Treatment as Prevention Challenges in HBV

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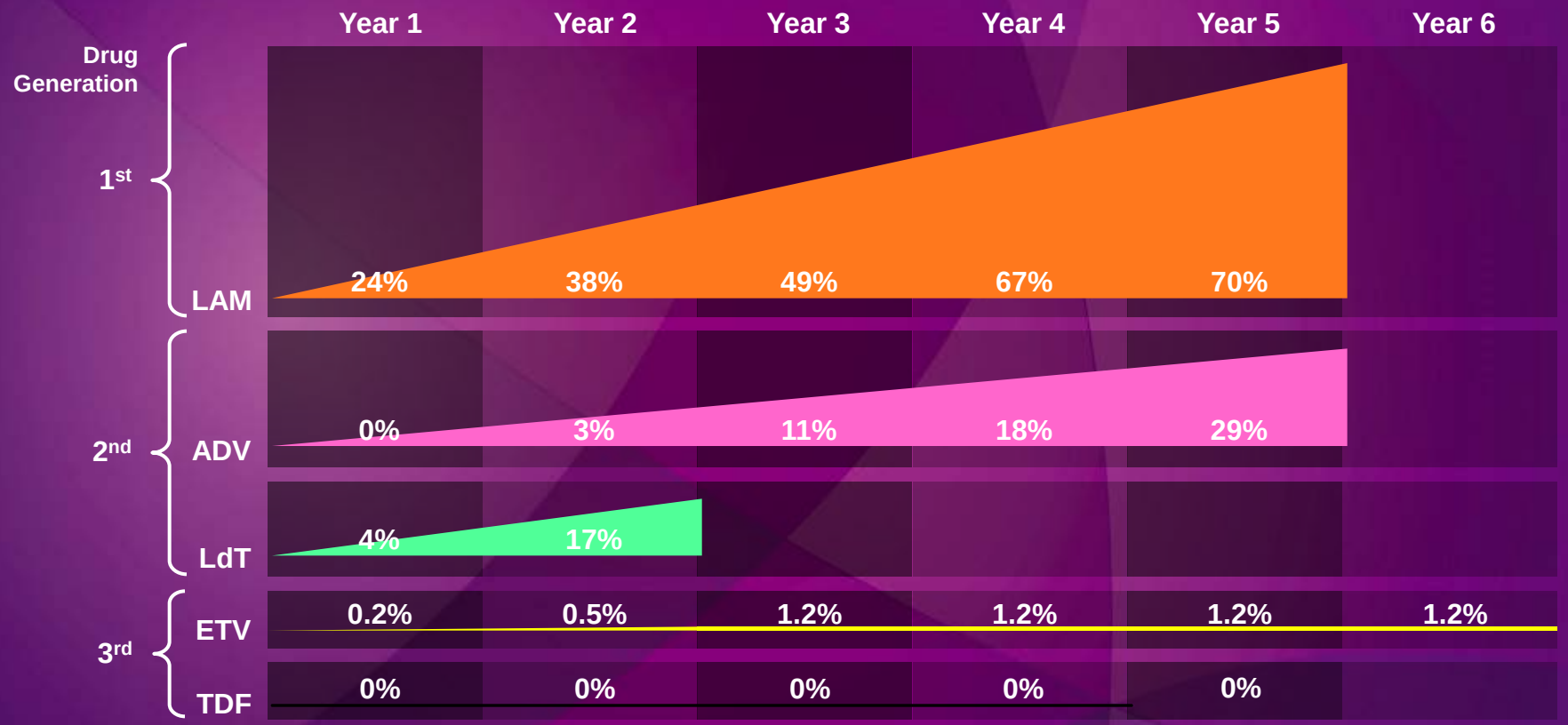
Entecavir and Tenofovir are the first line NA treatment for CHB

Not head-to-head trials; different patient populations and trial designs



Adapted from 1. EASL. J *Hepatol*. 2009;**50**:227-42. 2. Tenney DJ, *et al*. *EASL* 2009. Oral presentation #20. 3. Marcellin P, *et al*. *Hepatology* 2009;**50(4, Suppl.)**:532A-3A. 4. Heathcote EJ, *et al*. *Hepatology* 2009;50(4, Suppl.):533A-4A 5. Marcellin P, *et al*. *Lancet* 2013;381:468-75.

