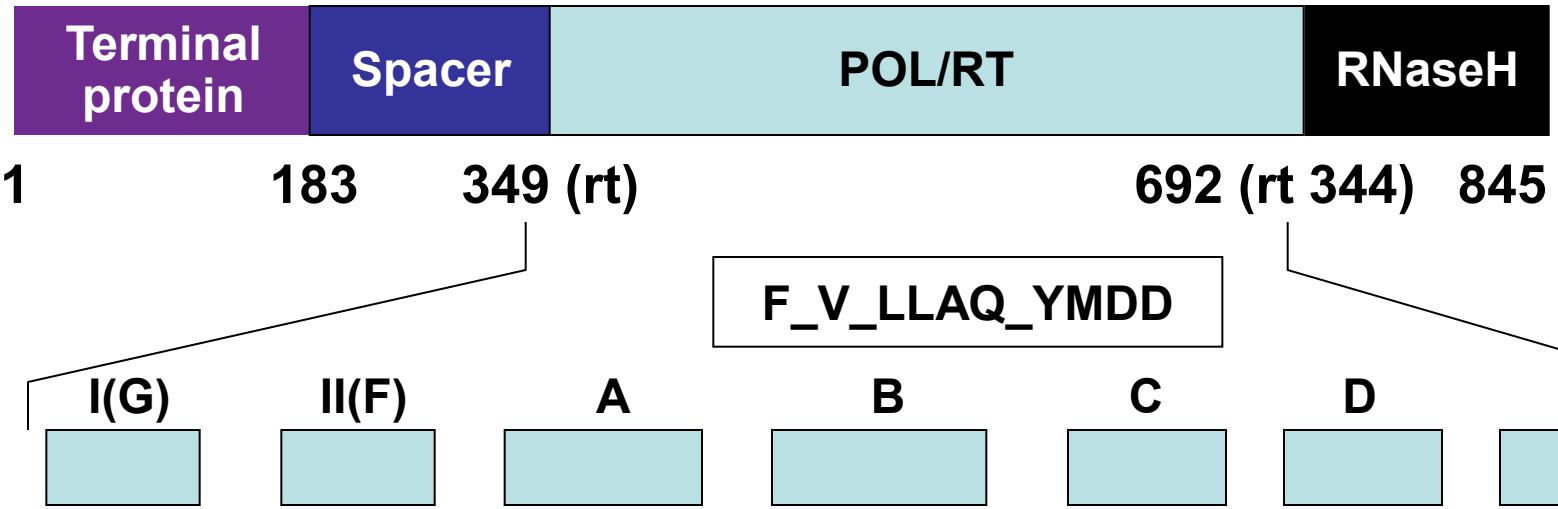
Treatment failure

- **Primary non-response**
  - Viral load decrease < 1 log10 IU/mL at M3
  - Mainly with ADV
- **Partial virological response**
  - Persistence of detectable viremia
    - At W24 for drugs with low barrier to resistance (LdT, LAM)
    - At W48 for high barrier to resistance drugs (ETV, TDF)
- **Virological breakthrough**
  - Rebound of viral load by > 1 log10 IU/mL
- **The case of multidrug resistance**

EASL CPG, J Hepatol 2009 & 2012



Zoulim F, *et al. Gastroenterology* 2009;**137**:1593-1608.



LMV resistance/ LdT resistance	rtL80I	**rtV173L** **rtL180M** **rtA181T/V**	**rtM204V/I**		
ADV resistance		**rtA181T/V**		**rtN236T**	
TDF resistance*		**?**			
ETV resistance		**rtL180M** **rtT184*** ** **rtI169T**	**rtM204I/V** **rtS202****		**rtM250I/V**

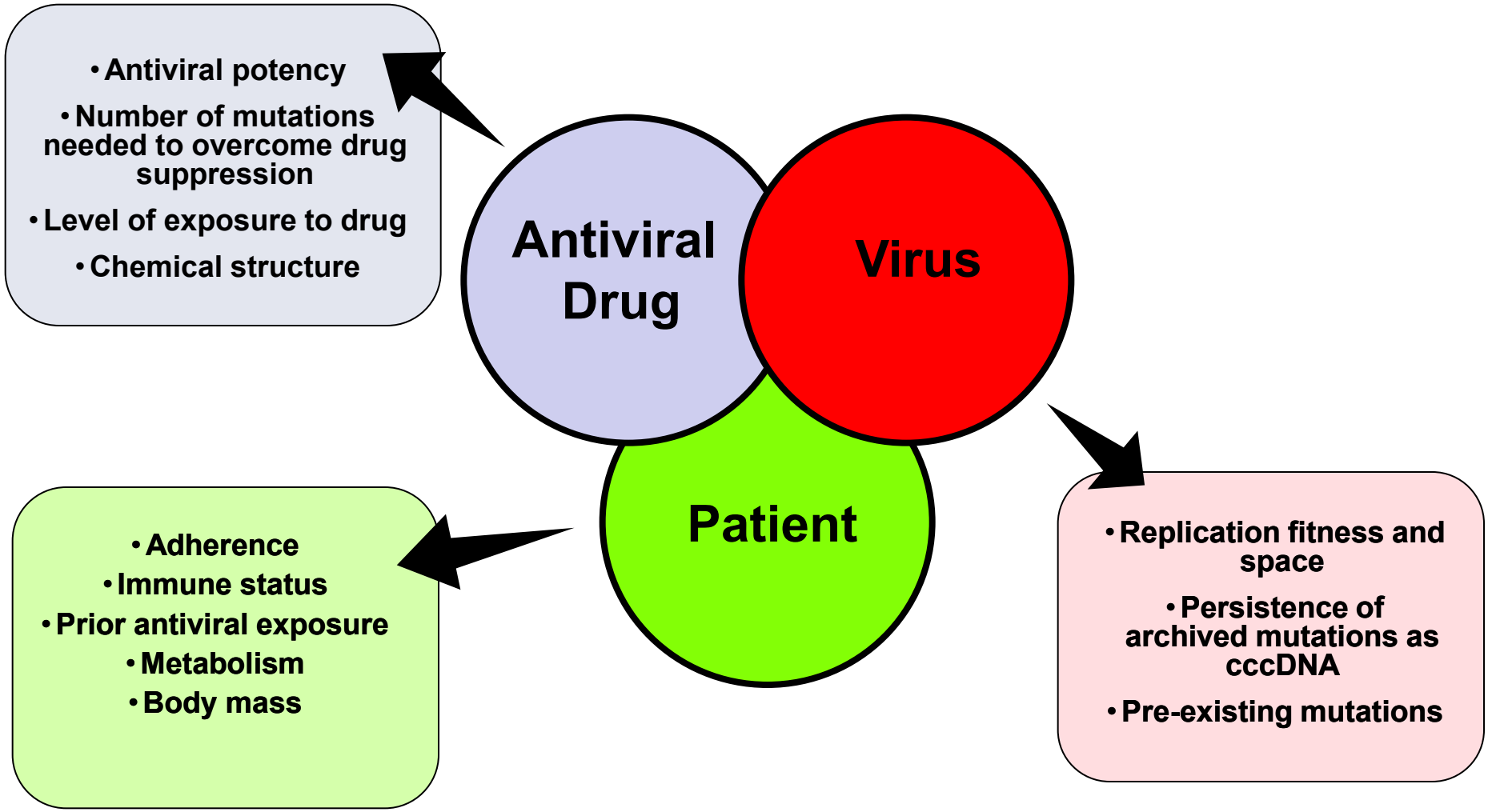
*rtA181T/V and/or rtN236T cause reduced sensitivity
*rtA194T association with rtL180M+rtM204V (to be confirmed)

***S/A/I/L/G/C/M
****C/G/I

*** Role of complex mutants: rtA181T+rtN236T ?**

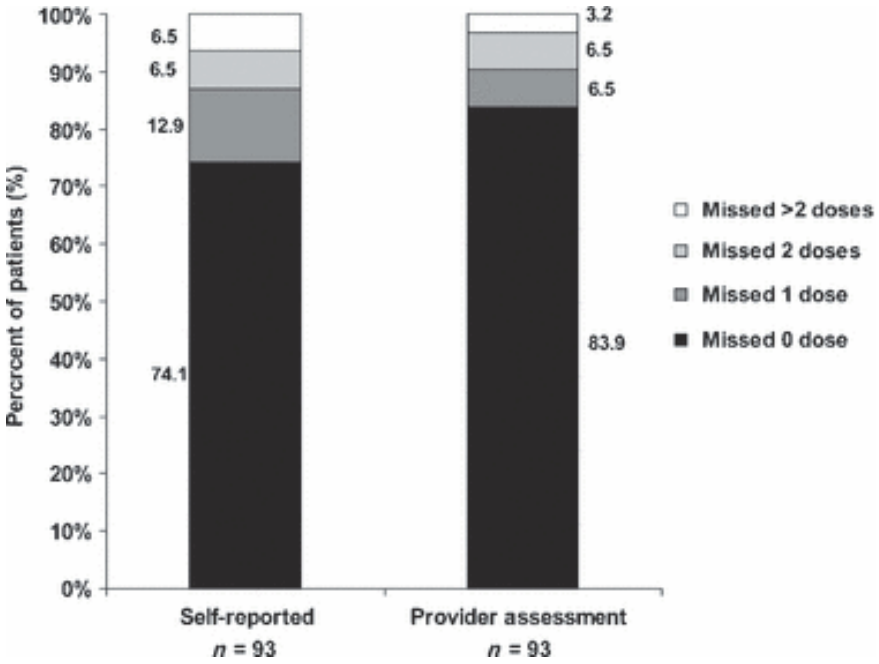
Zoulim F & Locarnini *Gastroenterology* 2009;**137**:1593-1608.

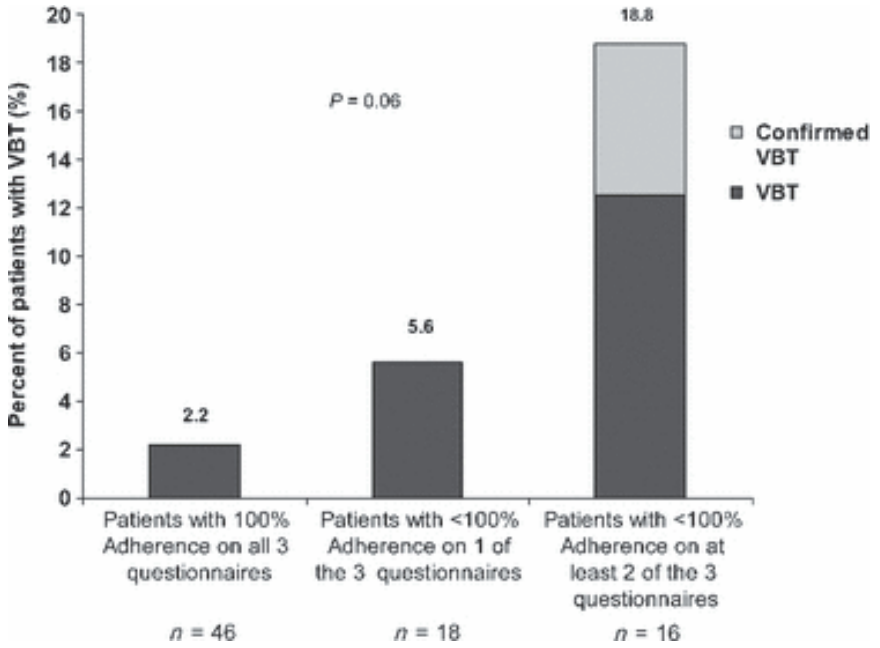
Multiple factors are associated with the barrier of resistance



Zoulim & Locarnini Gastroenterology 2009; Gish, Jia, Locarnini, Zoulim, Lancet Infect Dis 2012

Adherence to nucleos(t)ide analogues for chronic hepatitis B in clinical practice and correlation with virological breakthroughs





W. Chotiyaputta et al, Journal of Viral Hepatitis, Volume 19, Issue 3, pages 205-212, 14 JUL 2011

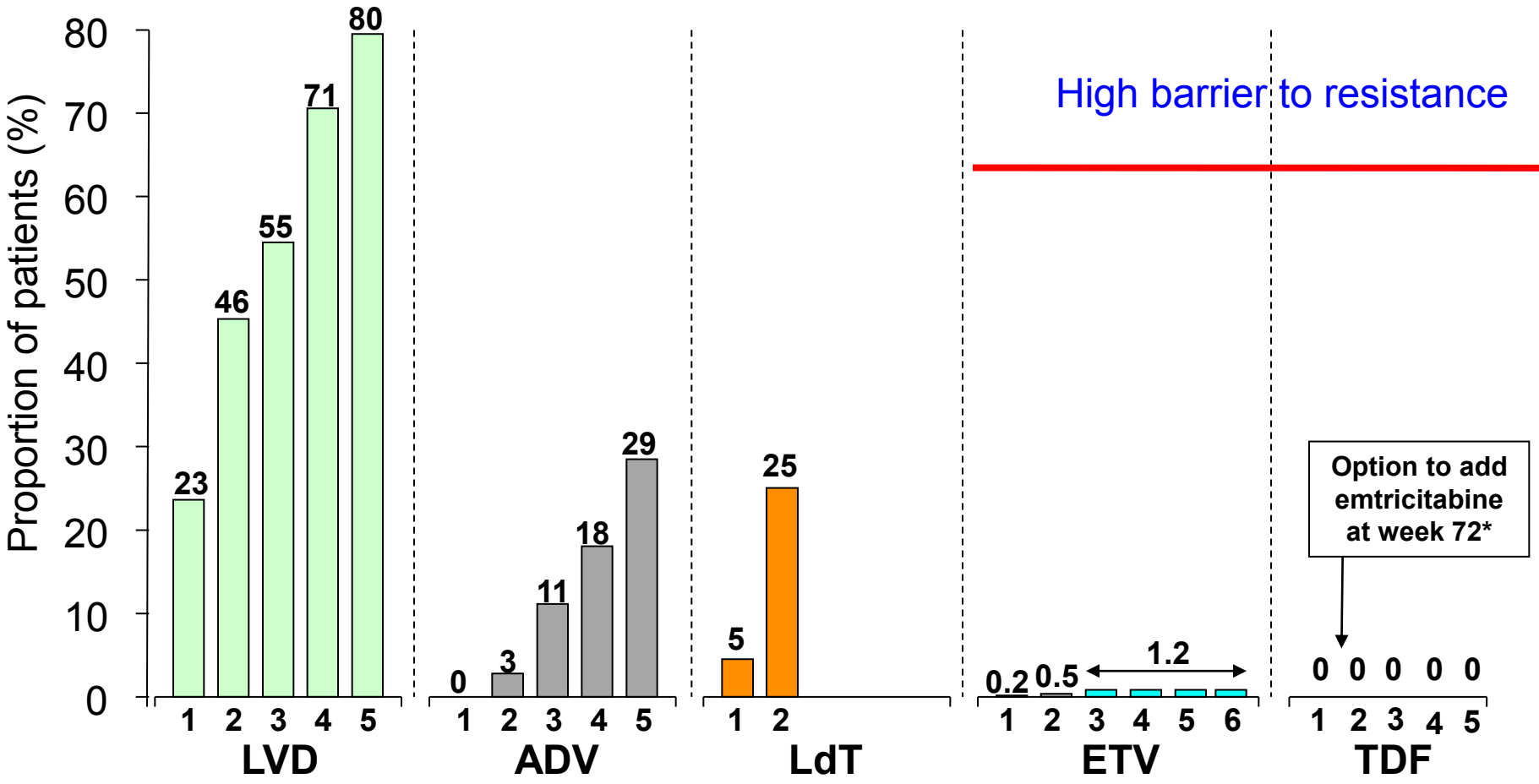
Prevention of resistance
Impact of first line therapy

- Choose an antiviral drug with

    1. A potent antiviral activity

    2. A high barrier to resistance

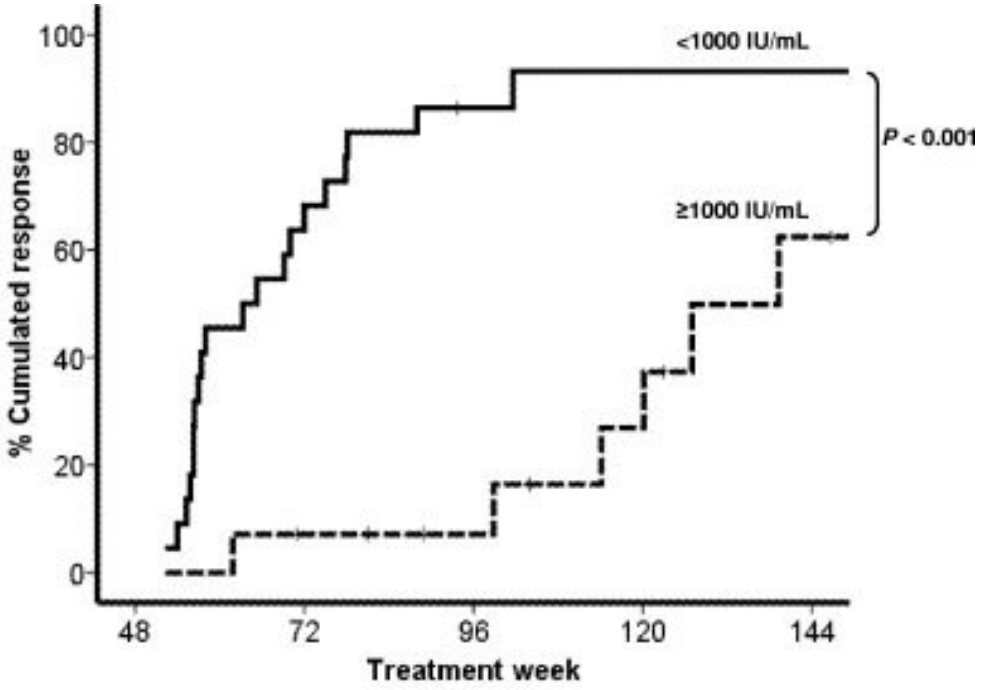
Rates of resistance with lamivudine (LVD), adefovir (ADV), telbivudine (LdT), entecavir (ETV) and tenofovir (TDF) among NA-naïve patients



*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

Gish, Jia, Locarnini, Zoulim, Lancet Infect Dis 2012

Entecavir treatment for chronic hepatitis B: Adaptation is not needed for the majority of naïve patients with a partial virological response



Number of patients without response					
<1000 IU/mL at week 48	22	8	2	1	1
≥1000 IU/mL at week 48	14[a]	12	10	7	3
Total number of patients in follow up	36	31	23	16	9

.Kaplan-Meier curve for the probability of achieving a VR for NA-naïve patients with a PVR according to HBV DNA at week 48. Three patients were switched to TDF plus emtricitabine, and one patient received TDF add-on therapy. P value was determined using log-rank testing.

Zoutendijk et al Hepatology Volume 54, Issue 2, pages 443-451, 25 JUL 2011

Mangement of antiviral drug resistance

- Impact of second line therapy
  - Early treatment adaptation to prevent accumulation of mutations
  - Choice always based on cross-resistance data
  - Add-on strategy versus switch ?
    - Good results with TDF switch
    - Some cases of suboptimal responses
    - Combination to increase the barrier to resistance

Zoulim & Locarnini, Gastroenterology 2009; EASL CPG J Hepatol 2009 & 2012

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

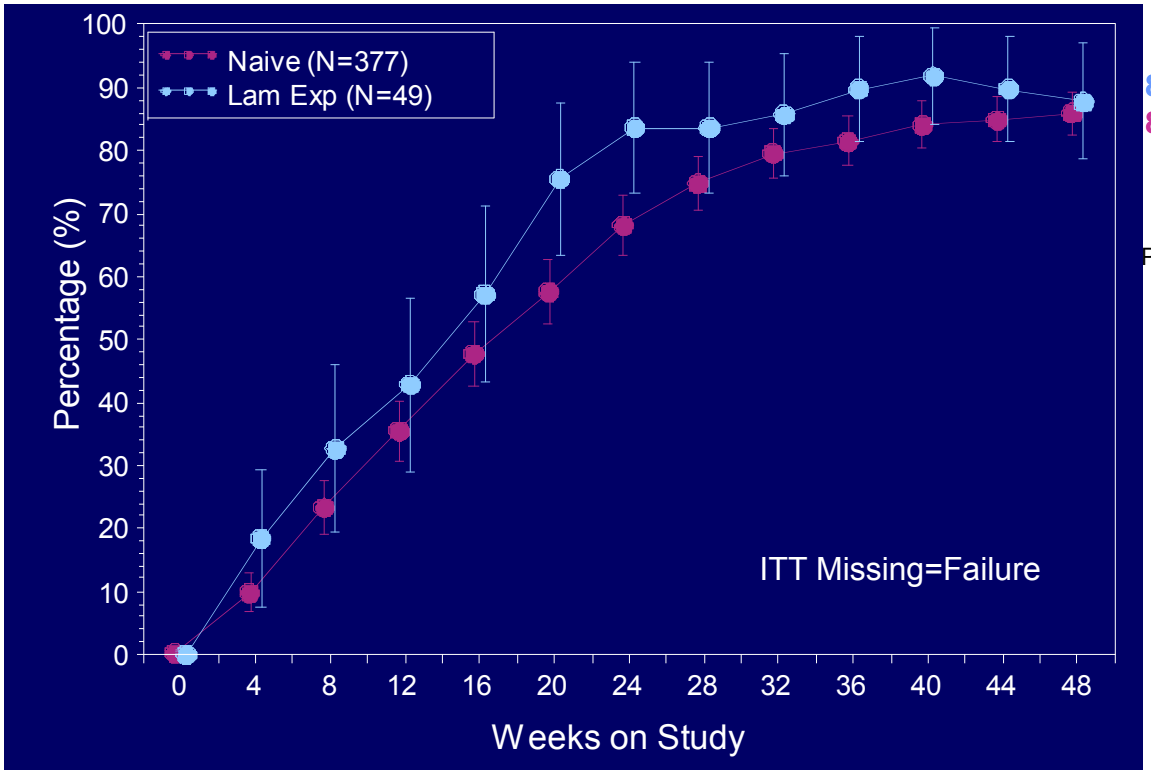
Pathway	Amino Acid Substitutions in the rt Domain	LMV	LdT	ETV	ADV	TFV
	Wild-type	S	S	S	S	S
L-Nucleoside (LMV/LdT)	M204I/V	R	R	I	S	S
Acyclic phosphonate (ADV)	N236T	S	S	S	R	I
Shared (LMV, LdT, ADV)	A181T/V	R	R	S	R	I
Double (ADV, TFV)	A181T/V + N236T	R	R	S	R	R
D-Cyclopentane (ETV)	L180M+M204V/I ± I169 ± T184 ± S202 ± M250	R	R	R	S	S
Multi-Drug Resistance	A181T+N236T+ M250V	R	R	R	R	R

Zoulim & Locarnini Gastroenterology 2009; Liver Int 2013

Tenofovir efficacy in LAM Experienced vs. Naïve

	Study 103: N=176	Study 102: N=250	Total
LAM-Naïve, n	168	209	377
LAM-Experienced, n	8	41	49