The issue of cost

- Drug cost needs to be considered in Asia
- Cost-effectiveness studies need to be performed in different countries

Country	Nuc (USD)	PegIFN (USD)	GNI/capita (USD)
China	704-1935	7968	470
Thailand	913-2774	16464	3400
Taiwan	1095-2665	5760	17930
South Korea	1314-3285	9600	19690

Liaw YF, et al. J Hepatol 2009

Reimbursement policies differ across Asia-Pacific countries

Low reimbursement	Partial reimbursement	High reimbursement
Lamivudine is most commonly used	Drug use according to reimbursement policy	Entecavir & Tenofovir are most commonly used
Drug resistance		High cost
Thailand, Indonesia, Philippines, Vietnam	Hong Kong, Taiwan, Korea, China	Japan, Singapore, Australia, New Zealand

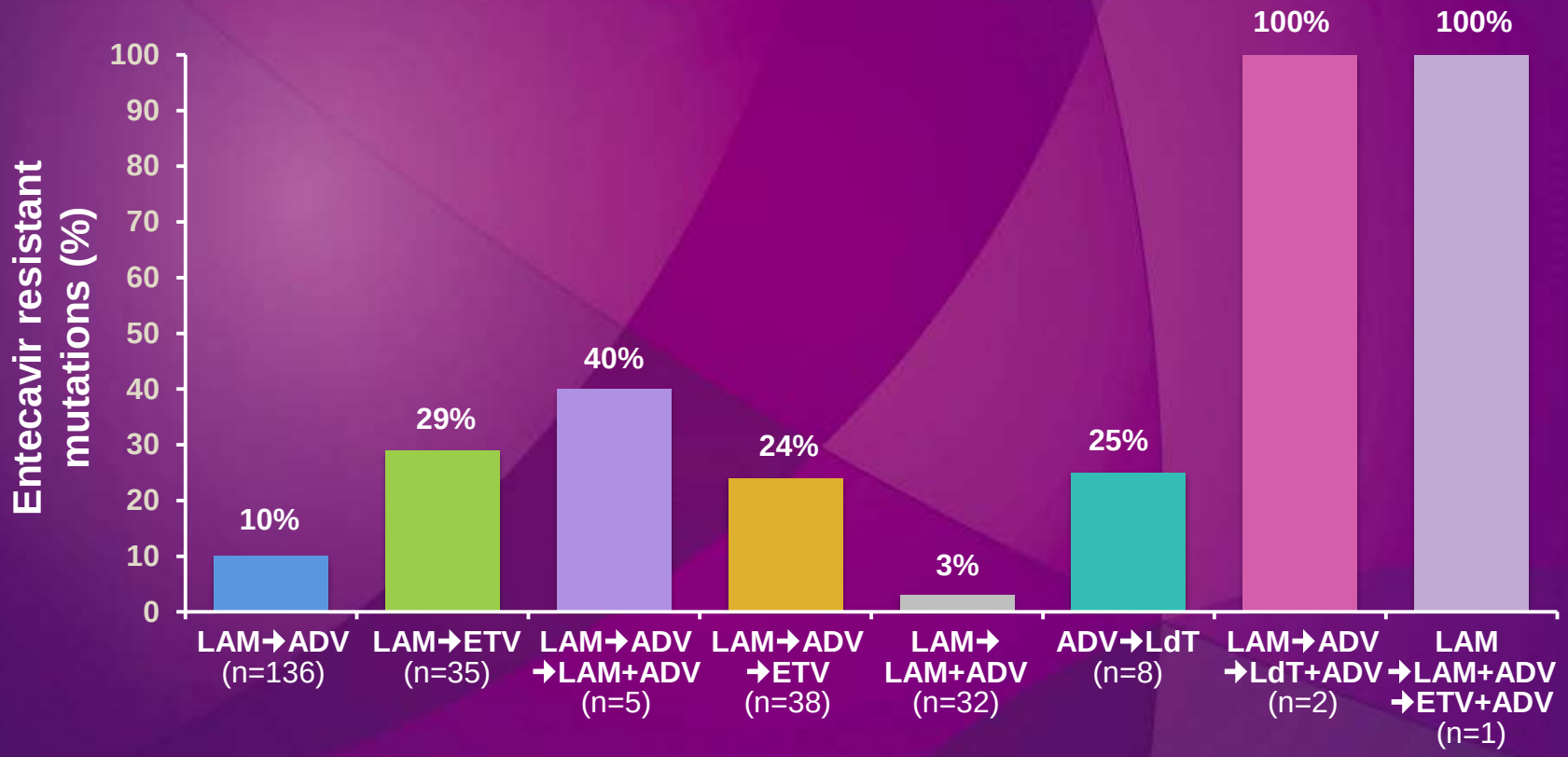
Problems of Partial Reimbursement Policies