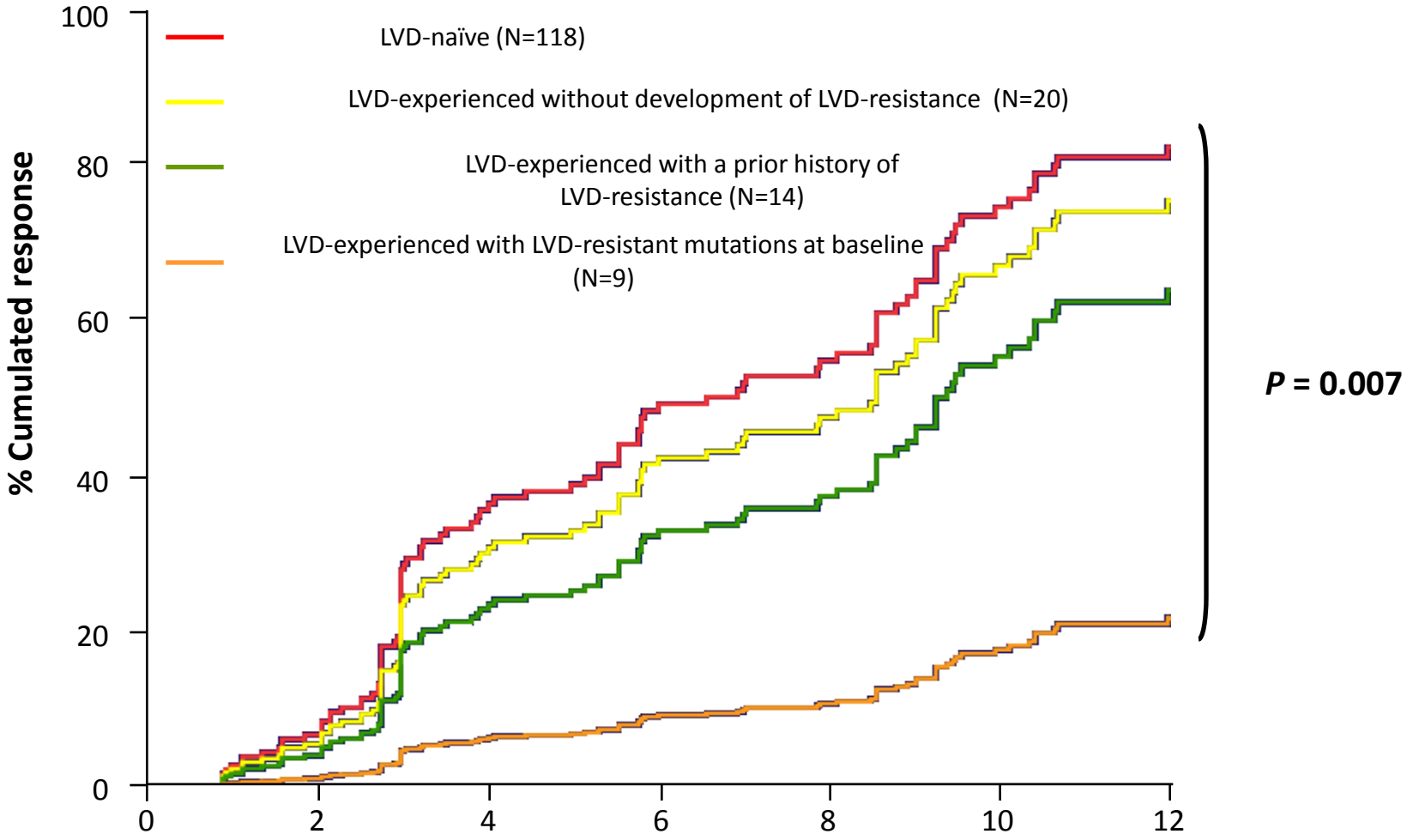
- Study 102 actively enrolled both LAM experienced and LAM-naïve patients
- Study 103 enrolled eight LAM experienced patients despite LAM-naïve inclusion criteria



Combined data includes both HBeAg +/- patients

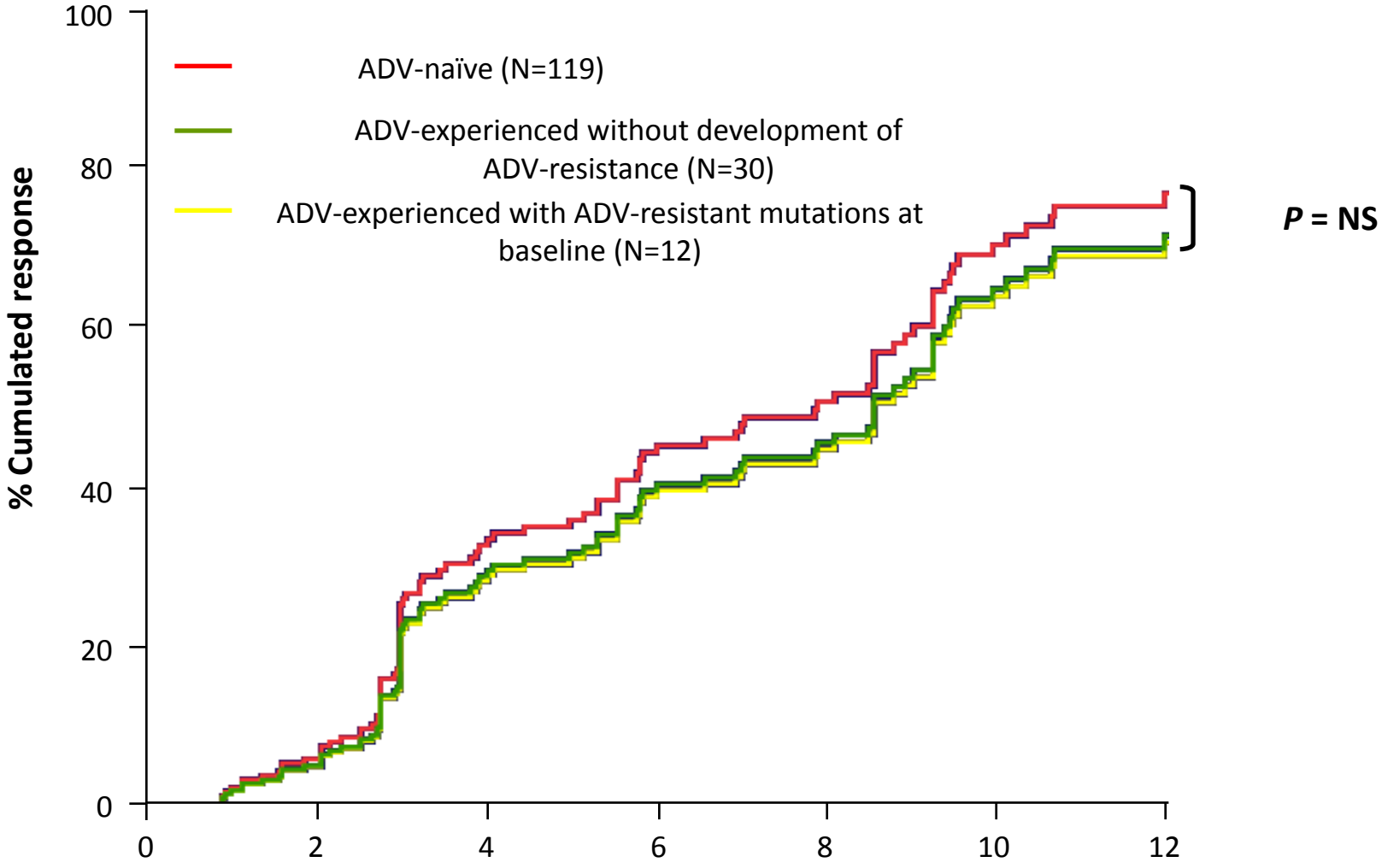
Manns M, et al., EASL 2008; Oral # 1587.

Virologic response to Entecavir according to Lamivudine exposure



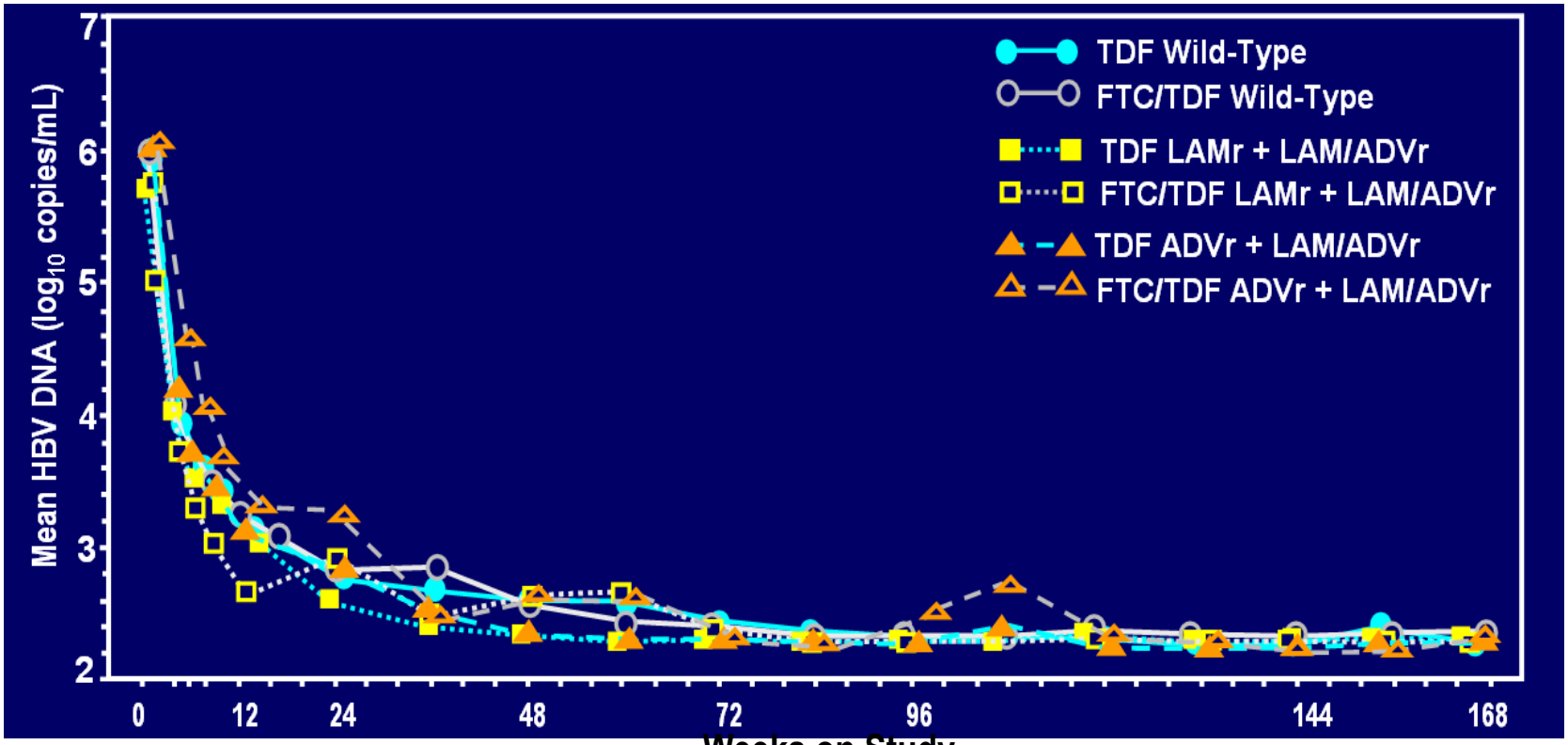
Reijnders, JGP et al. J Hepatol 2010

Virologic response to Entecavir according to Adefovir exposure



Reijnders, JGP et al.. J Hepatol. 2010

TDF vs. FTC/TDF for Treatment-Experienced Patients: Response by Baseline Resistance at Week 168



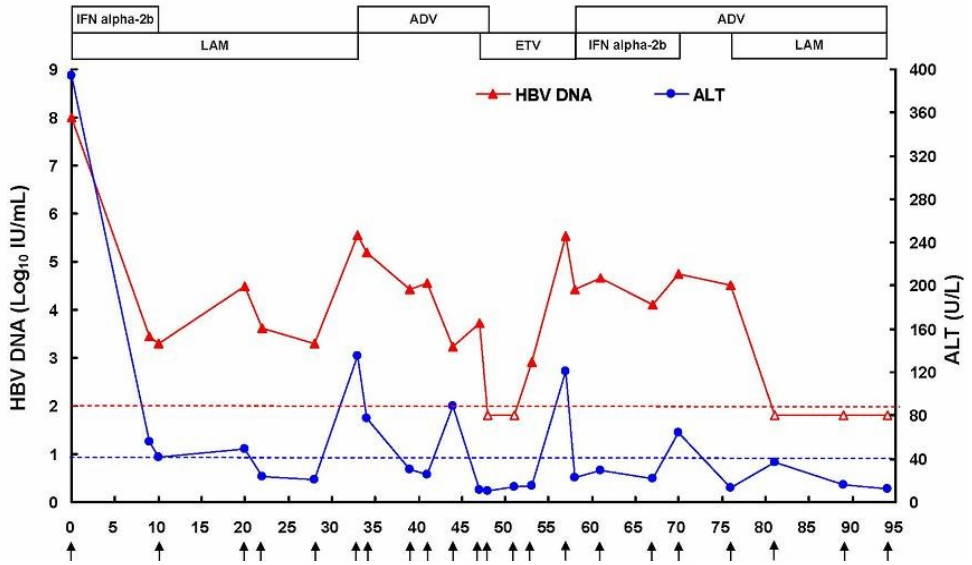
n =	29	29	29	29	27	26	24	24
n =	33	33	33	31	30	29	27	26
n =	14	14	14	14	14	14	14	14
n =	11	11	11	11	10	10	10	10
n =	17	16	16	16	16	16	16	16
n =	12	12	12	12	12	11	10	10

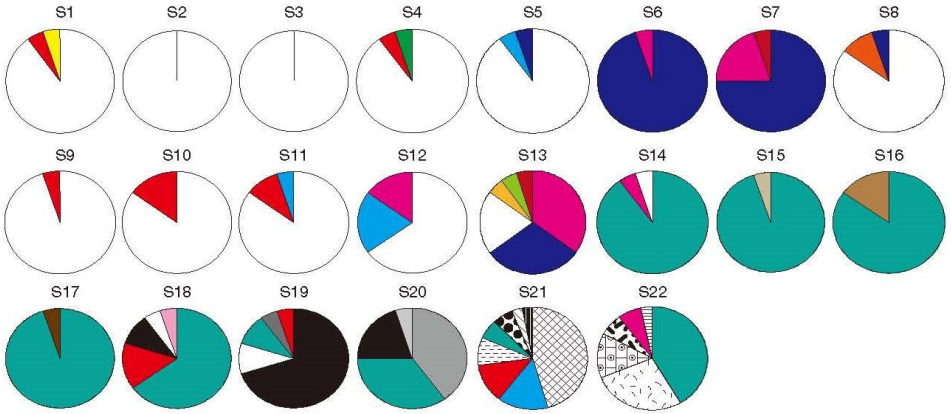
Berg et al, Gastroenterology 2010; Ms submitted

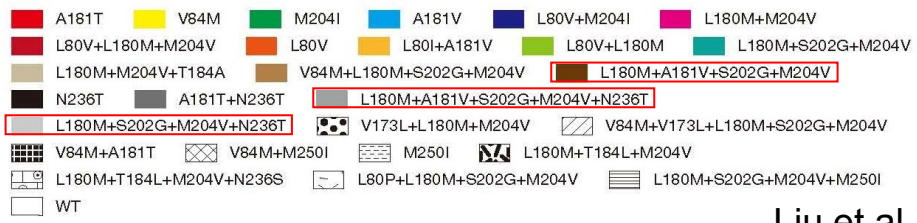
Patients heavily exposed to NUCs with low barrier to resistance – Risk of MDR selection

- Risk of multidrug resistance by sequential accumulation of resistance mutations
- Risk of partial response, even with the newest NUCs -> long-term impact ?

Sequential therapy with NUCs 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.

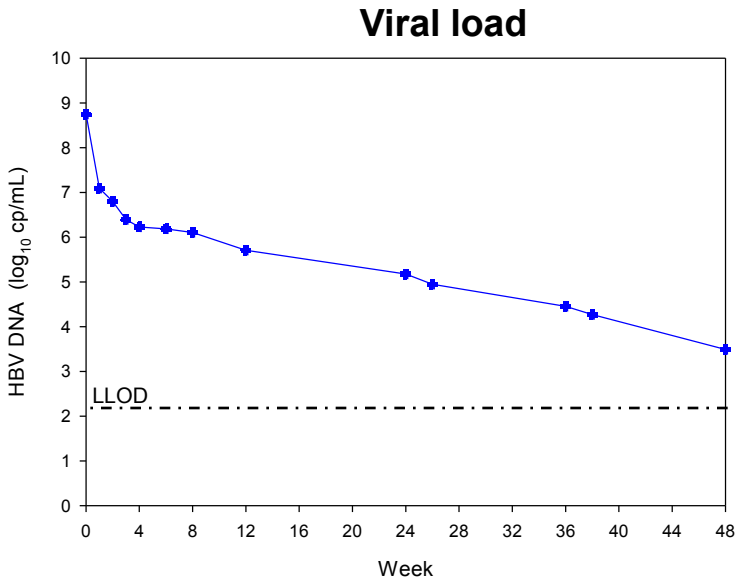
Impact of rtA181 and rtN236 mutations on antiviral drug efficacy and cross-resistance

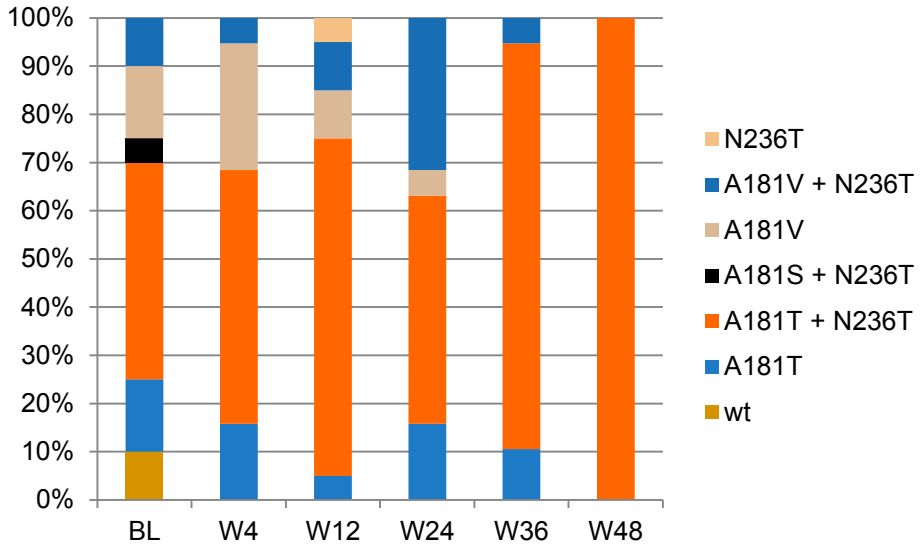
In vitro **susceptibility to nucleos(t)ide analogs of the rtA181T, rtA181V, rtA181T+N236T, rtA181V+N236T, and rtN236T+N238T mutants isolated from patients with virological failure**

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 previously failed ADV





Patient 1051 data:

BL viral load = 8.75log

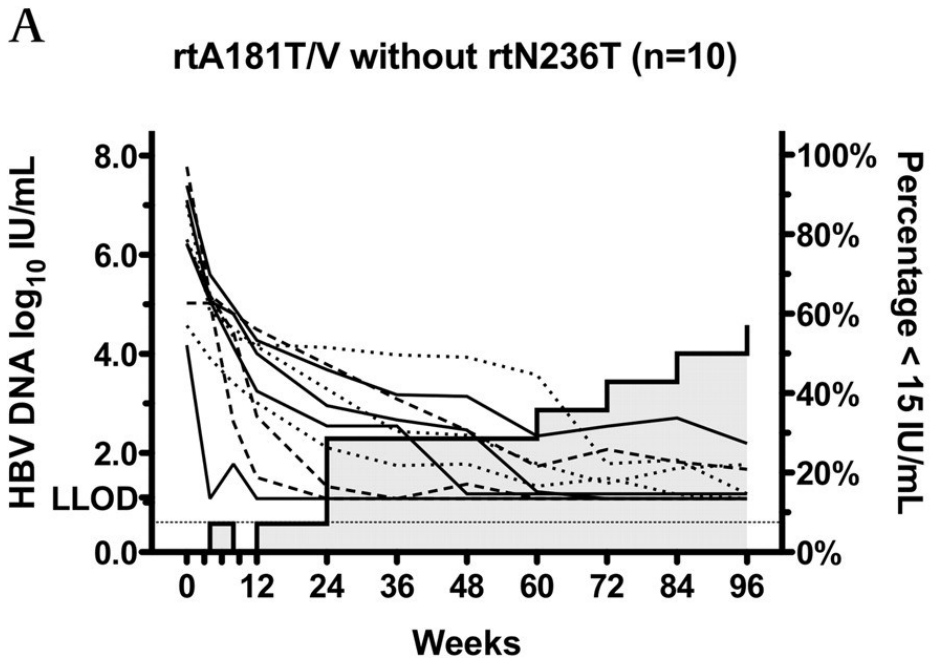
Treatment: TDF

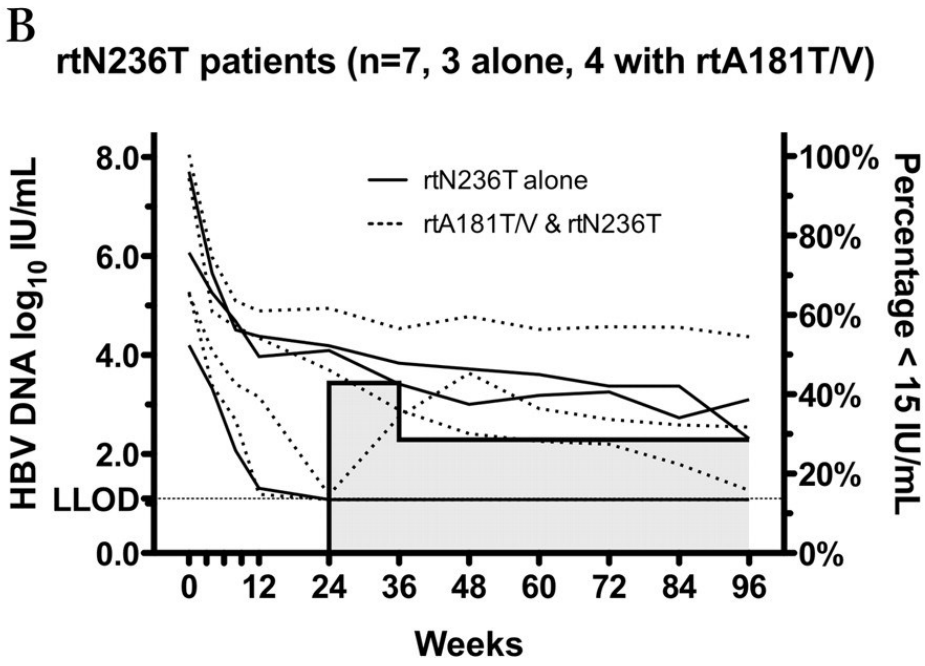
Adherence : 95.2%

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

Lavocat et al, AASLD 2010 & Ms submitted

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

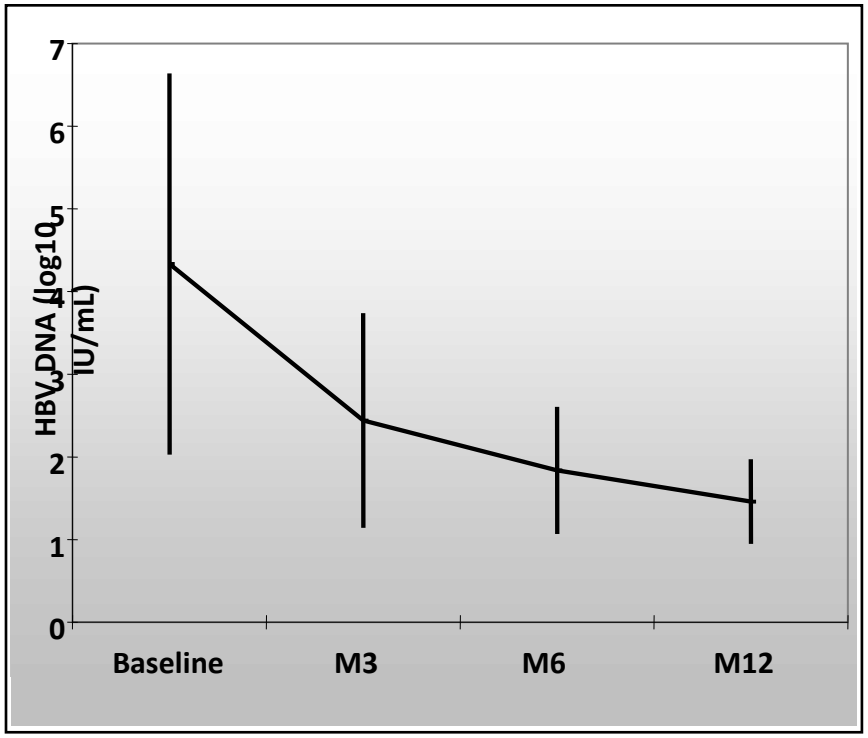




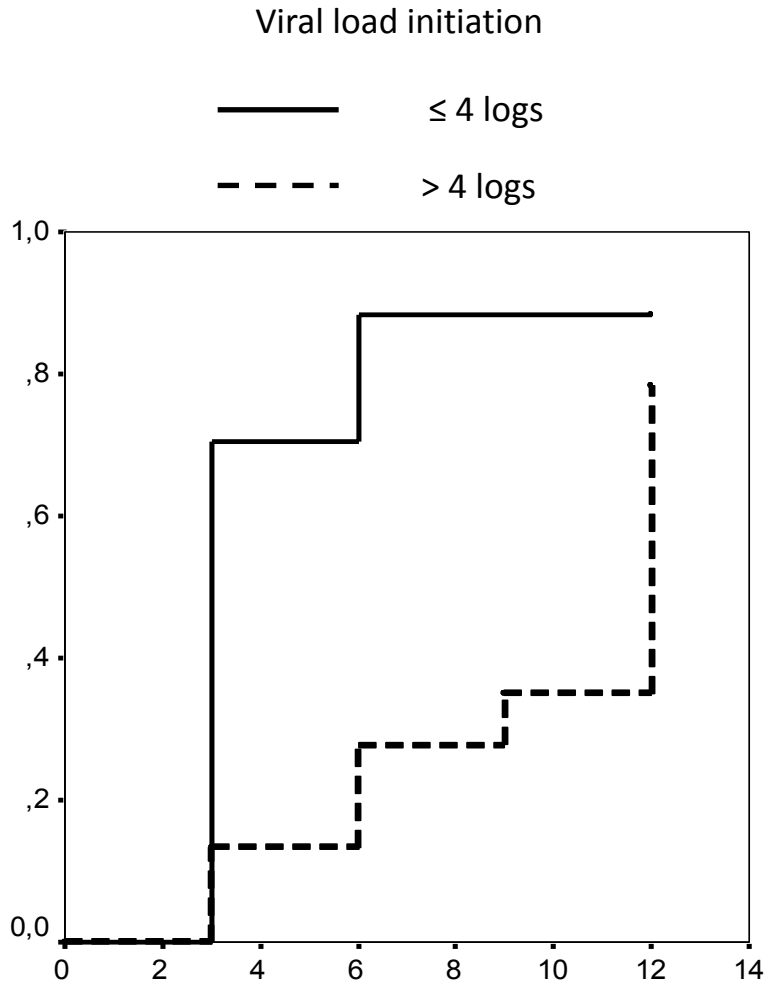
Patterson S J et al. Gut 2011;60:247-254