- Limited indications (eg. Hong Kong, Korea, Taiwan)
  - Limited indications defined by HBV DNA, ALT and cirrhosis status
  - Some patients do not fall into reimbursement criteria and need to pay for their own medication
- Limited duration
  - NA for 3 years among non-cirrhotic patients in Taiwan
  - Entecavir for 3 years in China
  - Hepatitis relapse with premature drug cessation

The increasing problem of HBV drug resistance in Asia

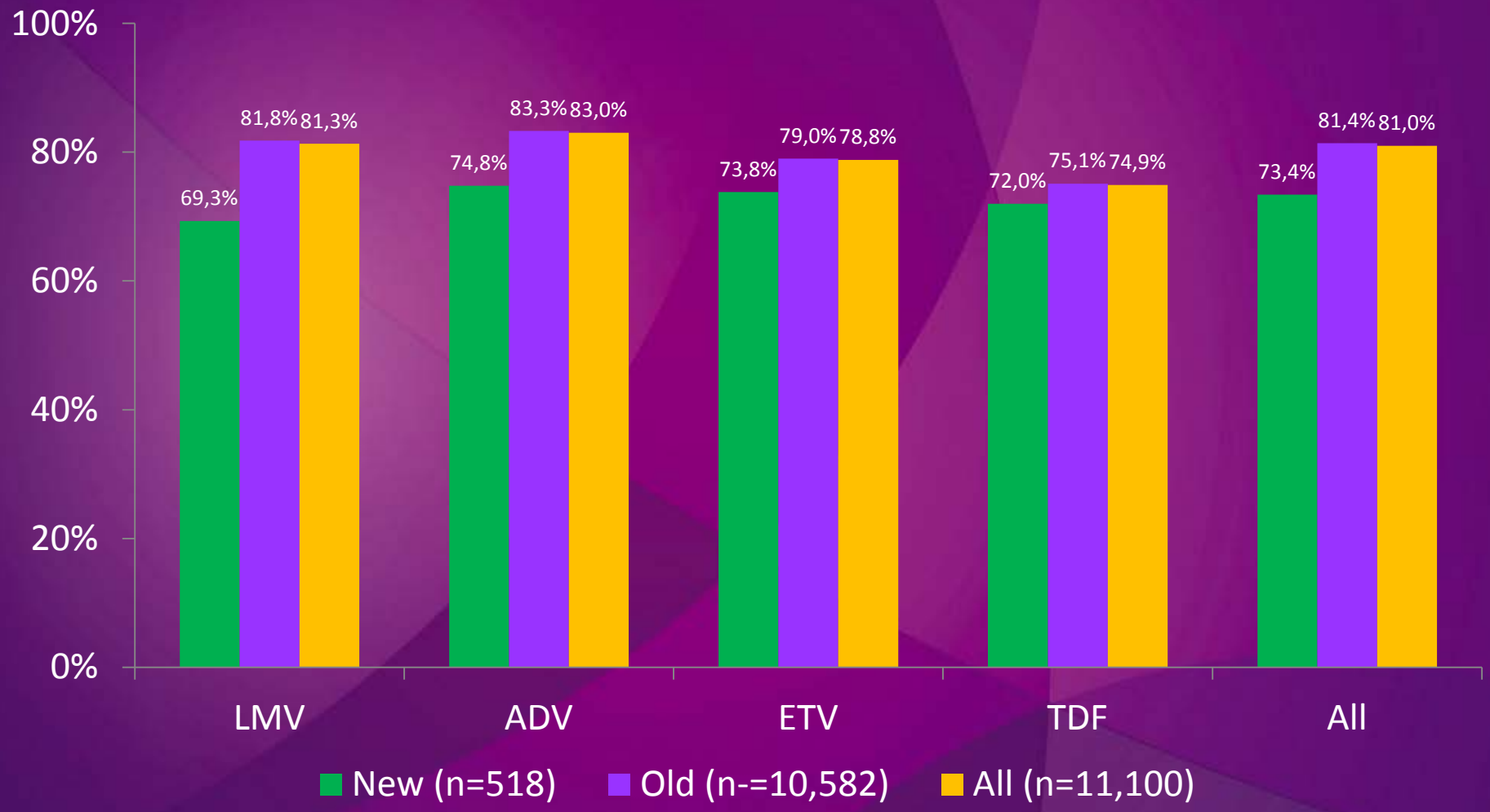
794 patients receiving sequential/combination NUCs