Tenofovir + Emtricitabine in patients with treatment failure – treatment intensification

HBV DNA kinetics after TDF+FTC initiation in 59 patients with treatment intensification



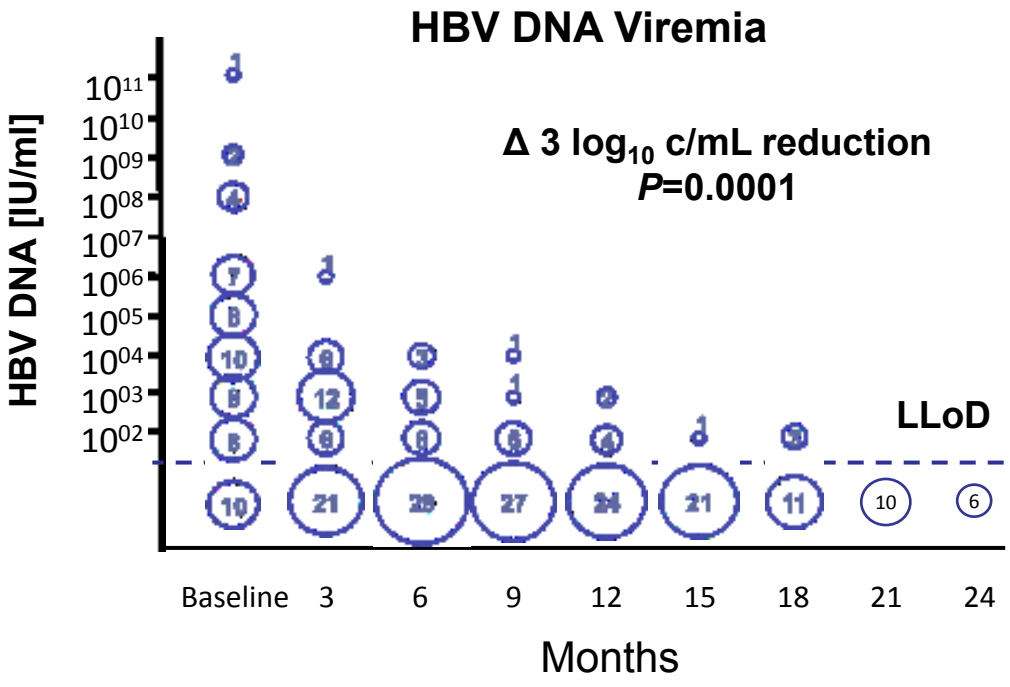
Time after TDF+FTC initiation (months)



Time to undetectable DNA (<50 IU/mL)

Si-Ahmed et al, Antiviral Research 2011

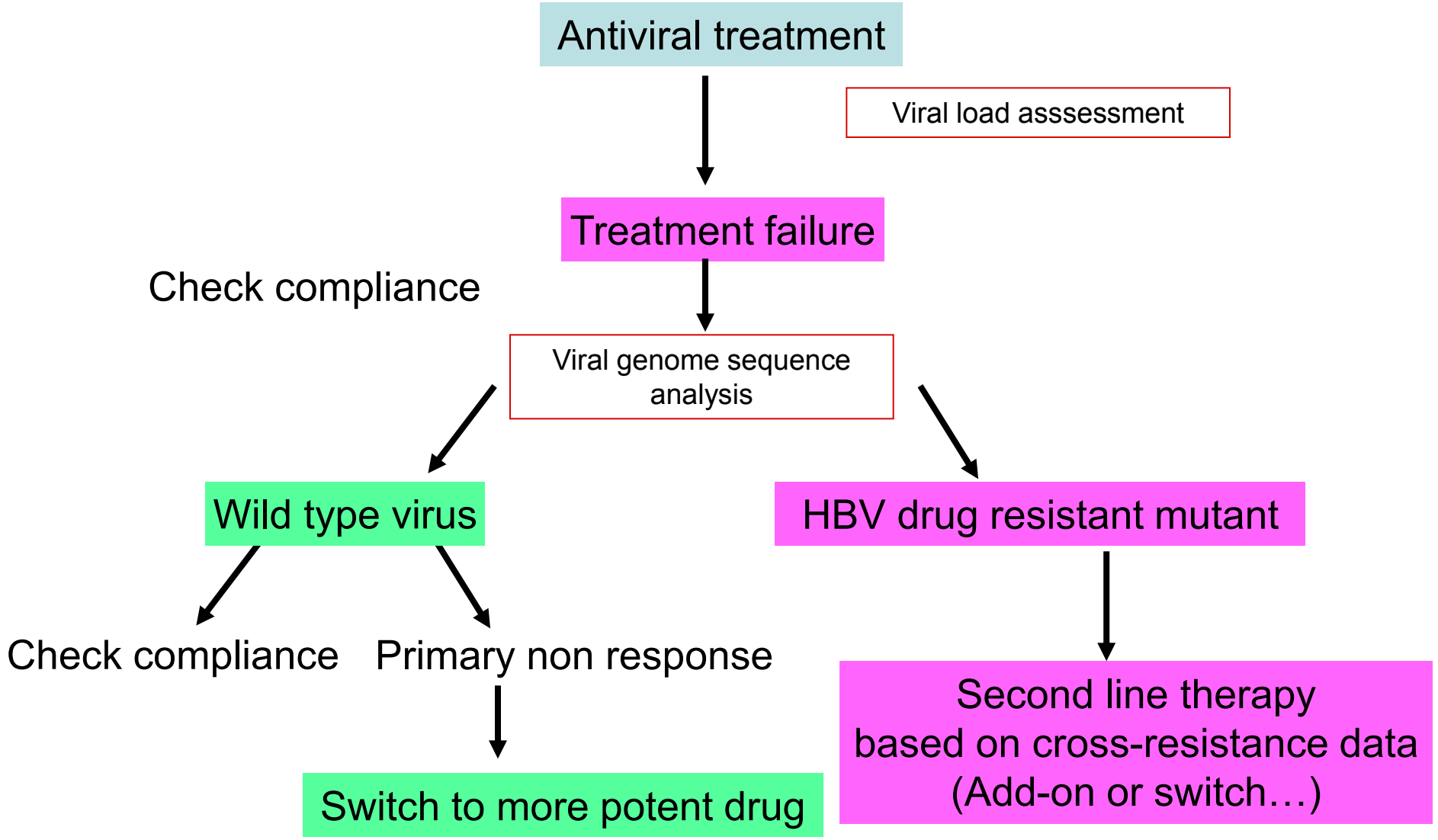
ETV + TDF combination in patients with treatment failure



Rescue therapy with ETV + TDF in CHB patients with advanced liver disease and complex viral resistance patterns or showing partial antiviral responses to preceeding therapies (Virgil network)

Petersen J, et al. J Hepatol 2012

Management algorithm



Zoulim and Perrillo, J Hepatol, 2008; EASL CPG J Hepatol 2012

Suggested treatment adpatation in patients with treatment failure

Type of failure	Treatment adaptation
Lamivudine resistance	1) add TFV (add ADV if TFV not available) 2) a switch to TFV is also advised by some guidelines
Adefovir resistance	1) switch to TFV (if available) and a 2nd drug 2) if no history of LMV, switching to ETV is also effective. 3) If rtN236T substitution, consider adding LMV, ETV, or LdT to the TFV or switch to TFV plus FTC 4) If rtA181V/T substitution, alone or in combination with rtN236T, switch to TFV plus ETV
Telbivudine resistance	1) add TFV 2) a switch to TFV has been considered in some guidelines 3) a switch to ADV is not recommended
Entecavir resistance	add TFV
Tenofovir resistance	1) not been confirmed so far 2) genotyping and phenotyping required 3) may add ETV

EASL CPG, J Hepatol 2009 & 2012; Zoulim & Locarnini Liver Int 2013

Acknowledgements

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Clinical studies

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INSERM U1052

Innate responses

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M. AitGoughoulte
B. Testoni
N. Isorce

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F. Lavocat
G. Billioud
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D. Durantel

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M. Levrero, Roma
XX Zhang, Shanghai
D Xu, Beijing
J Petersen, Hamburg
H Janssen, Rotterdam

Suggested treatment adpatation in patients with treatment failure

Type of failure	Treatment adaptation
Lamivudine resistance	1) add TFV (add ADV if TFV not available) 2) a switch to TFV is also advised by some guidelines 3) a switch to ADV is not recommended due to a high rate of resistance and its low potency
Adefovir resistance	1) switch to TFV if available and add a second drug without cross resistance. 2) if no history of LMV, switching to ETV is also effective. 3) If rtN236T substitution, consider adding LMV, ETV, or LdT to the TFV or switch to TFV plus FTC; if no history of LMV prior, consider switching to ETV 4) If rtA181V/T substitution, alone or in combination with rtN236T, switch to TFV plus ETV; as before, if no history LMV, consider switching to ETV;
Telbivudine resistance	1) add TFV 2) a switch to TFV has also been considered in some guidelines 3) a switch to ADV is not recommended
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Tenofovir resistance	1) not been confirmed so far 2) genotyping and phenotyping required 3) may add ETV