- Diverse drug mutations found in 306 (38.5%)
- ETV-R ±LAM-R ±ADV-R in 45 (5.7%)



Adapted from Liu Y, *et al. J Viral Hepat* 2011;18:e29-39.

Persistence to antiviral treatment in US, 2007-2009



Chotiyaputta W, et al. J Hepatol 2011

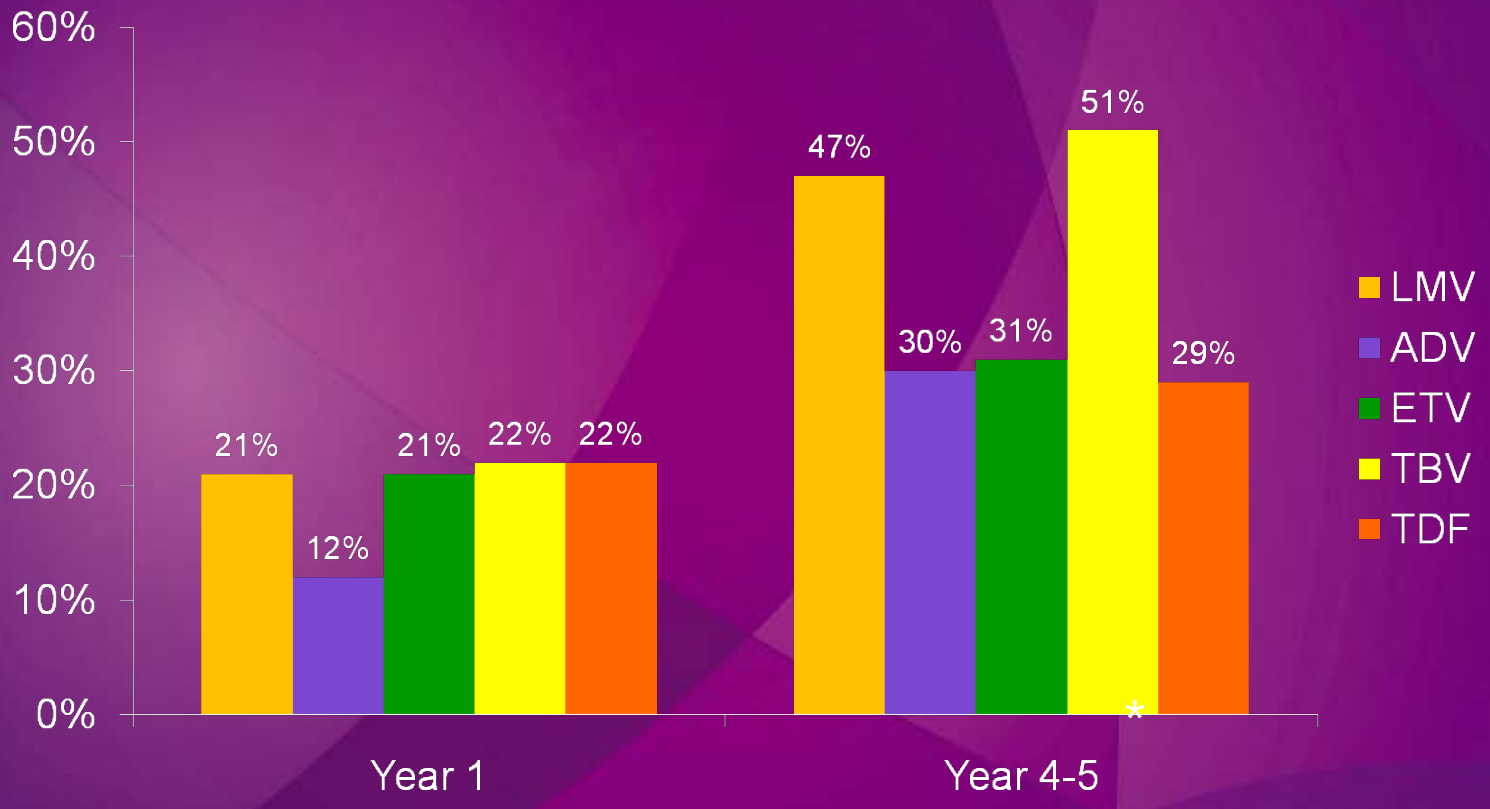
Stopping rules with NUCs for HBV therapy