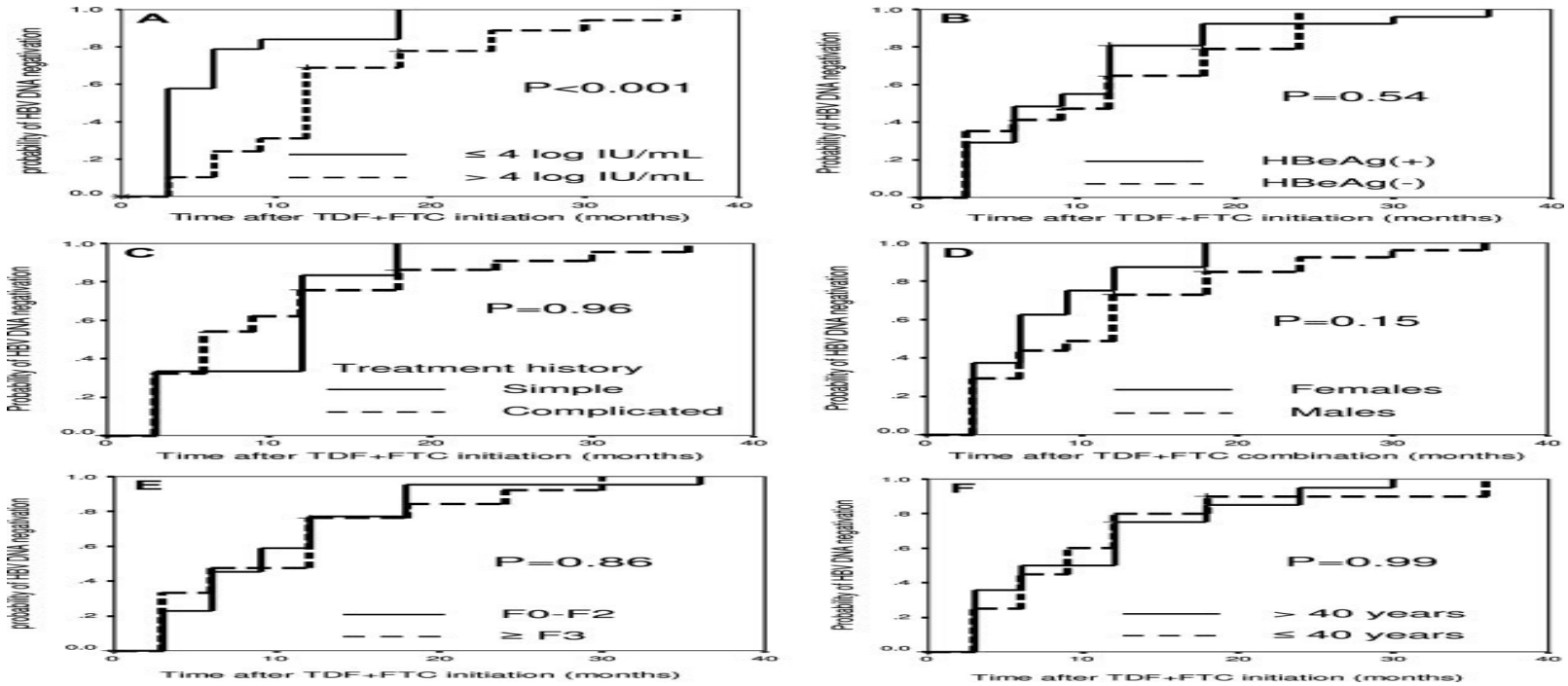


Fig. 2 Kaplan?Meier analysis giving the probability of HBV-DNA negativity according to HBV-DNA level at baseline (A), HBeAg status at baseline (B), previous treatment history (C), gender (D), fibrosis at baseline (E), and age (F).

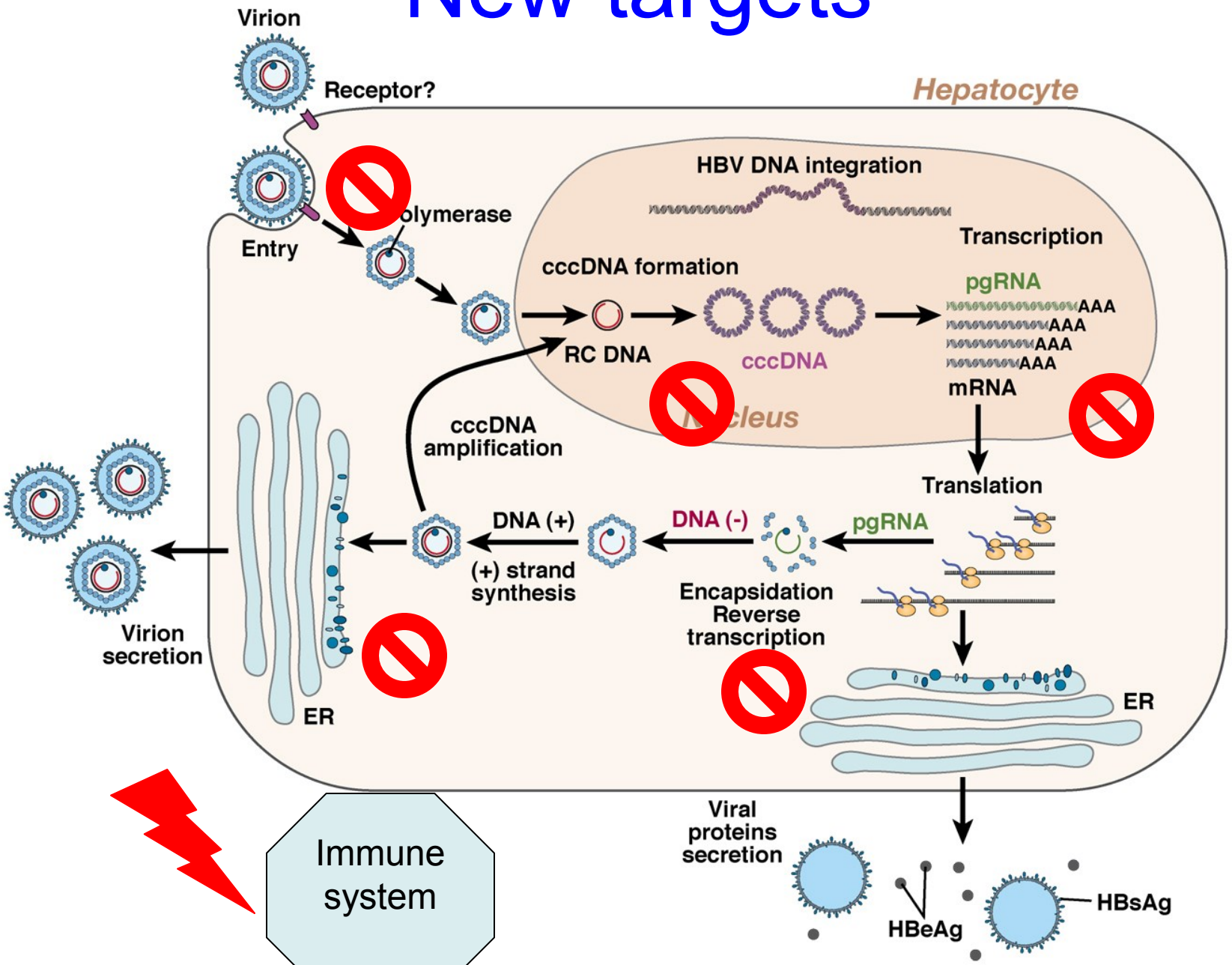
Si-Nafa Si-Ahmed , Pierre Pradat , Roeland Zoutendijk , Maria Buti , Vincent Mallet , Claire Cruiziat , Katja Det...

Efficacy and tolerance of a combination of tenofovir disoproxil fumarate plus emtricitabine in patients with chronic hepatitis B: A European multicenter study

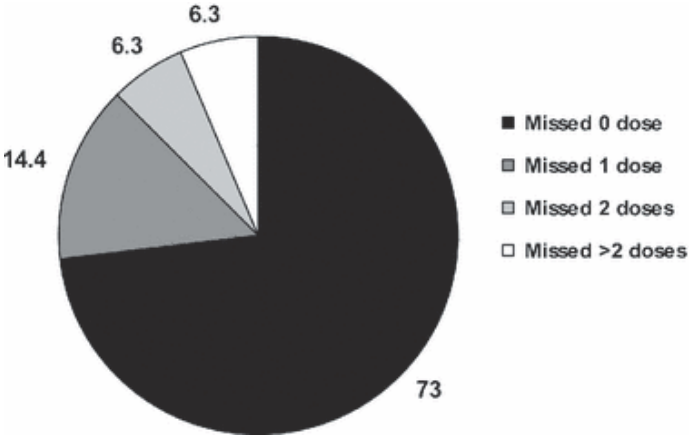
Antiviral Research Volume 92, Issue 1 2011 90 - 95

http://dx.doi.org/10.1016/j.antiviral.2011.07.003

New targets


Virion
Receptor?
Hepatocyte
Entry
olymerase
HBV DNA integration
Transcription
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
Viral
proteins
secretion
HBeAg
HBsAg
Immune
system

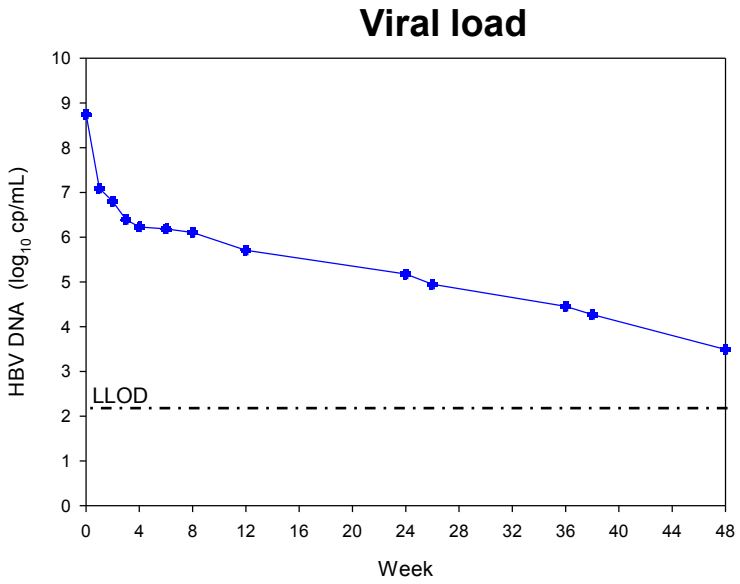
Adherence to nucleos(t)ide analogues for chronic hepatitis B in clinical practice and correlation with virological breakthroughs

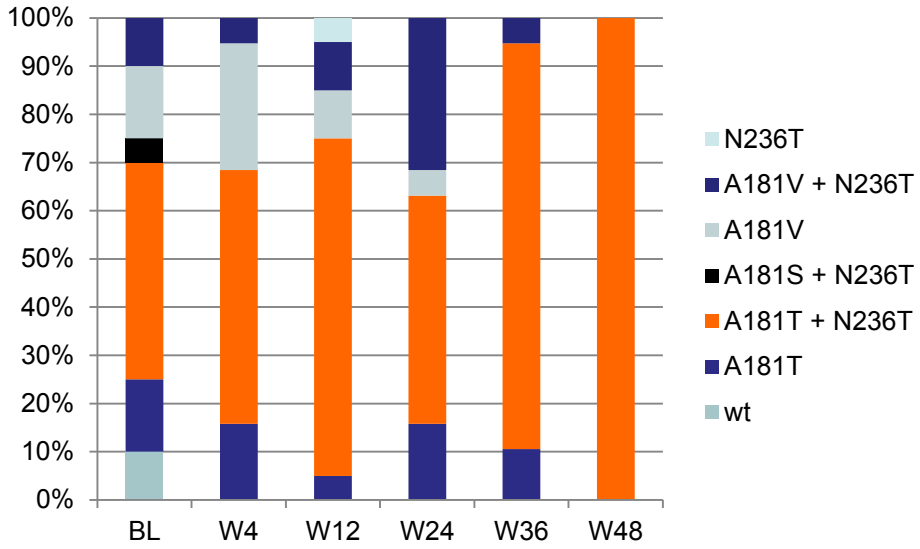


Journal of Viral Hepatitis
Volume 19, Issue 3, pages 205-212, 14 JUL 2011 DOI: 10.1111/j.1365-2893.2011.01494.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2893.2011.01494.x/full#f1

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

Patient #1051





Patient 1051 data:

BL viral load = 8.75log

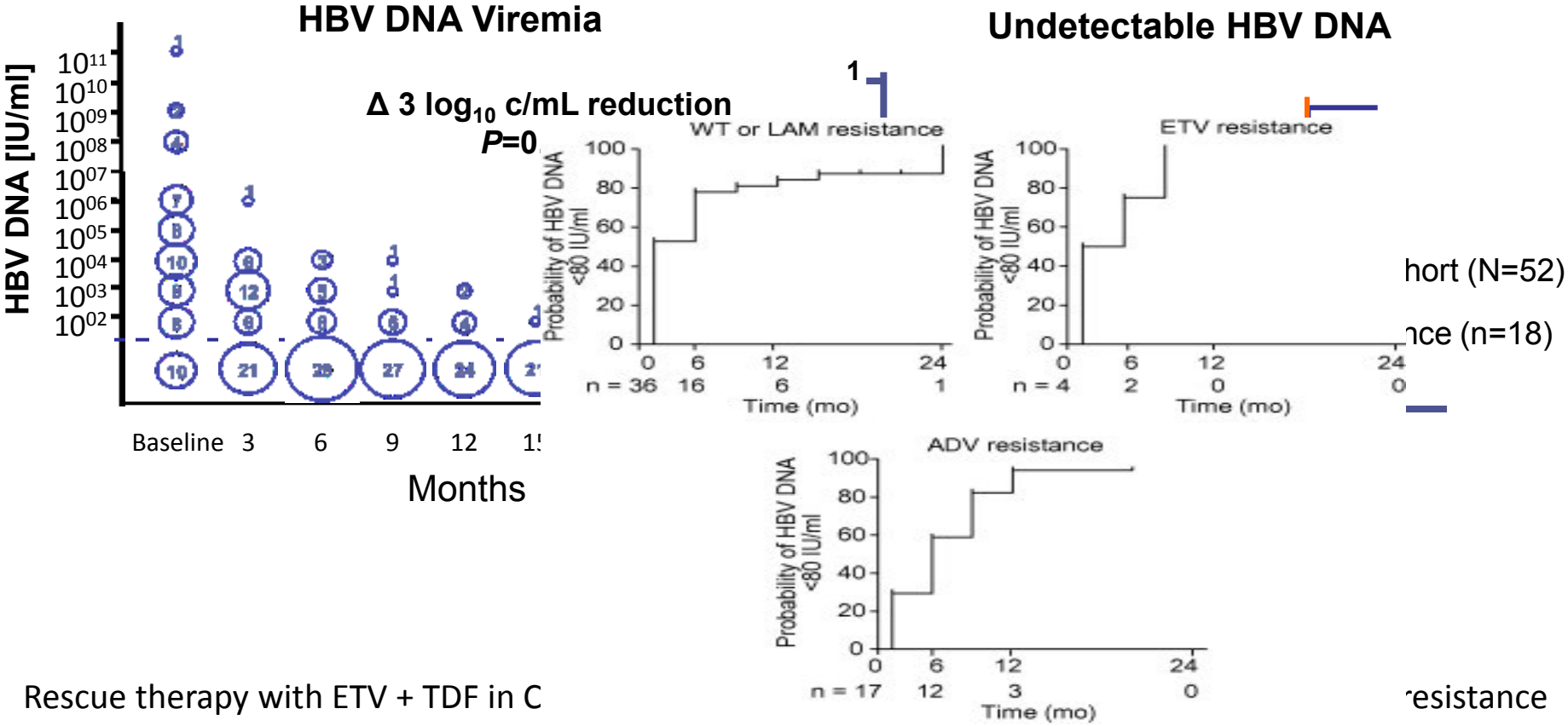
Treatment: TDF

Adherence : 95.2%

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

Lavocat & Zoulim, AASLD 2010.

ETV + TDF combination in patients with treatment failure

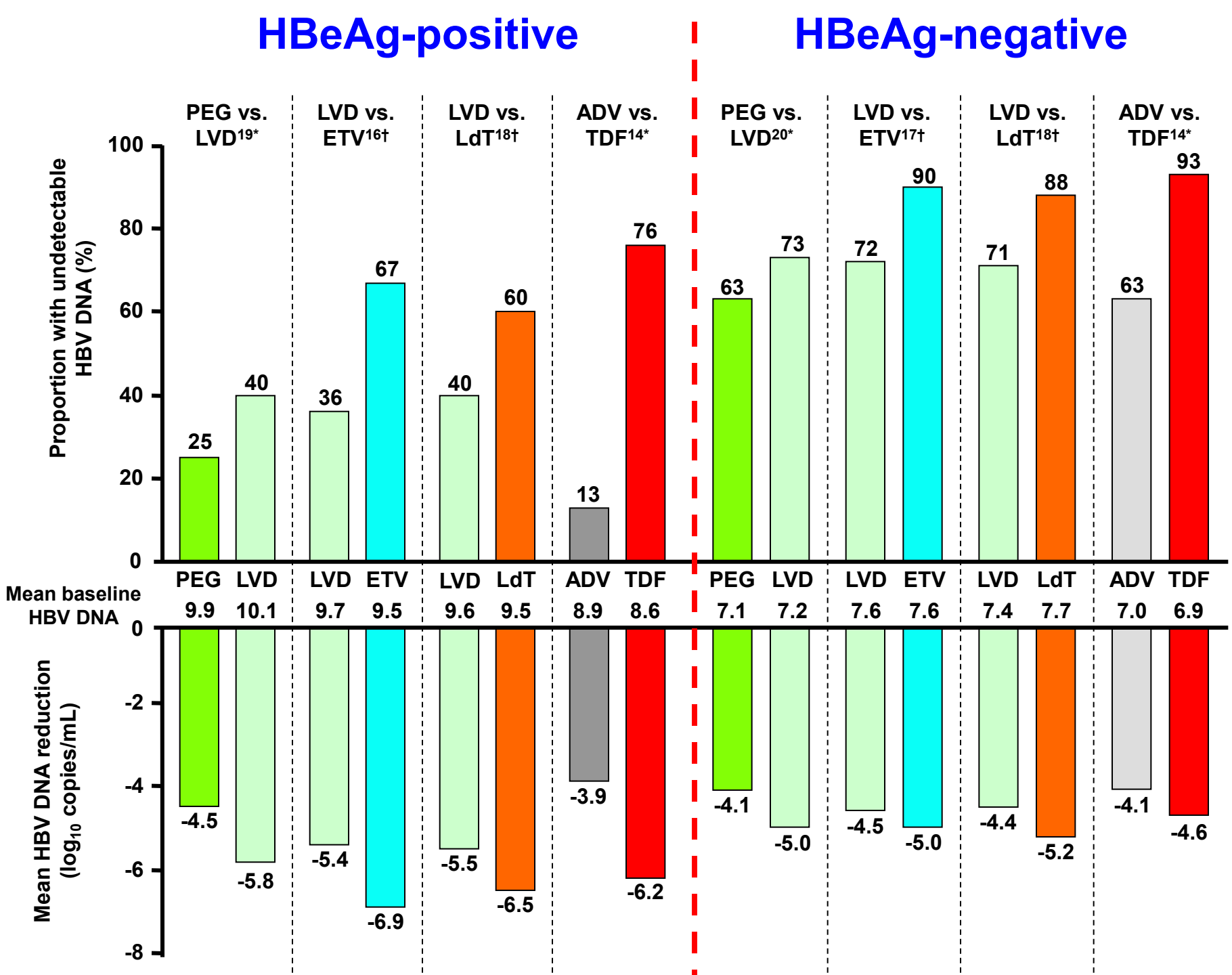


hort (N=52)

nce (n=18)

Rescue therapy with ETV + TDF in C esistance patterns or showing partial antiviral responses to preceeding therapies (Virgil network)

Petersen J, et al. J Hepatol 2012.


HBeAg-positive
HBeAg-negative
PEG vs. LVD[19*]
LVD vs. ETV[16†]
LVD vs. LdT[18†]
ADV vs. TDF[14*]
PEG vs. LVD[20*]
LVD vs. ETV[17†]
LVD vs. LdT[18†]
ADV vs. TDF[14*]
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
Mean baseline HBV DNA
PEG 9.9
LVD 10.1
LVD 9.7
ETV 9.5
LVD 9.6
LdT 9.5
ADV 8.9
TDF 8.6
PEG 7.1
LVD 7.2
LVD 7.6
ETV 7.6
LVD 7.4
LdT 7.7
ADV 7.0
TDF 6.9
Mean HBV DNA reduction (log_{10} 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

Entecavir treatment for chronic hepatitis B: Adaptation is not needed for the majority of naïve patients with a partial virological response

Zoutendijk et al **Hepatology**
Volume 54, Issue 2, pages 443-451, 25 JUL 2011 DOI: 10.1002/hep.24406
http://onlinelibrary.wiley.com/doi/10.1002/hep.24406/full#fig3

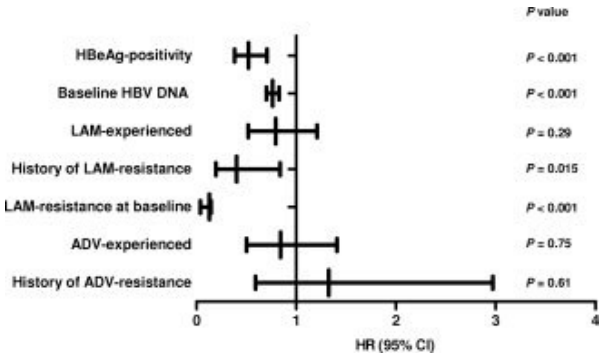
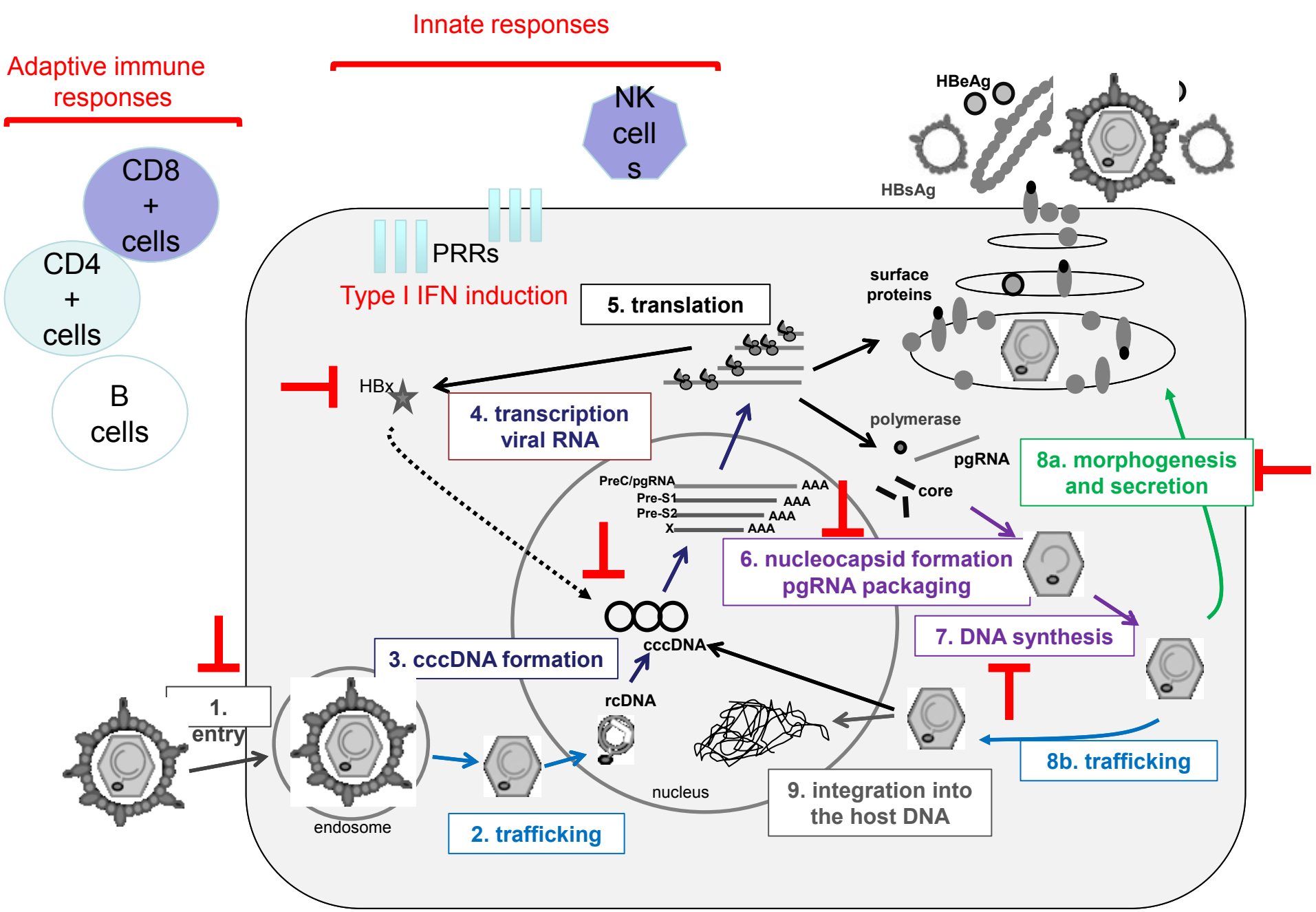


Figure 3. Adjusted HR of achieving a VR for both NA-naïve and NA-experienced patients. Based on the Cox model adjusted for HBeAg status, mean baseline HBV DNA, LAM experience, history of LAM resistance, LAM resistance at baseline, ADV experience, and history of ADV resistance.