CHB Treatment Guidelines	EASL[1] (April 2012)	AASLD*[2] (Nov 2009)	APASL[3] (Feb 2012)
HBeAg+ve	HBeAg seroconversion with 12 months of consolidation	HBeAg seroconversion with 6 months of consolidation + undetectable DNA	HBeAg seroconversion + undetectable DNA for 12 months
HBeAg-ve	HBsAg clearance	HBsAg clearance	Treatment for at least 2 years + DNA undetectable 3 times 6 months apart

1. EASL. J Hepatol 2012;57:167-85;
2. Lok A, et al. Hepatology 2009;**50**:1-36.
3. Liaw YF, et al. Hepatol Int 2012;6:531-61

On-treatment HBeAg seroconversion by different antiviral drugs is low in pivotal clinical trials

e+

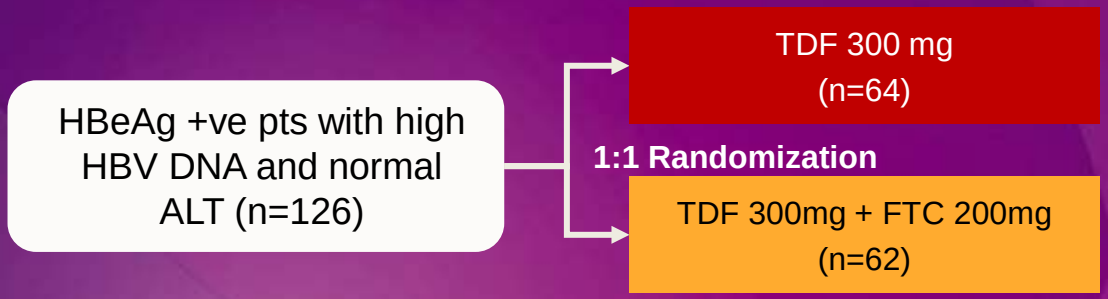


*Year 4-5 are not full ITT dataset

Chang et al., J Gastroenterol Hepatol 2004, Marcellin et al, Hepatology 2008
Han et al, AASLD 2008, Wang et al, AASLD 2009, Heathcote AASLD 2010

Very low HBeAg seroconversion rate in immune tolerance patients

e+



Response = HBV DNA < 69 IU/ml at week 192

	TDF n=64	TDF/FTC n=62	p-value
Primary endpoint			
HBV DNA <69 IU/mL	55%	76%	0.016
Secondary endpoints			
HBeAg loss	6%	2%	0.365
HBeAg seroconversion	5%	0%	0.244
HBsAg loss	0%	0%	

Chan HL, et al. Gastroenterology 2014;146:1240-8

Partial response from treatment naïve CHB to entecavir 0.5mg daily

Low HBeAg seroconversion rate at 3 years

e+

	Wong et al Hong Kong	Bang et al Korea
Total (N)	440	355
Partial response	23.5%	17.7%
3 year undetectable HBV DNA	**58%**	**45%**

Partial response = > 1 log reduction but detectable HBV DNA at month 12

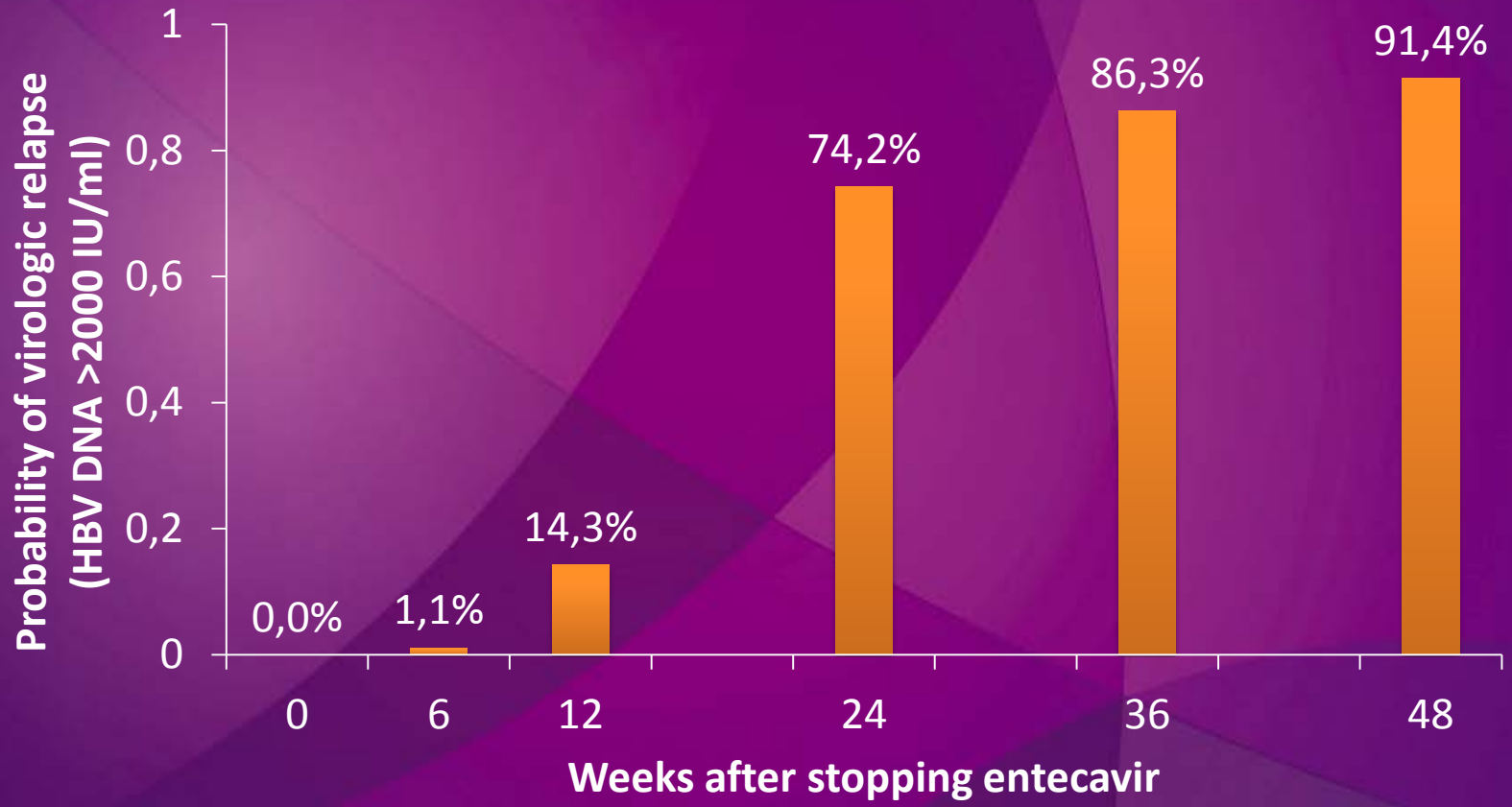
HBeAg positive (N)	160	206
3 year HBeAg seroconversion for partial responders	**19%**	**10.5%**

Wong GL, et al. Aliment Pharmacol Ther 2012;35:1326-35
Bang SJ, et al. Dig Dis Sci 2013;45:600-5