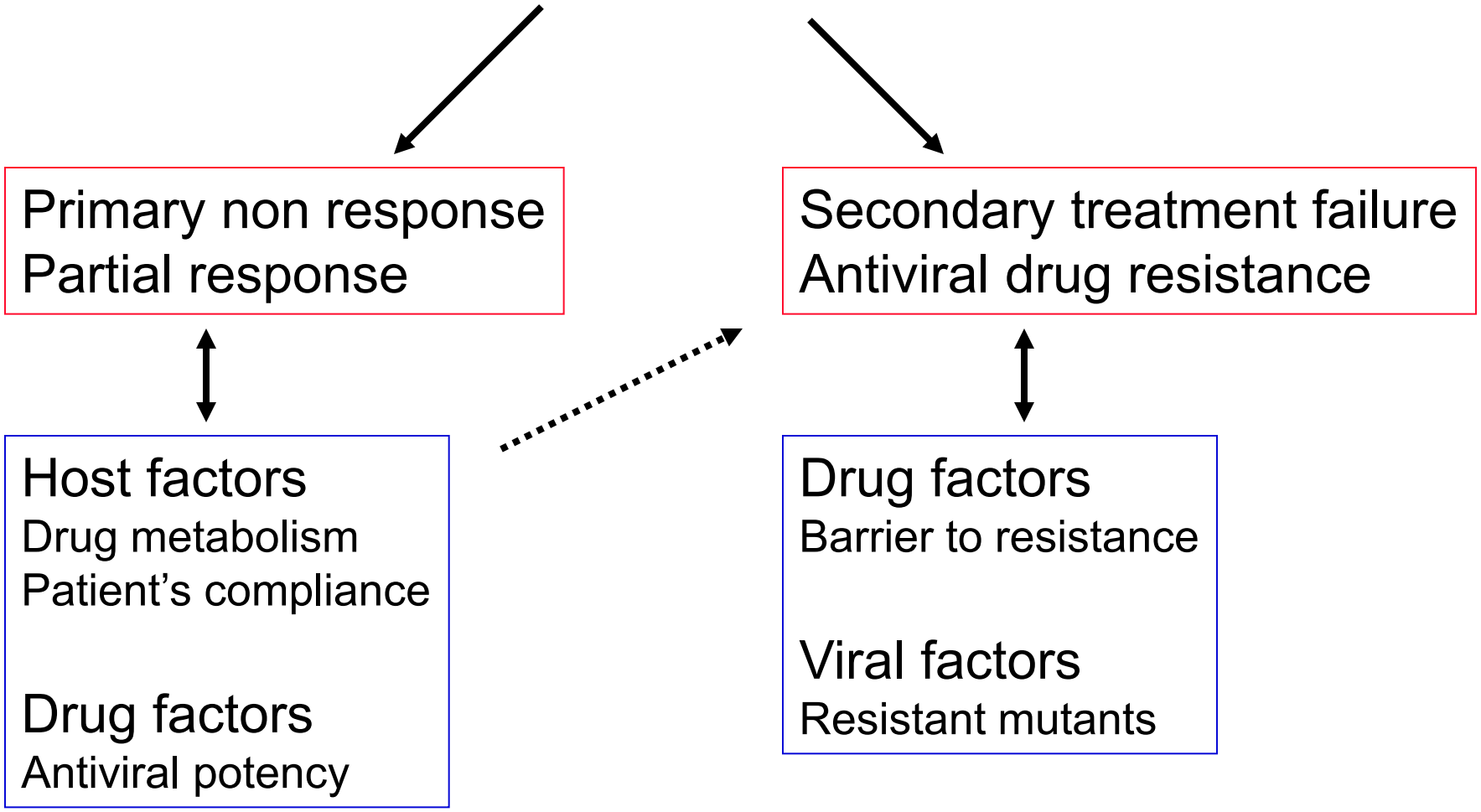


Zoulim, Antiviral Research, 2012

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

Treatment failure



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

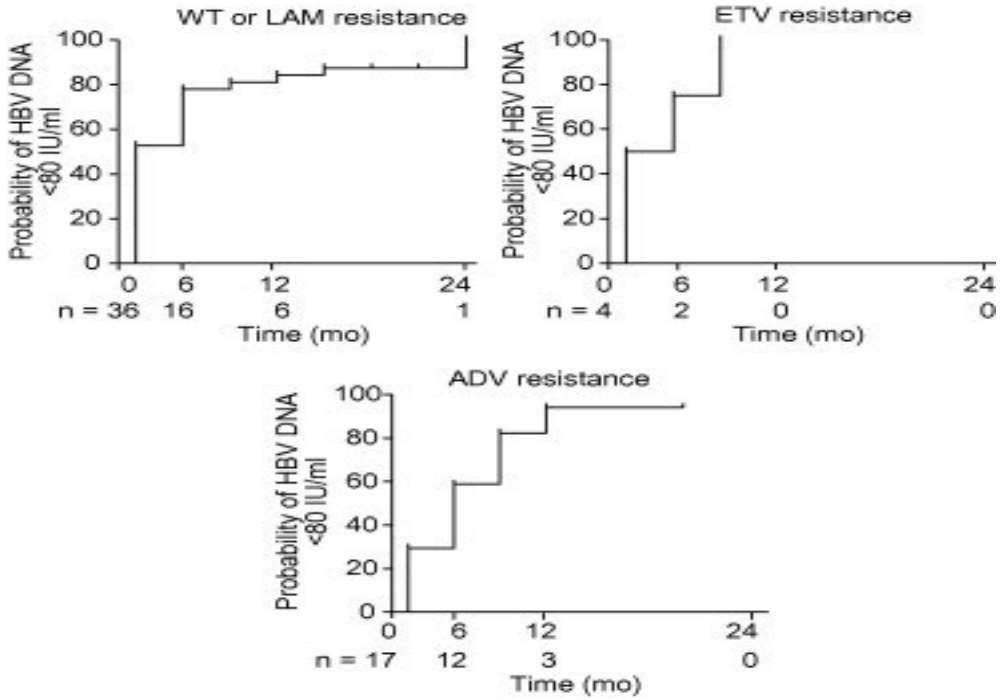


Fig. 2 Probability of HBV DNA below LLoD (80<ce:hsp sp="0.25"/> IU/ml) . A Kaplan?Meier analysis was used to analyze the probability of reaching HBV DNA undetectability. For the entire cohort, the median time to HBV-DNA undetectability was 6<ce:...

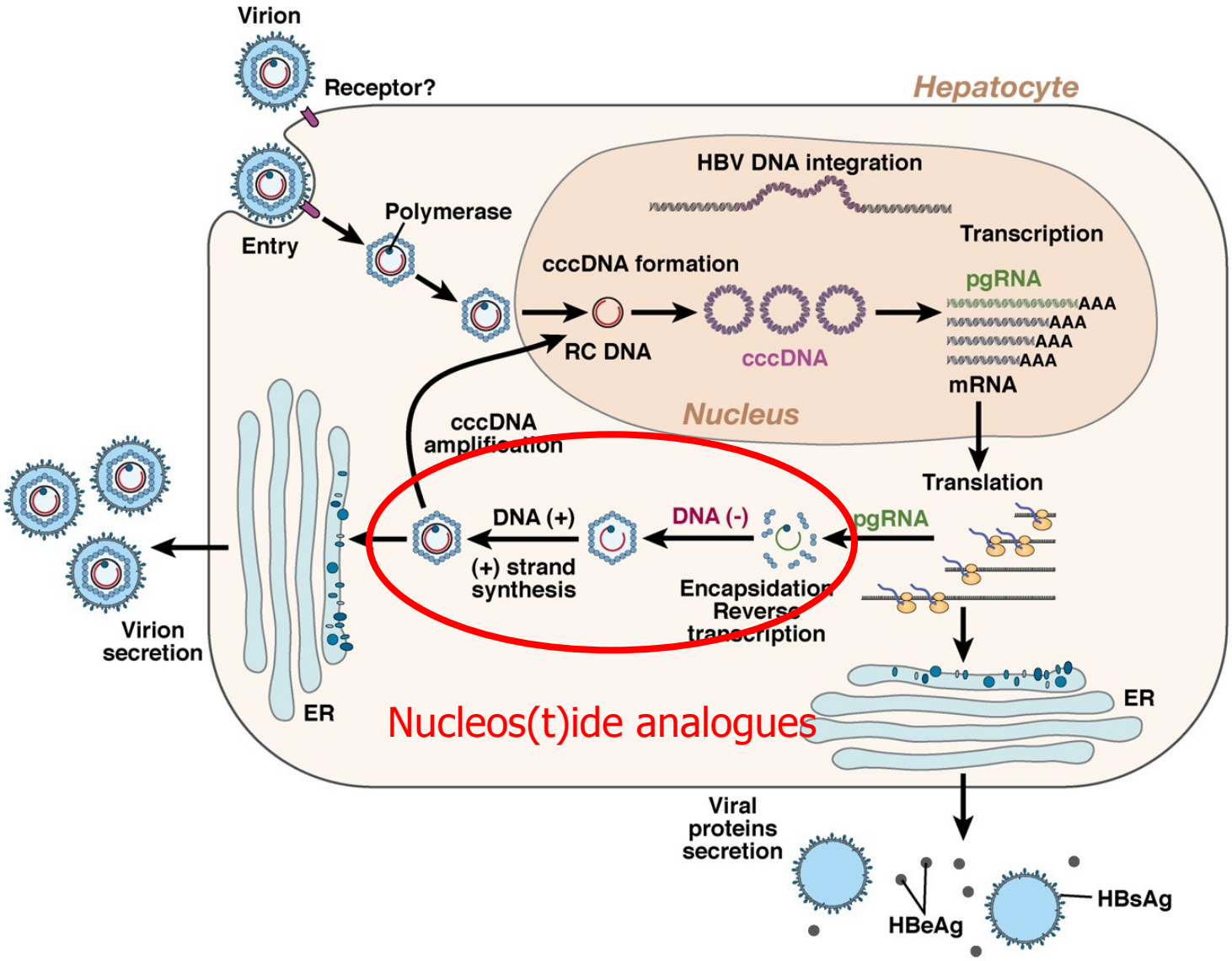
Jorg Petersen , Vlad Ratziu , Maria Buti , Harry L.A. Janssen , Ashley Brown , Pietro Lampertico , Jan Schollmeye...

Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: An international multicenter cohort study

Journal of Hepatology Volume 56, Issue 3 2012 520 - 526

http://dx.doi.org/10.1016/j.jhep.2011.09.018

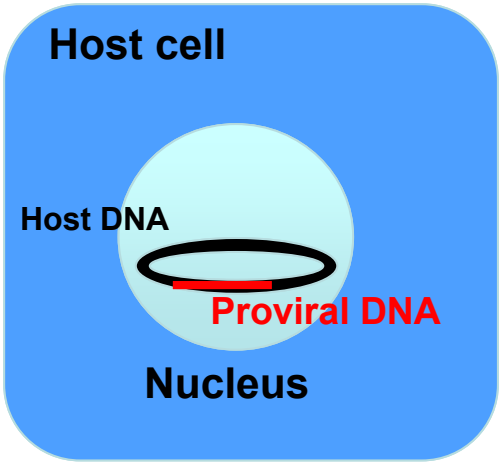
The target of nucleos(t)ide analogues



Zoulim F & Locarnini, *Gastroenterology* 2009;**137**:1593-1608.

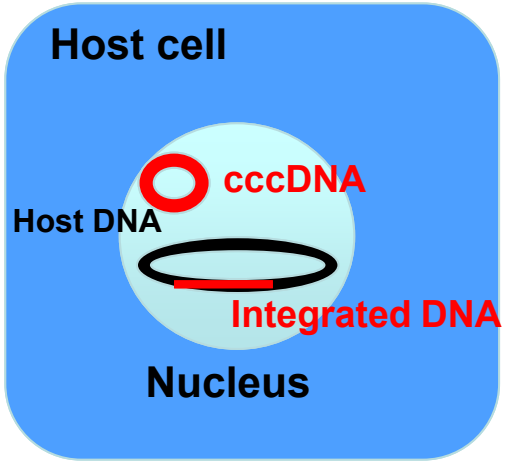
The main differences between HIV, HBV and HCV

HIV



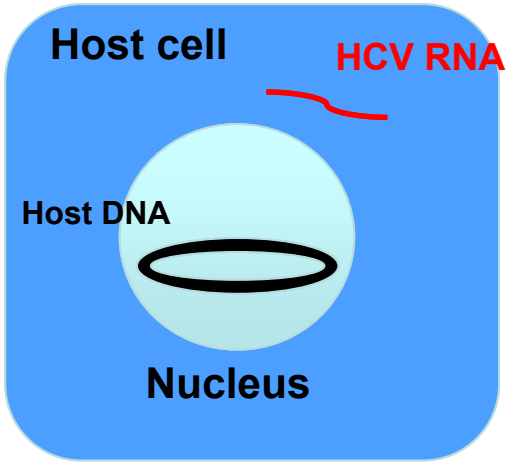
Lifelong suppression of viral replication

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