Virologic relapse is common after stopping entecavir in HBeAg-negative patients

e-

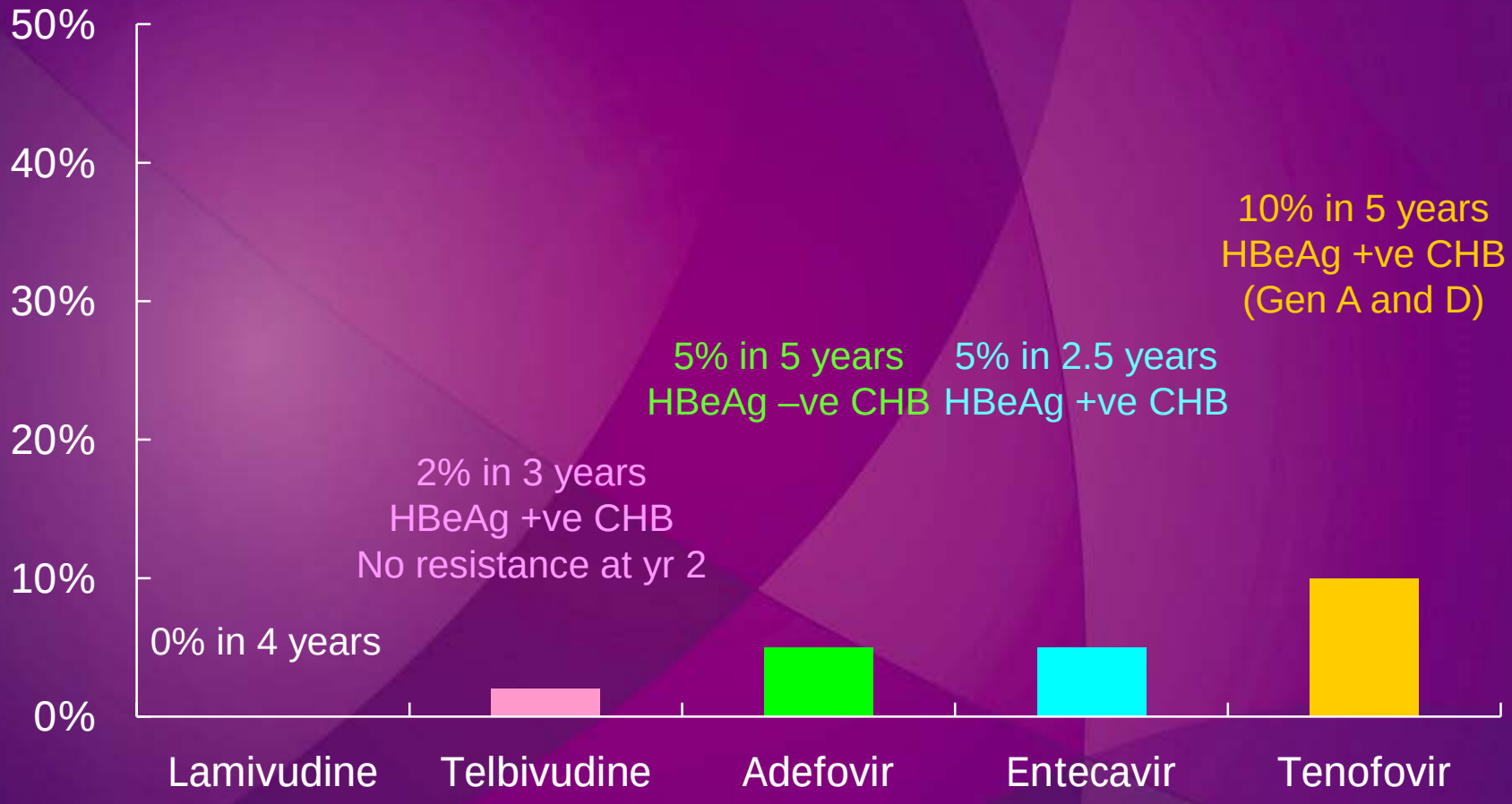
184 HBeAg negative CHB patients on ETV on 3.06±0.64 years
Prospectively stopped ETV according to APASL criteria with undetectable HBV DNA >18 months



Only 10 patients had HBsAg <100 IU/ml

Seto WK, … Chan HL. Gut 2014 (in press)

HBsAg clearance is the ideal treatment endpoint for NA, but it is difficult to achieve



Chang et al., JGH 2004; Hsu et al., APASL 2009;
Hadziyannis et al., Gastroenterol 2006;
Han et al., AASLD 2008, Marcellin et al., Lancet 2013

Challenges of HBV Treatment